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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.

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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.

In this regard identification of the competences required from geneticists and allied professionals would be an important contribution to the harmonization of the practices and to the improvement of the overall quality of the services (Coviello et al. 2007). Finally, some important unresolved ethical aspects of the services, such as the consent for minors for testing, could also contribute to further harmonization of the practice (Borry et al. 2006).

The participant patient organizations developed a series of 15 leaflets describing different aspects of a visit to a genetic service (Lewis et al. 2007). These have been translated in 27 different European and other languages. Development of new sets of leaflets on "What Happens in the Genetic Laboratory" and on some multifactorial diseases are in progress.

The document "Core Competence in Genetics for Health Professionals in Europe" has been extensively reviewed and is ready for publication. To harmonize the activities of Nurses/counselors in Europe, a network of European Genetic Nurses/Counselors has been launched and training sessions are being planned in collaboration with the ESHG.

Review of the literature and surveys on genetic testing in minors have focused on attitudes of clinicians regarding predictive genetic testing in minors and on the attitudes of European clinicians regarding carrier testing in incompetent children. A consensus document is being finalized in collaboration with the ESHG committee on Public Professional Policy issues of the ESHG. The booklet "Genetic Testing and Counseling. European Guidance" has been published and distributed widely.

An analysis of the status in the MS of the European Convention on Human Rights and Biomedicine and the status of the provisions on rights of patients/users of genetic services has been accomplished. Booklets on "Patient Rights in the EU" have been published for 15 MS and more will follow. The interest for this activity in the different MS was responsible for the creation of a separate website providing all this information and more (www.europatientrights.eu).

Dissemination

Training

In addition to the training sessions detailed higher on quality management and counseling, more than 30 fellowships for training were provided by the NoE. These fellowships allowed young scientists either to be trained in a laboratory of one of the participants of the NoE or to attend training courses of relevance to the activities of the NoE.

The Eurogentest Website and Publications

All the documents mentioned here and many more, either developed by the NoE or based on literature reviews, can be easily searched by the different stakeholders on the website of the NoE (www.eurogentest.org).

In addition the website provides an overview of the different events of the NoE and of related activities and publishes an electronic newsletter about 4 times a year.

Regular press releases cover important achievements of the NoE.

The Road Shows

To make sure that the message of EuroGentest about the importance of the quality issues is heard in Europe and elsewhere, participants of the NoE present regularly the achievements of the network at national and regional society meetings, at workshops and expert meetings in Europe and abroad and of course at the ESHG annual congresses.

In Conclusion

Since the start the EuroGentest NoE has succeeded in becoming a "trade mark" for quality genetic services. International awareness of the existing problems has improved.

The will to remedy and to move to harmonization is present within and outside the NoE. Many tools necessary to allow for these improvements have been developed and have already had a substantial impact on the quality of the services. It is clearly the intent of the participants to continue this effort in the future, in collaboration with the ESHG.

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The CanGèneTest Pan-Canadian Research Consortium on Genetic Laboratory Services

François Rousseau

Key Points

Most important issues of Chapter:

- There is a need to enhance translation of genetic innovations into better care;
- Building of the evidence-base for their clinical validity and utility is necessary;
- One approach to streamline this process is multidisciplinary research;
- Involvement of decision makers at all levels is necessary to accelerate uptake;
- A systematic knowledge translation strategy is also important.

Keywords Interdisciplinary network · Technology transfer · Genetic laboratory services · Health technology assessment · Evidence-based laboratory medicine

The Human Genome Project Holds Great Promises for Medicine

Since the completion of the Human Genome Project in 2001, the pace of genetic discovery has been exponential and showed that genes are a significant determinant of health and response to healthcare, and that most diseases have a genetic contribution to their causation; creating expectations that genetic discoveries will strongly impact health care. Indeed, 70% of medical decisions rely on laboratory results and genetic innovations are seen as a major source of diagnostic and prognostic information in the next century. A 2008 report from the US Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) on Oversight of Genetic Testing (2008)

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highlights that the fraction of the general population for which genetic testing is applicable will grow from the actual 2% to over 60%.

The Need to Enhance Translation of Genetic Innovations into Better Care

Even developed countries failed to effectively deliver medical innovations to their population especially new biomarkers of disease issued from the human genome project (Ioannidis 2006; Khoury et al., 2007). Decision-makers at all levels face challenges in technology assessment, organization and delivery of genetic services, oversight mechanisms, education of health professionals and the population, to name a few. They must ensure the equilibrium between potential benefits of genetic innovations, their clinical usefulness, risks and costs. There is a need to understand the process of transferring genetic innovations from "bench to bed side", to strengthen the evidence-base along this process and streamline the transfer to clinical practice of useful genetic innovations. To improve their translation to the health care system, it is crucially important to conduct research both on technology transfer processes and knowledge transfer strategies.

Challenges in Uptake of the Most Effective and Efficient Technologies

In Canada, over 3 billion dollars ($3G) were invested since 2000 in genetic/genomic research from CIHR (1.4 G$) or Genome Canada (1.6 G$ with partners). There are no available estimate of the proportion that has been allotted for clinical validation and applied research, but it is likely that Canada does not fare much better than the rest of the world which spent less than 3% of health research funding towards such research (Khoury et al., 2007). Recent literature emphasizes the lack of research and, as a corollary, of evidence in the fields downstream of basic-research discoveries (Ioannidis 2006; Khoury et al., 2007). Research typically costs increasingly more as it gets closer to clinical implementation and, once a genetic/genomic discovery is published in high profile Journals, the downstream mandatory building of the evidence-base prior to its clinical use is left to a passive uptake by researchers and stakeholders. Many reasons can explain this state of facts, including *lack of* (1) validation and downstream studies after an initial discovery, (2) research capacity, (3) multidisciplinary communication, (4) systematic evidence-based approaches to research, (5) understanding of the pathways of successes and failures in translation, and (6) lack of systematic synthesis of research findings from many studies and teams of investigators (Ioannidis 2006; Khoury et al., 2007; SACGHS 2008).

In Canada these challenges have been tackled in part through activities initiated by the APOGEE Knowledge Network and the CanGèneTest Research Consortium on Genetic Laboratory Services.

Building a Pan-Canadian Team in Genetics Health Services Research

Following a Canadian Institutes for Health Research (CIHR) funding program in Health Services Research (HSR) in Genetics, the APOGEE-Net Team was created in 2003 with the objective of initiating an original Knowledge Network to link genetics, health services researchers and decision makers at the macro (e.g. government), meso (e.g. health-related agencies) and micro (e.g. clinicians, laboratories and users) levels to support the development of health policies in genetics. In 2005 another CIHR initiative on HSR in Genetics, the pan-Canadian CanGèneTest Research Consortium in Genetic Laboratory Services was created. These two initiatives were successful in fulfilling many of their objectives and in creating a small yet synergistic research community in this field in Canada. They have been close to each other from the beginning, sharing several investigators.

CanGèneTest established a broad 17 PIs interdisciplinary research team to study genetic laboratory services from many complementary angles, namely, organization of services (Lamothe et al., 2007), test validation (Giroux et al., 2006; 2007; 2007b), technology assessment (AÉTMIS 2007; Andermann et al. 2008), health economics (Gagné et al. 2007), shared decision-making in primary care (Gravel et al., 2006; Légaré et al. 2007a, b; St-Jacques et al., 2008), regulation of services (Tassé and Godard, 2007; Petit et al., 2008), knowledge translation, public health (Gagné et al. 2007; Gekas et al. 2009). APOGEE-Net created a new breed of students, by proposing multidisciplinary training awards coupled with a tailor-made program in specific fields of research as well as with decision- and policy-makers at various levels. Many students dramatically reoriented their careers and training. They now participate in increasing the capacity and understanding of genetic issues within organizations such as PHAC, Health Canada, INSPQ, *Bureau du commissaire à la Santé du Québec*, HTA-USA, Safety-Net.

We developed and implemented a knowledge transfer strategy involving stakeholders throughout the knowledge cycle (Fig. 1), from priority setting of research topics to the interpretation of research results. APOGEE-Net included decision-makers from Québec and the Atlantic provinces from the outset, and citizens joined the network in 2005. CanGèneTest, initiated shortly after APOGÉE-Net's priority setting exercise, studied some of the prioritized topics such as models of service organization for genetic laboratory services and technology transfer processes. It also established working links with Canadian health care decision makers. For instance, CanGèneTest received research questions from the Québec National Institute of Public Health on genetic screening programs and provided answers on cost/effectiveness of potential screening scenarios for genetic diseases (INSPQ 2009). It also provided decision makers with empirical measures of mutation prevalence, needed to produce HTA reports dealing with genetic diseases such as neonatal screening for MCADD (AÉTMIS 2007). It generated several cross-cutting projects that are now developing into full research proposals involving two or more PIs of different academic horizons. It developed a decision-support guide for population-based genetic screening (Andermann et al. 2008) after a systematic

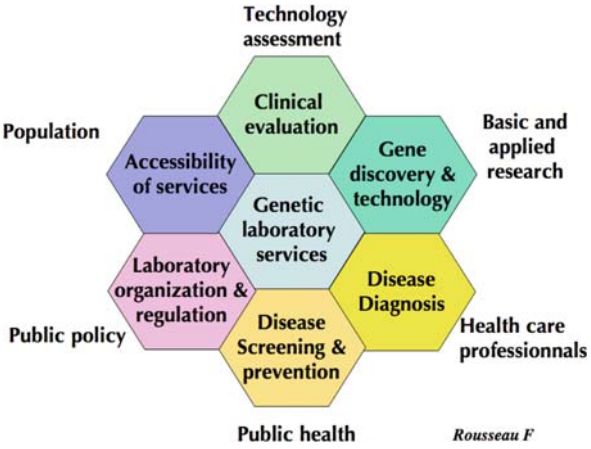

Fig. 1 Stakeholders in genetic laboratory services

review of published principles and criteria and a broad consultation of stakeholders and experts. It published systematic reviews on barriers and facilitators of shared decision making (SDM) in the context of clinical decisions (Gravel et al., 2006). It reviewed decisional needs regarding Down's syndrome screening (St-Jacques et al., 2008) and performed a study on implementation of an approach of SDM in this field. Synergistic links were built between basic researchers, laboratory physicians, clinicians and experts in diffusion of innovation in the health care system which led to the development of original research programs on knowledge translation of genetic innovations to the health care system.

The CanGèneTest consortium further reached out into the scientific and Canadian community by linking to other research initiatives such as the Canadian Molecular Cytogenetics Consortium and by involving more decision makers as well as the general public. It participated in an OECD initiative to increase international awareness of the need to promote quality standards for evidence and develop an agreed framework for genetic test evaluation (Zimmern and Kroese 2007). Between March 2007 and November 2008, the Consortium published over 40 horizon scanning e-newsletters on practical applications of genetic/genomic discoveries targeted at decision-makers from all levels.

The CanGèneTtest research consortium addresses six main objectives and themes. We will briefly describe the work that has been realized in each of them.

Organization of Laboratory Services in Canada

CanGèneTest performed in 2007 a 99-questions survey of molecular genetics clinical laboratories in Canada. Nine clinical laboratories, from Alberta, Ontario and Québec, completed the survey. Together, they produce about 50,000 genotype results per year, which is about half of the total number of molecular genetics tests performed yearly in Canada. In summary, all clinical laboratories were accredited by either the Federal Canadian Council on Health Services Accreditation or by provincial bodies such as the Ontario Laboratory Accreditation (OLA). They tested from 5

to 38 different genes, and 10 to >200 different mutations. Six laboratories subscribed to the CAP External Quality Assessment (EQA) programs relevant to their test offer. Some were also participating to the OLA QMPLS, the European EMQN program or to other EQA programs. Other aspects of laboratory services were also surveyed, such as accessibility, turn around time, mechanisms to introduce new tests, consent, interpretation, reporting, confidentiality, etc.

Validation of Tests

We developed an *Evidence-base tracking tool* aiming to systematically identify the evidence-base for introducing a molecular test in routine use, to collect and present the data, and to identify knowledge and evidence gaps. It comprises 29 clearly defined items, grouped into 10 categories, including disease epidemiology and genetics, available diagnostic tools, analytical and clinical performances, availability of quality control programs, methodological and clinical best practice guidelines, clinical utility, impact on health care and psycho-social, ethical and legal implications. It also summarizes the evidence and identifies research priorities.

Tools for Decision Makers

Apart from establish links with and between decision-makers at various levels (Health technology assessment agency; National institute for public health; Ministry of health; Health Canada), the Consortium has created tools to provide data for decisions relative to the implementation – or not – of new genetic technologies. Simulating the cost/effectiveness (C/E) of screening algorithms for preventable or treatable diseases is a relevant for a health-care system that aims to promote a stronger evidence-base component in its policies. This procedure is useful because C/E of countless strategy options, based on a general model, can be dynamically and simultaneously estimated through simulation, without the need to represent them graphically or to program them individually. This allows testing scenarios related to different populations (demographics, prevalence, etc.), testing properties (diagnostic performances, costs, etc.), models of testing, algorithms, etc, which may represent many hundreds of combinations. As an example of this approach applied to population-based screening we studied C/E of hereditary hemochromatosis population-based screening options involving either biochemical and/or DNA-based tests (Gagné et al. 2007). We evaluated the C/E of 165 population-based screening algorithms tested in 91 different virtual populations of one million individuals involving several screening tests using a computer simulation. The simulator uses true costs of each individual health interventions, analytical and clinical performances of each test, as well as the population profile and demographic projections. We identified a robust screening algorithm that remained in the top 5 most C/E scenarios in most settings of prevalence/penetrance of HFE mutations.

Health Technology Assessment (HTA) and Genetics

Despite huge investments to discover and develop new technologies, Canada has minimal and dispersed capacity to evaluate the utility of innovations, as mentioned by the Romanow and Kirby commissions and the 2003 Federal, provincial, territorial Health Care Renewal Accord. Canada is not alone with such a critical lack of capacity as highlighted in a 2008 US SACGHS report (2008). There is a crying need for research to evaluate the analytical and clinical validity and utility of new emerging genetic tests and methods. As stated in the SACGHS 2008 report: "*Much of current clinical practice is not based on high-quality evidence or evidence-based assessments, and even the promulgation of evidence-based guidelines is often limited in scope and speed of implementation.*" OECD highlighted the need to strengthen the evidence-base to help decision makers at all levels in their evaluation of new approaches and methods (OECD 2005). The Romanow Report proposed that expansion of the health research knowledge base was a key component of a better health care system in Canada, that must be rely on evidence-based decision making. Cost/effectiveness and cost/utility studies are also needed for potential genetic interventions in the health care system (SACGHS 2008), particularly in terms of genetic screening. The evidence base has to be synthesized into a format understandable by decision makers, at various levels of the health care system (Ioannidis 2006). Health technology assessment (HTA) is another essential component of the uptake by the health care system of appropriate and cost-effective new technologies including genetic innovations. HTA in genetics is not mature and methodological progress mainly addressed tests for monogenic conditions. Many of the CanGèneTest investigators were closely involved (as writers or experts) in the production of 8 HTA reports on genetic testing (CETS 1997 to 1999, AÉTMIS 2001 to 2007) some of which called for broadening of the scope of HTA evaluation into such aspects as the organization of services, ethical issues, etc. Methodological and conceptual advances are required to deal with more complex applications (such as multiplex technologies), and international collaboration and capacity enhancement are most needed. Dissemination of the culture of evidence-based medicine in genetics will improve the quality of the knowledge base [11], and methods to diffuse this knowledge have to be studied with respect to their relative efficiency for implementing high quality genetic care.

KT Tools

The CanGèneTest research consortium and other CIHR initiatives in HSR in Genetics led to the creation of a specific HSR community in genetics, that needs to attract researchers from the broader field of HSR (Miller et al., 2008). In response to growing demands and advances in genetic medicine, the role of primary care in delivering genetic services is increasing. Genetic counselling and patient information is moving out of specialized clinics and is rapidly being incorporated into the routine workload of primary care health professionals. Clearly communicating genetic information is challenging and the way information is provided by the

clinician is crucial in assisting patients to construct preferences and then decide on a course of action. People generally misunderstand probabilistic data despite receiving information. Probabilities of risks and benefits estimated in a population are rarely directly applicable to an individual. Consequently health decisions related to most genetic issues in primary care involve a level of uncertainty, the "grey zone" of decision making. In this "grey zone", Shared Decision Making (SDM), a process by which healthcare choice is made by clinicians together with the patient, should be fostered. SDM relies on the best evidence about risks and benefits associated with all available options (including doing nothing) and on the values and preferences of patients, without excluding those of clinicians (O'Connor 2007). It emphasizes and operationalizes the patient-clinician relationship phenomena. Most studies in clinical decision making have ignored the cognitive interdependence of patients and health providers. This is a source of concern since "the right thing to do" often emerges in the course of the professional's contact with patients. A dyadic approach to SDM refers to attending simultaneously to both perspectives of the decision making process (patient and health provider) in the clinical context. Despite observed benefits of SDM, empirical data suggest that it is not occurring in clinical care. Through CanGèneTest we studied: (1) barriers to shared decision making (SDM) (Gravel et al., 2006), (2) effective implementation interventions of SDM in clinical practice (Légaré et al. 2007c), (3) measurement of the physician's perception of the decision making process (Légaré et al., 2007b); (4) sources of difficulties for decision on prenatal screening tests (St-Jacques et al., 2008) and (5) a mixed descriptive study in the context of primary care genetic health decisions using dyadic approaches (ongoing research).

Also CanGeneTest consortium has produced a horizon scanning electronic newsletter on Genetic Testing (http://www.cangenetest.org/en/bulletin.html) distributed worldwide. It is e-published every two weeks, has over 600 subscribers (one third outside of Canada) and the web site receives 1,200 unique visitors per month.

Regulation and Legal Framework of Genetic Clinical Laboratory Services

The Consortium has reviewed the regulatory framework of clinical laboratories in the different provinces of Canada, which are each responsible for health services according to the Canadian constitution (Petit et al., 2008). This has showed, for instance, that clinical laboratory accreditation was not mandatory in all provinces but that proficiency testing was mandatory everywhere.

A working Interface with Decision Makers and Stakeholders

The *APOGEE-Net experience* showed that it is possible to create a knowledge network that materializes into an interdisciplinary forum where all stakeholders are represented, from the researchers to the citizen. There was a period of understanding

and learning about other "cultures", their vocabulary, concerns, questions and tools. This "lag time" was an investment in the next steps. From all stakeholders that participated in this knowledge network, there was a consensus about the essential need for such a forum to establish working bridges between and across disciplines in the field of genetic services and policy. In CanGèneTest, close involvement of decision makers with consortium activities allowed to identify research questions of immediate interest and to rapidly produce the evidence-base data to provide timely answers, when possible. In doing so, there is an upward spiral of synergy that enables stakeholders to realize the feasibility of evidence-building research activities and their possible timelines and, most importantly, to communicate these to the very researchers that can perform the experiments within currently funded research projects. In this sense, this approach creates a *two-sided empowerment*: first, that of the decision-makers over the research agenda, and second, that of the research base that is able to produce high-impact data, in terms of its use to the Canadian publicly funded health care system, for the benefit of all Canadians.

Access to New Expertise, Tools and Infrastructures

The CanGèneTest experience showed that researchers can join into an "umbrella" organization that does not provide significant funding for research but rather allows them to synergize and have access to tools and expertise that is needed to pursue their research endeavors. New multidisciplinary research projects were initiated, building on the product of these synergistic activities between consortium researchers.

Leverage of Funding

The scientific synergy between different research projects or Groups paved the way to co-funding of specific cross-cutting spin-off pilot projects, that led to grant applications into open competitions.

Streamlining the "Pipeline"

For any specific research project within the Team's agenda, knowledge of relevant upstream discoveries, but most importantly dialogue with PIs that are experts of the downstream "pick-up" of their research findings, streamlines technology assessment and the innovation diffusion process. We have shown that linking the different segments of the pipeline together indeed accelerates the efficiency of the value-creation chain.

Overall and Systematic KT Plan

The research agenda obviously also benefits from having an overarching KT strategy, that systematizes timely diffusion of new knowledge as soon as it is produced by the various research groups. They also benefit from the other more operational KT initiatives such as Team meetings, the e-newsletter, and the KT-plan improvement process in place.

Links with International Partners

Another added value is the coordinated positioning of Canadian researchers on the international scene. Several international research initiatives in applied genetics and genomics joined the Team through the participation of their PIs. Some were initiated by Canada such as the CIHR Team in familial breast cancer or the P3G consortia. Others stem from other countries such as EuroGenTest and European projects: TECHGEN on "Technological innovation of high throughput molecular diagnostics of clinically and molecularly heterogeneous genetic disorders" and SPIDIA on "Standardization and improvement of the pre-analytical phase for in-vitro diagnostics". Indirect links also exist between our Emerging Team and other international projects through scientific collaborations of investigators such as with GFOS, the Human Variome Project, Graph-Int (Genome-based Research and Population Health International Network), HumGen, PHGEN, InnoGenome4EU, PHGET, Instit. for Public Health Genetics&Center for Genomics&Healthcare Equality-U. of Washington.

Sharing of Students/Transdisciplinary Training

This experience also showed how transdisciplinary training, even for short periods of time, can create new career paths for students, and enhances capacity by producing a new breed of students with multidimensional training.

Conclusion

Laboratory diagnostic procedures are a major source of health care costs. Clinical laboratory services constitute about 7% of all hospital costs in publicly funded health care systems and play a critical role in clinical decisions. In Canada, in 2007, their cost was 3.1 billion dollars. Given that (i) inappropriate utilization of laboratory testing is estimated to range from 10 to 50% of tests ordered, (ii) the share of gene-based testing grows yearly at 19–25%, (iii) genetic testing can significantly contribute to reduce costs of screening (e.g. RB, FAP) and diagnosis (e.g. Fragile-X syndrome, cancer); (iv) within the next decade, genetic testing may

predict disease susceptibilities of healthy people as well as individual response to drugs, it appears clear that efficient implementation of validated and cost-effective new genetic laboratory services will have a huge economical impact on developed countries.

Multidisciplinary research teams are one major approach to deal with the many challenges faced in the context of the large output of potential diagnostic markers generated by the human genome project as well as by the breathtaking pace of technological advances in genotyping and sequencing.

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Regulating Genetic Testing: The Relevance of Appropriate Definitions

Jorge Sequeiros

Key Points

- It is essential to delineate clearly the purpose and scope of regulation.
- Clear, operational, *context-dependent definitions* should be used when regulating genetic testing.
- It is fundamental to separate the use of human and non-human biological material, and *medical* from *non-medical applications*.
- Clinical genetics applications need to be clearly separated from other medical uses of genetic tests.
- It is crucial to differentiate testing to confirm/exclude a medical *diagnosis* from genetic tests in *healthy persons*.
- The concept of *genetics laboratory-based tests* should be weighted against that of *genetic information* (which includes as well other sources and methods), depending on the purpose and scope of regulation.
- Always test your definitions of genetic testing against concrete practical examples.

Keywords Medical applications · Clinical genetics testing · Genetics laboratory-based tests · Genetic information · Genetic screening

Establishing and laying out the adequate definitions is a quality issue in itself. Several authors have alerted to the need of clear definitions of genetic testing (Holtzman 1994; Harper 1997; Zimmern 1999), and the European Commission (EC) called to the development of consensus definitions (McNally et al. 2004). The most important aspect when regulating genetic testing is to have an operational definition that is clear, serves its purpose and is applicable to the context intended; however, this is not an easy task, as the range of definitions of genetic testing contained

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in international guidelines and recommendations (Sequeiros and Guimarães 2007), or in legal documents (Varga and Sequeiros 2009) is indeed extremely wide. Even among genetics professionals, these definitions vary considerably (Pinto-Basto et al. 2009).

Definitions of genetic testing adopted by regulators and legislators should be explicit and unambiguous. The scope of the definitions used will necessarily impact on the issues and activities they plan to address. Categorizing the various items that should be covered, the contexts to be included or excluded, and having beforehand a clear framework of definitions of genetic testing would be a good starting point.

This was the case, for instance, with the expert group at OECD that elaborated guidelines for quality assurance in molecular genetic testing (OECD Guidelines for Quality Assurance in Molecular Genetic Testing). At the very beginning of its work (2000–2007), several sessions were used to debate what it was going to be meant exactly by molecular genetic testing. The option went, naturally, for the (narrow) concept of clinical DNA-based testing, what included specifying also the types of tests that would be out of scope (e.g., forensics, pharmacogenetics, somatic mutations and research purposes). At the other extreme, the Council of Europe chose a very broad definition for its additional protocol on genetic testing related to health (Council of Europe. Additional Protocol 2008), as had done before the EC expert group (McNally et al. 2004).

Defining the Scope of Genetic Testing

If we put aside *non-human genetic applications* (i.e., tests in animals and plants, and of DNA, RNA or proteins from viruses and bacteria) (Table 1), if that is the intention of regulation, the first decision is perhaps to define what kind of medical and non-medical applications are to be covered (Table 2).

Five large applications of *human genetic testing* that are often excluded from the scope of clinical genetic testing are: identity (forensic) testing and ancestry testing,

Table 1 Decision framework about "genetic testing"

A. Purpose and scope:
1. Human genetic testing (B)
   vs.
   non-human genetic testing (bacteria and viruses)
2. Clinical genetics testing (diagnosis and counselling)
   or
   other medical applications of genetic testing (research, screening, pharmacogenetics, somatic mutations)?

B. Methodologies and type of human 'material':
1. Source of genetic information (genetic material or other sources)?
2. Type of genetic material (DNA, RNA, proteins, metabolites)?

Table 2 Context definitions of human and medical applications of genetic testing, and of clinical genetics testing

NON-HUMAN

- *microbiology*
- *plant*
- *animal*

HUMAN APPLICATIONS

NON-MEDICAL

- *Identity testing (civil, criminal)*
- *ancestry testing*

MEDICAL APPLICATIONS

BIOMEDICAL RESEARCH

- *basic research*
- *clinical research*

PUBLIC HEALTH GENETICS

- *population genetic screening*

CLINICAL GENETICS TESTING

Heritable

Patient diagnosis:	■ *diagnostic testing (confirmation, exclusion)*
Genetic counselling:	■ *presymptomatic testing (Mendelian diseases of high penetrance)*
	■ *familial cancer testing (Mendelian cancers, with high or reduced penetrance)*
	■ *susceptibility testing (complex diseases or traits)*
	■ *prenatal diagnosis (Mendelian diseases, congenital malformations)*
	■ *pre-implantation genetic diagnosis (Mendelian diseases)*

OTHER MEDICAL APPLICATIONS

	■ *pre-implantation genetic screening (aneuploidy screening)*
Drug treatment:	■ *pharmacogenetics testing (adverse drug reactions, drug efficacy)*

Somatic

Cancer prognosis*:*	■ *testing for somatic mutations in cancer*

which are not health related, tests for the purpose of biomedical research, population genetic screening, and somatic mutations in cancer, though at least the last two are also clearly related to changes in the genetic material and to human health.

(1) *Identity testing*, either to determine twin zygosity or family relationships (paternity testing and other), for civil identification, criminal investigation or other forensic purposes, is an (usually) non-medical activity that has practical and ethical implications very different from medical applications of genetic tests. This field is usually treated separately, at the national and international level, and is one area where specific regulation is well developed for a long time.
(2) *Ancestry testing* and ethnic background are currently the object of a profitable activity, often sold directly to consumers, but one that is also quite different from the clinical applications of genetic testing. It has been described as a recreational use of human genetics. It is very new and is largely unregulated, at least in a specific way. Regulation of these tests will tend to deal more with its commercial aspects, as publicity and advertising, quality, transparency and labelling, etc. But attention should be given also to the fact that, on occasion, medically relevant information may (inadvertently or not) be elicited and provided.
(3) *Biomedical research* may or may not be directly health related. In any case, the study of chromosomes, DNA, RNA, proteins or metabolites for research purposes needs to be treated separately from the use of the same type of tests in actual clinical practice. If no research results are to be conveyed to physicians and patients (as they should not), its procedures and implications (including quality, professional and ethical issues) will be rather different during this phase, even if the same genetic test is to be later applied in a clinical context. Research activities and clinical practice should always be clearly separated.
(4) *Genetic screening* is the application of a genetic test (usually DNA or gene product) to a population or large population subgroup (ethnic group, pregnant women, neonates). It is a particular context, deserving special consideration in public health. It should be distinguished from the application of genetic testing in the diagnosis of individual patients and counselling of relatives. Though the laboratory component (and quality issues) are similar, its regulation should be specific, as there are many other different issues, as the characteristics of the test, frequency of the disease being screened, availability of treatment or preventive measures, and other economic and health policy considerations.
(5) *Somatic mutations in cancer*, both at the DNA and chromosomal level, are often of great medical value in terms of prognosis or response to a given treatment. Nevertheless, they usually do not provide information on constitutional genotypes and inherited forms of cancer. Thus, they do not have the same familial and social implications as the detection of germline mutations that cause or predispose to familial cancers. Also, they are often tested in pathology rather than in medical genetics laboratories.

These are all particular uses and contexts of genetic or of gene testing, that legislators and regulators need to bear in mind and explicitly exclude (if that is the

case), whenever dealing with clinical applications of genetic testing for diagnosis and counselling. Also, any of the above are usually employed in clearly defined settings (either medical or non-medical), and thus not as prone to the ambiguities (and its consequences) in the definition and interpretation of the concept of "genetic testing".

Defining the Methods and Biological Materials to Be Used

The next decision to be taken by regulators may be to define if they are to concentrate on particular *laboratory methodologies and procedures*, e.g., as when (1) assessing health technologies to evaluate a specific genetic test, (2) addressing laboratory quality assurance and control, (3) licensing medical genetics laboratories, or (4) defining policies for reimbursement of genetic tests. Though any of these must include some consideration of pre and post-analytical issues, from the criteria for acceptance of samples and the medical indications of a test, to the interpretation and reporting of its results, the main focus will be on the laboratory component.

Thus, the methodologies employed and the material (source of information) used for the test will be determinant for that matter. Legislators and regulators need then to concentrate on the particular laboratory assay and the specific analyte (the chemical substance being analysed or measured). The major distinction to be made will be among (1) *cytogenetics*, (2) *molecular genetics* and (3) *biochemical genetics* tests (and, thus, to the analysis of chromosomes, DNA or RNA, and proteins or their metabolites). Other medical exams that may provide the same information content as these *laboratory-based genetic tests* should not be relevant here.

Deciding as to the Context(s) of Clinical Application and Type of Testing

If the main target of regulation or policy making is clearly the clinical applications of laboratory genetic testing, in diagnosis and counselling (i.e., in patients or affected families), then it will be important to define the context and target group for testing (Table 2).

The major decision here will be to define if the laboratory genetic test is to be applied to patients (affected individuals) with a genetic disorder or in healthy-persons. These are usually relatives at risk for the disease (as genetic screening, i.e., testing being offered to the whole population or large population group, has already been left out – see above).

That is, we should now be dealing either with the (1) request of a physician for a laboratory test or another exam to confirm or exclude the presence of a presumably genetic disease in an affected individual (*diagnostic testing*); (2) the confirmation or exclusion of a genetic defect or congenital malformation in an ongoing pregnancy (*prenatal diagnosis*); (3) the in-vitro selection of embryos obtained by medically

assisted procreation after the diagnosis of a genetic condition in the family (*preimplantation diagnosis*); (4) the request of a genetic test to detect or rule out a mutation for a highly-penetrant dominant disease, usually on a healthy relative at a 50% risk (*presymptomatic test*); (5) the identification of heterozygous carriers for an (autosomal or X-linked) recessive disease (*carrier* or *heterozygosity testing*); (6) the search for genetic variants predisposing to a complex multifactorial disease or trait (*susceptibility testing*); or (7) a predisposition test for a differential response to a pharmacological treatment (*pharmacogenetics*).

It should be noted, however, that though pharmacogenetics testing is indeed a type of susceptibility testing, it poses different regulatory issues. It is a "predictive" test in an otherwise healthy person, neither affected, nor to be affected with a given genetic disease. It tests mainly for predispositions to adverse reactions or to absence of response to some drugs ("personalized therapy" is not yet a current choice). Its rationale is the potential for a serious situation that may happen only when someone is exposed to that treatment. Its medical, ethical and social implications are, thus, different from other "predictive tests" in healthy people, partly because the person is being treated in the context of a disease already present and usually non-hereditary; its immediate medical nature is thus the critical factor, not the genetic susceptibility. In a sense, it is closer to the nature of genetic screening (these tests will tend to be widespread and sold with the drug), and thus *pre-test* specialized genetic counselling is considered not to be needed.

Clarifying Other (Ambiguous) Situations

Cancer genetics is often a source of ambiguity and deserves a special comment. Most cancers are of multifactorial aetiology; thus, tests related to those predispositions (if indicated at all) will fall under "susceptibility testing". But, cancers are hereditary (Mendelian, monogenic) in, roughly, 5% of all cases (largely depending on the type of cancer). Testing for familial forms of cancer in healthy relatives will be "presymptomatic" in nature, particularly in case of high-penetrance (e.g., *APC* testing in familial polyposis coli); however, tests for mutations with reduced penetrance (e.g., *BRCA1* and *2* genes in breast and ovarian cancer) have a lesser predictive value, but are not mere susceptibility testing.

Life-style testing, including obesity and nutrigenomics, physical fitness and exercise performance, and personality and behaviours (regardless of their small predictive value or clinical utility if any) are directly or indirectly related to human health and, thus, should be included together with susceptibility testing for medical complex traits.

Cascade testing is the sequential testing, performed within a family, for healthy mutation carriers (either for a dominant, recessive or X-linked disease), in the context of genetic counselling after the genetic diagnosis of a proband, and progressing along the possible line of transmission of the mutation identified. It is also sometimes called "cascade screening", though this type of testing is not population-based, but rather family-centred (and thus not a "genetic screening" test).

Preimplantation genetic screening (PGS) is a term used in medically assisted procreation to set apart the systematic search for aneuploidies (linked to embryo quality and viability), before implantation of any embryos in the maternal uterus. This relates only to pregnancy success rate and, thus, is very different from preimplantation genetic diagnosis (PGD), which is performed only after genetic counselling and the diagnosis of a serious genetic disease in the family.

Deciphering Meanings in Genetics versus Colloquial Usage

It should be clear now that, in spite of being employed frequently with different meaning, the term "screening" is used in medical genetics in the sense of systematic testing of (tentatively) the whole population or an entire population group (and merely to sieve those at elevated risk, who must then be diagnosed with a high-specificity test). Though it has a much wider significance colloquially, it should be reserved exclusively for population genetic screening.

The same kind of ambiguity happens sometimes with the term "carrier", which in medical genetics applies to any healthy subject carrying a gene mutation, either for a recessive condition (with which that person will never become affected), or for a late-onset dominant disease ("asymptomatic carrier", or "presymptomatic carrier" in case of high-penetrance).

Finally, the term "predictive testing" is often employed with various meanings, including by genetics professionals, either (i) as a synonym of "presymptomatic test", (ii) as a synonym for "susceptibility testing", (iii) bridging all types of genetic testing in persons as yet unaffected, or (iv) in an even broader sense encompassing also carrier, prenatal and preimplantation tests. For that reason, this term should perhaps be avoided at all, at least in legislation and policy-making, unless clearly defined.

Genetics Laboratory-Based Tests, Clinical Genetics Testing and Genetic Information

In many instances, however, it will not be the type of test, the methodologies or the biological material being tested that matter. The aim of regulation may be the various means through which genetic information is derived (i.e., not limited to genetics laboratory-based testing). For example, regulation about (1) privacy and confidentiality, (2) genetic data protection and (3) antidiscrimination (genetic testing and insurance, employment, education or adoption) should be independent of methodologies or the material used to derive genetic information (Table 3).

In addition to genetics laboratory-based tests, other subsidiary medical exams can provide (more or less) unambiguous information about the genetic status of affected (diagnostic information) or healthy relatives (presymptomatic or carrier status information). Many good examples are well known: e.g., the use of *ultrasounds*

Table 3 Context definitions of "genetics laboratory-based testing" and " genetic information "

	GENETIC INFORMATION
Genetics laboratory-based testing:	
Cytogenetics tests (chromosomal-based) – identification of numerical or structural anomalies of individual chromosomes or chromosomal complement	
Molecular genetics tests (DNA or RNA-based) – identification at the nucleic acid level of sequence alterations in the DNA molecule and its functional significance, and epigenetic (non-covalent) changes	
Biochemical genetics tests (proteins, metabolites) – identification at the protein level of sequence alterations in the DNA molecule and its functional significance	
Other sources of genetic information:	
Family history	
Personal history and physical examination	
Other laboratory exams (haematological, biochemical, physiological, image, functional) exams	

in polycystic kidney disease, an *electrocardiogram* (ECG) in the long QT syndrome, or a *blood smear* in a heterozygote for sickle cell anaemia. Several *biochemical tests* may provide a suspicion for a given genotype: e.g., higher levels of *creatine kinase* (CK) in sisters and daughters of obligate carriers for Duchenne muscular dystrophy, or decreased serum *ceruloplasmin* and elevated urinary copper in sibs of Wilson disease patients.

Also, a *personal history* of bilateral retinoblastoma in childhood is evidence for the hereditary (autosomal dominant) form of this cancer. A *physical examination* disclosing multiple café-au-lait spots, neurofibromas, axillary freckles and Lisch nodules is a very strong evidence for a diagnosis of neurofibromatosis type 1 (NF1). A *family history* of choreic movements, behavioural changes, motor deficits and cognitive loss is highly suggestive of Huntington disease. In these cases, a laboratory genetics test to find the causative mutation is important to confirm the clinical diagnosis, and will be crucial for genetic counselling. But, for instance, insurers may not need the results of that test, if they are to discriminate those persons and families: a personal history, a physical examination, some subsidiary medical exams or a simple family history may be more than enough to refuse health or life insurance or establishing higher premiums (underwriting).

Aims and Purposes of Regulation

In conclusion, definitions of human genetic testing can be constructed along two main axes: (I) *clinical genetics* versus *non-clinical genetics tests* (Table 2); and (II) the concept of *genetics laboratory-based tests* versus that of *genetic information* (Table 3).

If legislators or regulators are concerned about data protection, patient rights and discrimination, they should be interested in a definition of clinical genetic testing that includes both (1) laboratory-based clinical genetics tests and (2) any other medical exams that may derive information about a clinical phenotype, including personal and family history, physical and other medical exams (Table 3), i.e., in the concept of (A) *genetic information*. The same would apply for international organizations producing ethical recommendations about genetic testing, or for patient associations or medical genetics organizations discussing professional guidelines. Other human (3) non-medical applications of laboratory genetics testing will probably not be of interest, unless when regulating specifically, e.g., genetic tests in biomedical research, forensic genetic tests, or any type of direct-to-consumer testing.

On the other hand, if a professional organization is involved with laboratory best practices or regulators are occupied with quality assurance measures, then, their major focus must be (B) *laboratory-based genetic testing* (either just clinical, or also non-clinical applications, depending on the organization and their interests), and specifically either (i) cytogenetics, (ii) biochemical genetics, or (iii) molecular genetics testing. That will include external quality assessment (EQA, or proficiency testing), licensing of medical genetics laboratories, certification and accreditation, health technology assessment, and defining policies for reimbursement of laboratory tests.

Conclusions

We propose here a framework of context-dependent definitions of genetic testing to be used when regulating this activity, particularly in the case of its medical applications. We provide a decision-framework along two major axes (context and methods) to be followed beforehand, to enable a clear definition of the purposes and aims of regulation.

Thus, we suggest consideration for the concepts of (1) “human applications”, which include (2) “clinical genetics testing” and (3) “other medical applications of genetic testing” (according to the context of its use); and (4) “genetics laboratory-based genetic testing” and (5) “genetic information” (depending on the source of information and the ‘material’ and methods used to obtain it).

This set of definitions is not intended to be prescriptive. It cannot be overemphasized that the most important issue is for each document to provide very clear operational, context-dependent definitions, and to explicitly exclude the purposes out of its scope.

This structure should be useful to define or rule out various contexts, when regulating microbiology tests, population genetic screening, pharmacogenetics, cancer genetics, immunogenetics (e.g., tissue-matching for blood or bone marrow donation and organ transplantation), the establishment and governance of human biobanks and genetic databases (either for biomedical research, civil or criminal

identification), medically assisted procreation, direct-to-consumer testing, or any other application of genetic tests in humans.

We hope, however, this outline will provide a useful scaffold mainly in the field of clinical genetics testing, for the development of legislation and regulatory frameworks that are coherent and enforceable.

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Genetic Diseases as Rare Diseases: A European Policy View

Ségolène Aymé, Mariana Jovanovic, Ioana Caron, and Ana Rath

Key Points

- All genetic diseases are individually rare but collectively are frequent, so justifying a Public Health approach
- Research on genetic diseases requires collaboration between teams from different disciplines and access to data and biological material gathered at International level to ensure adequate sample size
- Research and development was unattractive for Industry, as the rarity of the diseases implies a restricted potential market, until a specific regulation in the USA (1983) and in the EU (1999) provided a set of incentives to convince Industry to invest. Orphan drugs for rare diseases now represent 20% of all innovative products.
- The development of European collaboration for the delivery of health care and medical services in the field of rare diseases has major potential for bringing benefits to European citizens as no single country can provide the full range of expertise to its citizens
- Easily accessible and validated information is a key element to improve quality of health care delivery. Orphanet, the European portal of rare diseases and orphan drugs, has been set up to provide information on each rare disease and on the relevant health care services in Europe and surrounding countries, based on the assumption that, not only are these diseases rare, but the experts are rare as well. All this information is freely accessible on the website www.orpha.net

Keywords Rare diseases · Genetic diseases · Policy · Public health · Database · Information Technology · Europe

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Introduction

All genetic diseases are rare, according to the definition currently applied in Europe, however, not all rare diseases are genetic ones. A disease is considered rare when it affects less than 5 out of 10,000 people in the European Union. Most Mendelian diseases become more rare when genetic knowledge on their aetiology increases, as they are then split into genetic sub-types down to the gene level, often creating thousands of entities (McKusick 2007; Robinson et al. 2008).

The impact of each disease is limited: collectively, however, they represent a true challenge for public health authorities when it comes to developing a public health policy as it is near impossible to work at disease level. A global rather than a piecemeal approach is necessary in the field of scientific and biomedical research, drug research and development, industry policy, information and training, social benefits, hospitalisation and outpatient care.

Since 1983 in the USA and 1999 in Europe, policies were developed to create an appropriate framework, especially in the field of Orphan Drugs (OD). Policies were also developed to support research and research networks, registries, databases and knowledge bases, and networks of expert centres. These policies were preceded and followed by national initiatives, some of which fully organised as national plans of action. In November 2008, the European Commission adopted a Communication entitled "Rare Diseases: Europe's challenge" (http://ec.europa.eu/health/ph_threats/non_com/rare_10_en.htm), a document defining the scope of action to be taken, both at EU and national level, making rare diseases an official public health issue. The legitimacy of such action is made clear when one associates the principle of subsidiarity (*"The Union does not take action (except in the areas which fall within its exclusive competence) unless it is more effective than action taken at national, regional or local level"*) with the legal basis for EU action in the area of Public Health, Article 152, which states: *"A high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities. Community action, which shall complement national policies, shall be directed towards improving public health, preventing human illnesses and diseases, and obviating sources of danger to human health"*. Legitimacy is also rendered through the implementation of European values, such as the fight against discrimination, including discrimination based on disabilities, and the protection of human rights. The third argument for a European approach is provided by the specificities of RD: these specificities are the limited number of patients and the scarcity of relevant knowledge and expertise, factors which single out rare diseases out as a unique case where a European added-value can be make a great difference. There is probably no other area in public health where national approaches cannot be as efficient and effective as a collaborative approach.

In this chapter, policies developed at EU and national level, are presented together with their ramifications for genetic services.

Policies Addressing Rarity in the Field of Research

The EC Communication states that RDs have proved to be very useful in developing a better understanding of the mechanism of common conditions such as obesity and diabetes, as they represent a model of dysfunction of a biological pathway. Research on RD has been fundamental in identifying most human genes identified to date and has also been essential in the development of a quarter of the innovative medicinal products which have received market approval in the EU. The obstacles to research in the domain of rare diseases are clearly identified: research is scattered throughout different laboratories across the EU with little coordination; moreover, there is a lack of shared resources such as databases and biobanks. Research on RD requires collaboration between teams from different disciplines and access to data and biological material gathered at EU level to ensure adequate sample size. Collaborative research projects and coordination projects are particularly relevant in this field, as is the challenge of establishing shared infrastructures: registries, databases, repositories and technical platforms.

The EU supports research into rare diseases since 1998 through its multi-annual Framework Programmes. Thanks to this funding process, European research networks were established, an initiative which sped up the discovery cycle. Most of these networks targeted genetic diseases.

At national level as well, several countries have addressed the problem of research fragmentation and have taken initiatives to overcome this problem. France, Germany and Spain have provided funding to enhance networking among scientists and to pool knowledge and resources through co-operative networks. Following the success of these three national initiatives, a European network of governmental funding agencies (E-Rare) was subsidised in 2006 to coordinate the research efforts of European countries in the field of rare diseases. Currently nine countries take part in the E-Rare (http://www.e-rare.eu/) project: Belgium, France, Germany, Israel, Italy, The Netherlands, Spain, Turkey and the Federation of Russia. Some of these partners launch joint calls for funding multilateral trans-national research projects on rare diseases. The objective is to establish and develop an effective collaboration for common research projects based on complementarities and the sharing of expertise. This effort represents a decisive step towards the optimal use of collective resources.

Policies Addressing Rarity in the Field of Medicinal Products

If one field where rarity is a serious issue had to be chosen, it would be the field of drug and device development. The rarity of the targeted disease implies a restricted potential market, making research and development unattractive for Industry. To address this problem, the USA passed a regulation on Orphan Drugs in 1983. A similar regulation was later introduced in Europe, on 27 April 2000 (Regulation (EC) No 141/2000 of the European Parliament and of the Council;

http://ec.europa.eu/health/ph_threats/non_com/rare_6_en.htm). Orphan medicinal products obtain market authorisation through a Community procedure, leading to a single marketing authorisation valid throughout the EU. They benefit from several attractive dispositions which have proved to be efficient for biotech and pharmaceutical companies. Over 600 products are in development since 2000 and 54 are on the market as of May 2009 (http://www.orpha.net/consor/cgi-bin/Education_Home.php?lng=EN). Many of them are intended for genetic diseases, such as cystic fibrosis, lysosomal storage diseases, metabolic diseases, hereditary angioedema, genetic forms of cancers, sickle cell anaemia, Wilson disease. . .

To obtain the full potential benefits of the EU orphan regulation, an optimised synergy between actions at EU and Member States levels is required. Examined from this angle, the past experience in this domain is not considered to be entirely satisfactory (http://ec.europa.eu/pharmaforum/; http://www.rdtf.org). There are still many hurdles to overcome before patients in developed and developing countries have equal access to the OMP that have been produced.

Policies Addressing Rarity in the Field of Public Health

The first European Community action programme on rare diseases was adopted for the period in 1999 and RD continue to be a priority today. The main lines of action were the exchange of information via existing European information networks on rare diseases, and the development of strategies and mechanisms for information exchange so as to encourage continuity of work and trans-national co-operation (http://www.rdtf.org)

Thanks to these programmes, several important projects received the necessary support to develop their activities at EU level, including Orphanet, Eurordis, and several networks of clinical centres that cooperate either to develop information services or to coordinate their clinical activities.

A European Rare Diseases Task Force (http://www.rdtf.org) was established in 2004 in order to promote the optimal prevention, diagnosis and treatment of RD in Europe: this decision concretely acknowledged the unique added-value that European coordination could provide for rare diseases. This Task Force worked through expert working groups and published several reports, of relevance for the genetic community, on the best way to establish and promote expert centres at country level and European reference networks of expert centres.

The development of European collaboration for the delivery of health care and medical services in the field of rare diseases has major potential for bringing benefits to European citizens by overcoming the limited experience of professionals confronted with very rare conditions; improving access to treatment requiring a particular concentration/pooling of resources (infrastructure and knowledge) or expertise; offering patients the highest possible chance of success by sharing expertise and resources; maximising cost-effective use of resources by concentrating these resources where appropriate; helping to share knowledge and provide training

for health professionals; acting as benchmarks to help develop and spread best practice throughout Europe; helping small countries with insufficient resources from their health care sector to provide a full range of highly specialised services of the highest quality.

Pressure for such change comes from all stakeholders. However, there are difficulties in establishing and funding such cooperation, as health services and medical care are not derived from a European competency and any type of cooperation could have potential consequences on the national/regional health care systems (http://www.rdtf.org).

Among the pilot projects of reference networks of expert centres is DYSCERNE, a network of dysmorphology centres engaged in an effort to share expertise in order to improve diagnosis of very rare developmental anomalies (http://www.dyscerne.org).

The Task Force has also produced recommendations in the field of patient registries which are of relevance for the genetic community (http://www.rdtf.org).

The EC Communication emphasises the need to produce and disseminate accurate information and the need for an inventory of rare diseases: these diseases should also be introduced into all existing coding and classification systems. These initiatives constitute what is seen by all stakeholders as the cornerstone of the effort to make RD understandable and visible in information systems.

It also calls for the development of e-Health which can contribute in a number of different ways to these objectives, in particular through electronic online-services and telemedicine.

Finally a harmonised approach to population screening policies and improved quality management of laboratories are cited as two important areas where a coordinated action at EU level is needed and should be undertaken in the coming years.

The Task Force on Rare Diseases will be replaced, in all probability, in the near future by an EU advisory committee of experts on rare diseases to be nominated following a call for expression of interest. This initiative guarantees a long-term coordinated action at EU level which should greatly benefit patients with genetic diseases.

Information as a Tool to Improve Services

Most genetic diseases are unknown to health care professionals outside the field of genetics. In 1997 Orphanet was established, jointly by the French Ministry of Health and the National Institute of Health and Medical Research (INSERM) to overcome this problem. Orphanet started as a national initiative and evolved into a European project after 2000, becoming a portal in five languages in 2008. The concept was to provide all stakeholders with a compilation of information on rare diseases and a directory of expert services, based on the assumption that, not only are these diseases rare, but the experts are rare as well. All this information is freely accessible on the website www.orpha.net

The inventory of rare diseases and the encyclopaedia are the core products of Orphanet. The identity card of each disease includes the disease name and its synonyms, MIM numbers and ICD10 codes, prevalence rates, causative genes, general description of the disorder, symptoms, causes, epidemiological data, preventive measures, standard treatments, genetic counselling and prenatal options.

So far, summary information is available in English, French, German, Italian and Spanish for 2,500 diseases out of the 5,850 currently listed in Orphanet. The encyclopaedia is expert-authored and peer-reviewed.

The level of aggregation of information differs from OMIM as the disease definition at Orphanet is based on the phenotype, not on the causative gene. Orphanet diseases are positioned in poly-hierarchies collected from the literature or established in-house with expert groups. Classifications are updated regularly as knowledge becomes available. The users of the website can query by disease name at any level of precision, and by gene or by sign. They can also visualise where the disease fits in each of the different classifications. This new service is expected to provide a bridge between clinicians and biologists through a mutually beneficial service. It is also expected that this will help make genetic diseases more visible in health care information systems by providing a stable nomenclature of all existing phenotypes and by allowing an interface between different databases. The data is available on request to any research or clinical groups which may need this information.

The Orphanet directory of services includes information on specialised outpatient clinics, clinical laboratories, research activities, clinical trials, registries, and support groups in 38 countries. This information is accessible through a relational database in which all the data is organised around the concept of disease. The search facility is by disease.

This directory of specialised outpatient clinics was a challenge to populate as the concept of clinics expert enough to be listed had to be established. We decided to target clinics offering a service of higher quality than a standard service in a teaching hospital. Criteria were defined such as the availability of a technical platform to investigate patients and of a multidisciplinary approach, as well as the attractiveness of the clinic demonstrated by the proportion of referrals from outside the region. All genetic counselling clinics are listed as they offer a unique service, as well as dysmorphology clinics. To date, 3,382 expert clinics in 2,372 institutions are identified.

Orphanet is the reference portal of medical laboratories. It includes 1,370 laboratories providing genetic testing (Fig. 1). Of those medical laboratories, only 112 of them are accredited and 282 participate in EQA schemes (10). The analysis of genetic test services in Europe in general shows that they provide potential testing for 1,895 diseases, either through a molecular, a biochemical or a cytogenetic test. The availability of these tests differs greatly from one country to another, demonstrating that cross border care in the field of genetic testing is a necessity due to the rarity of expertise. This directory helps clinicians to identify quality-assured laboratories, as recommended by the OECD.

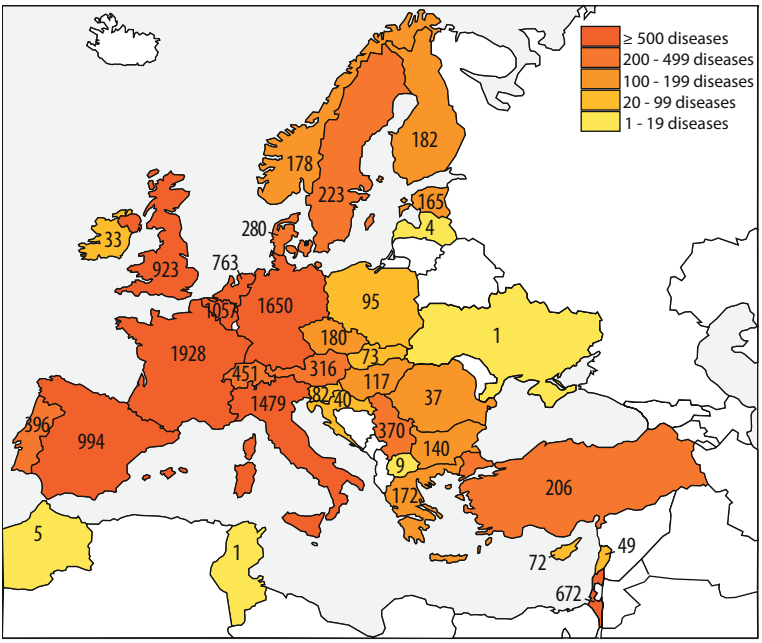

Fig. 1 Content of the orphanet directory of genetic services as of May 2009: number of diseases for which there is a test available in each country

The accessibility of information on research activities, clinical trials and registries is also instrumental in maximising collaboration between academic teams, but also public-private partnership. It gives researchers an opportunity to make their expertise known and to attract national and international partners. It allows biotechnology and pharmaceutical industry to identify experts in Europe, to identify new development opportunities and to accelerate patient enrolment in trials. So far, 2,931 research laboratories are listed with 5,392 projects on 1,293 diseases.

Providing a directory of patient organisations has an enormous added-value for patients, as these organisations offer a wide range of services susceptible to impact very favourably on the quality of life of patients and families. Their number increases rapidly. Today there are 1,803 of such advocacy groups in Europe.

Orphanet activities are equally funded by the INSERM, the French ministry of Health and by the European Commission (DG Public Health and DG Research). Definitively Europe requires a policy in the field of rare diseases, including support to an information portal to guide stakeholders in their search for adapted services and to contribute to networking. Rarity of diseases and of expertise at country level is Europe's challenge, calling for a strong partnership.

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http://www.rdtf.org

http://www.dyscerne.org

European Regulatory Issues Related to Quality in Provision of Genetic Service

Herman Nys

Key Points

- Regulation on the quality of health care services in general and clinical genetic testing in Europe is carried out at national level.
- The Additional Protocol on genetic testing to the Biomedicine Convention contains provisions to guarantee the quality of genetic services in Member States of the Council of Europe
- While respecting the wide variety of different systems, the European Union wants its Member States to define clear quality and safety standards for health care provided on their territory

Keywords Quality in clinical genetic services · Regulatory issues · Council of Europe · European union

The latest development within Europe regarding regulatory control of genetic testing is the 2008 Additional Protocol to the 1997 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the application of Biology and Medicine, concerning Genetic testing for Health Purposes (see chapter "Quality Issues in Clinical Genetic Services; Regulatory Issues and International Conventions" for a brief description). This Additional Protocol will be the first European legal instrument in this area (Kaye 2008) and has been opened for signing in November 2008.

Successive European treaties clearly state that the (quality of) health care is the responsibility of the member states of the European Union, but the delivery of health care involves people, goods and services that are subject to European law (Legido-Quigley et al. 2008). Indeed, the EU is built on the concept of free movement of goods, services, people and capital. European laws (so called directives)

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enacted to implement and protect these freedoms impact on the professional mobility, qualifications obtained in one country are automatically recognised in others. Citizens can travel freely within Europe, reassured that they will have access to health care should an emergency arise. The licensing of drugs and medical devices is harmonized across Europe. Yet, within Europe the approach to quality in different countries varies, often for historical reasons. These differences are becoming increasingly important for two reasons. First, the number of health professionals moving within the EU is increasing rapidly. Secondly, although it is still unusual for citizens of one country to obtain health care in another, in some places and for some groups, this phenomenon is important. In July 2008, the European Commission presented a proposal for a directive on the application of patients' rights in cross-border healthcare. Its aim is to establish a general framework for the provision of safe, high quality and efficient (cross-border) health care.

Council of Europe

The Convention on Human Rights and Biomedicine

The European Convention on Human Rights and Biomedicine (hereafter: the Convention) was adopted by the Committee of Ministers of the Council of Europe on 19 November 1996 and opened for signature in Oviedo, Spain, on 4 April 1997. After the fifth ratification, that of Spain, the Convention entered into force on 1 December 1999.

Thirteen Member States of the EU have ratified the Convention. The responsibility for the development and effective implementation of the Convention's norms lies primarily with each respective State Party, not with the common European institutions. Article 1 §2 is explicit in this respect: "Each Party shall take in its internal law the necessary measures to give effect to the provisions of this Convention".

This responsibility of the State Parties is reinforced by article 23 that obliges the Parties to provide appropriate judicial protection to prevent or to put a stop to an unlawful infringement of the rights and principles set forth in the Convention at short notice, and by article 25 obliging them to provide for appropriate sanctions to be applied in the event of infringement of the provisions contained in the Convention. Thus, the internal law of the State Parties has to conform to the provisions of the Convention. Chapter 4 of the Convention deals with the Human Genome. Article 11 prohibits any form of discrimination against a person on grounds of his or her genetic heritage. Article 12 deals with predictive genetic tests: Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counseling. Article 13 provides that an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is

not to introduce any modification in the genome of any descendants. Finally, article 14 prohibits the use of techniques of medically assisted procreation for the purpose of choosing a future child's sex, except where serious hereditary sex-related disease is to be avoided.

The Additional Protocol on Genetic Testing

The Convention is a so called framework treaty, containing the leading principles. Article 31 of the Convention provides that protocols may be concluded in pursuance of article 32, with a view to developing, in specific fields, the principles contained in this Convention. There are now four such additional protocols to the Convention: on human cloning (1998), scientific research with human beings (2002), organ transplantation (2006) and the already mentioned additional protocol on genetic testing (2008).

The Protocol on genetic testing applies to tests, which are carried out for health purposes, involving analysis of biological samples of human origin and aiming specifically to identify the genetic characteristics of a person which are inherited or acquired during early prenatal development (hereinafter referred to as "genetic tests") (article 2). It does not apply to genetic tests carried out on the human embryo or foetus and to genetic tests carried out for research purposes.

Chapter III of the Protocol (Genetic Services) contains provisions to guarantee the quality of genetic services. According to article 5 Parties shall take the necessary measures to ensure that genetic services are of appropriate quality. In particular, they shall see to it that (a) genetic tests meet generally accepted criteria of scientific validity and clinical validity; (b) a quality assurance programme is implemented in each laboratory and that laboratories are subject to regular monitoring and (c) persons providing genetic services have appropriate qualifications to enable them to perform their role in accordance with professional obligations and standards. Article 6 provides that clinical utility of a genetic test shall be an essential criterion for deciding to offer this test to a person or a group of persons. Article 7 §1 requires that a genetic test for health purposes is only be performed under individualised medical supervision. In the (non binding) Explanatory Memorandum to the Protocol, is explained that article 7 §1 has been " driven by the concern to enable the person concerned to have suitable preliminary information with a view to an informed decision regarding the carrying out of this test and, if appropriate, to have access to appropriate genetic counseling. A precise evaluation of the situation of the person concerned, involving direct contact with him of her, is a determining element in that respect. A mere telephone conversation with a medical doctor, for example, does not allow for such evaluation". Discussion might arise about what is being regulated by the Protocol. According to its scope, it should apply to "genetic tests" (article 2). However, some direct-to-consumer companies make a distinction between making claims that directly affect healthcare decision making (which might fall under the Protocol) and making health-related claims (which does not fall under the

Protocol) (Borry 2008). Moreover, article 7 §2 allows for exceptions to the general rule referred to in §1 by a Party, subject to appropriate measures being provided, taking into account the way the test will be carried out, to give effect to the other provisions of the Protocol. However, such an exception may not be made with regard to genetic tests with important implications for the health of the persons concerned or members of their family or with important implications concerning procreation choices.

Chapter IV of the Protocol deals with information, genetic counseling and consent. When a genetic test is envisaged, the person concerned shall be provided with prior appropriate information in particular on the purpose and the nature of the test, as well as the implications of its results (article 8 §1). For predictive genetic tests as referred to in Article 12 of the Convention on Human Rights and Biomedicine, appropriate genetic counseling shall also be available for the person concerned. The tests concerned are tests predictive of a monogenic disease; tests serving to detect a genetic predisposition or genetic susceptibility to a disease and tests serving to identify the subject as a healthy carrier of a gene responsible for a disease. The form and extent of this genetic counseling shall be defined according to the implications of the results of the test and their significance for the person or the members of his or her family, including possible implications concerning procreation choices. Genetic counseling shall be given in a non-directive manner (article 8 §2). According to article 9 §1 a genetic test may only be carried out after the person concerned has given free and informed consent to it. Consent to tests referred to in article 8 §2 shall be documented. Following article 9 §2 the person concerned may freely withdraw consent at any time.

European Union

Training of Professionals

There are many differences in the ways professionals are trained within the EU (Legido-Quigley 2008bis). Mobility of health professionals within the EU is based on the principle of mutual recognition. As long as the training programme meets minimum standards (expressed in hours of study) its graduates are assumed to be safe to practice throughout Europe. The assumption that health services provided according to mutual regulations in any EU country will be of adequate quality is confirmed by the European Court of Justice, which has applied the principle of mutual recognition in its rulings (Legido-Quigley 2008). The system has been criticized because the criteria for recognition relate almost exclusively to the length of the study, with no consideration of the content. They also do not take account of the growing use of competence-based approaches in professional education. Overall, the effects of the directives on professional training appear to have been limited (Hervey and McHale 2005). Moreover; clinical genetic is still not recognized as an EU medical specialization (ESHG 2008).

Approval of Drugs and Medical Devices

Approval of drugs is one of the few areas within health care where practice is harmonized within Europe (Legido-Quigley 2008). Manufacturers can submit new products for approval centrally, to the European Agency for the Evaluation of Medicinal Products (EMEA). Alternatively, they may seek approval by a national evaluation agency, which then circulates details to the relevant agencies in all other EU countries; if no objection is received, the product is approved for sale throughout the EU (principle of mutual recognition). Some products, such as those involving biotechnology, must be approved centrally. The EU has also legislated to require that drugs are accompanied by detailed patient information leaflets. It may be the case that a similar centralized body as EMEA for diagnostic and prognostic tests for medical purposes would be a useful development. Genetic tests are considered to be regulated by the In Vitro Medical Devices Directive (1998), but the current pre-market evaluation mechanisms do not sufficiently apply to genetic tests (see for more details on the In Vitro Medical Devices Directive, chapter "Ensuring Education and Quality in the Practice of Health Professionals (Non-Medical) Working in Genetic Services").

Common Quality and Safety Standards for Healthcare in Europe

In July 2008 the European Commission presented a proposal for a Directive on the application of patients' rights in cross-border health care. The aim of this proposal is to establish a general framework for provision of safe, high quality and efficient cross-border healthcare in the European Union and to ensure free movement of health services and a high level of health protection, whilst fully respecting the responsibilities of the Member States for the organization and delivery of health services and medical care. Although the title only refers to cross-border health care, the scope of the proposal is clearly much broader: "The proposed directive applies to all health care provisions, regardless of how it is organized, delivered or financed. (Given that) it is impossible to know in advance whether a given health care provider will supply health care to a patient coming from other member states or to patients from his own member state, it appears necessary that the requirements to ensure that health care is provided according to clear quality and safety standards are applicable to all health services, without discrimination between different types of organization, delivery or financing of the provision of that health care". This implies two elements. The first is clarity over which is the member state that should be responsible for ensuring compliance with common principles for health care. However, this is not sufficient. The second element is a minimum degree of certainty about what the authorities of the responsible member states will ensure for all health care in their territory. Whilst respecting the wide variety of different systems, structures and mechanisms put in place by the member states in this area, this will ensure a minimum core set of common principles on which patients and professionals from

other member states know they can rely. In order to ensure that the degree of harmonisation that this implies remains proportionate, the principles in the proposed directive take as a basis the Council conclusions on "Common values and principles in European Health Systems" of June 2006.

Chapter II of the proposed directive is entitled: "Member state authorities responsible for compliance with common principles for health care". Article 5 is the only article of this chapter. Its first paragraph stipulates that member states of treatment shall be responsible for the organisation and the delivery of health care. In such a context and taking into account principles of universality, access to good quality care, equity and solidarity, they shall define clear quality and safety standards for health care provided on their territory, and ensure that:

(a) mechanisms are in place for ensuring that healthcare providers are able to meet such standards, taking into account international medical science and generally recognised good medical practices;
(b) the application of such standards by healthcare providers in practice is regularly monitored and corrective action is taken when appropriate standards are not met, taking into account progress in medical science and health technology;
(c) health care providers provide all relevant information to enable patients to make an informed choice, in particular on availability, prices and outcomes of the health care provided and details of their insurance cover or other means of personal or collective protection with regard to professional liability;
(d) patients have a means of making complaints and are guaranteed remedies and compensation when they suffer harm arising from the health care they receive;
(e) systems of professional liability insurance or a guarantee or similar arrangement, which are equivalent or essentially comparable as regards their purpose and which are appropriate to the nature and the extent of the risk are in place for treatment provided on their territory;
(f) the fundamental right to privacy with respect to the processing of personal data is protected in conformity with national measures implementing Community provisions on the protection of personal data, in particular Directives 95/46/EC and 2002/58/EC;
(g) patients from other Member States shall enjoy equal treatment with the nationals of the Member State of treatment, including the protection against discrimination provided for according to Community law and national legislation in force in the Member State of treatment.

Any measures taken by Member States, when implementing this Article, shall respect the provisions of Directive 2005/36/EC on the recognition of professional qualifications (article 5 §2). In so far as it is necessary to facilitate the provision of cross-border health care and taking as a basis a high level of protection of health, the Commission, in cooperation with the Member States, shall develop guidelines to facilitate the implementation of §1 (article 5 §3).

The proposed directive has created heated debates among the healthcare professionals, patients' representatives and the EU political world. However, the proposal

has little chance of going through the co-decision procedure during the Barroso Commission, ending in June 2009. First reading in the Parliament may still take place next spring, but the readings will have to begin again from scratch after the June 2009 parliamentary elections.

Conclusion

Much of the regulation on the quality of health care services in general and clinical genetic testing in Europe is actually carried out at a national level. Although from different perspectives, the Council of Europe and the European Union have recently shown the ambition to take a more active position in the regulatory process. While the Council of Europe is acting from a human rights perspective, the European Union aims at protecting the free mobility of persons, goods and services. Nonetheless, the provisional results of these approaches that have been made public in 2008 (the Additional Protocol on genetic testing and the proposed Directive on patients' rights in cross-border health care) both concentrate on the protection of quality and safety of the services, respect for informed consent and protection of confidentiality.

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The European IVD Directive and Genetic Testing

Stuart Hogarth, David Barton, and David Melzer

Key Points

- As part of the In Vitro Diagnostics (IVD) sector, genetic tests fall under the broader statutory regimes for the regulation of medical devices. The EU IVD Directive governs the safety, quality and performance of devices by setting out requirements for: placing a product on the market, production, labelling, clinical evaluation/investigation and post-marketing surveillance.
- Based on the EUs New Approach legislation, the Directive sets out broad and general standards for safety and effectiveness in a series of essential requirements with which all IVDs must comply before being placed on the market.
- The regulatory controls to ensure that IVDs are compliant with the Directive are known as conformity assessment procedures. These vary depending on the risks posed by the test. Higher risk tests are subject to independent pre-market review by Notified Bodies, for low risk tests the manufacturer has sole responsibility for assessing conformity with the Directive.
- There has been a prolonged policy debate about how best to ensure the safe and appropriate use of clinical genetic tests and many believe that genetic tests should be subject to independent pre-market evaluation before entering clinical use.
- The IVD Directive, as currently implemented by member states, is considered by many to be an inadequate mechanism for ensuring the safety and effectiveness of genetic tests. In particular there is concern about a number of ambiguities and variations in interpretation and enforcement.

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This chapter draws on work by Stuart Hogarth and David Melzer in collaboration with members of EuroGentest, in particular the outcomes of a EuroGentest meeting about the IVD Directive organised by David Barton in 2007, the report of that meeting written by Barton and a subsequent briefing on the Directive which Hogarth and Melzer prepared (Hogarth and Melzer 2007). This briefing was presented to the regulatory authorities of EU member states in 2007, it was then adopted as a EuroGentest report and formed the basis of a EuroGentest response to the EC consultation on the future of medical device regulation in the EU

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- Key issues which need to be addressed are classification of nearly all tests (including most genetic tests) as low risk and consequent lack of premarket review; confusion about regulatory status of laboratory-developed tests (LDTs) produced by commercial laboratories, and ambiguity about whether manufacturers must provide data on the clinical validity of their tests.
- Revision of the Directive is now being considered by the European Commission who have indicated an interest in addressing some of the issues outlined.

Keywords Regulation · IVD directive · Clinical validity · Reference materials

As part of the in vitro diagnostics sector, genetic tests fall under the broader statutory regimes for the regulation of medical devices. Although generally less burdensome than the regimes for pharmaceutical products, they share a number of key features: they are concerned with ensuring the safety and efficacy of healthcare products and their most powerful tool is their authority both to grant new products permission to enter the market and to remove existing products from the market should serious problems arise. Failure to comply with the medical device regulations is a criminal offence (although criminal sanctions vary across EU member states (Pilot 1999).

In Europe medical device regulation is controlled by three EU Directives, the third of these is the In Vitro Diagnostics Directive which provides a regulatory framework for all IVDs which are to be sold or used within the EU. The Directive governs the safety, quality and performance of devices by setting out the requirements for: placing a product on the market, production, labelling, clinical evaluation/investigation and post-marketing surveillance. The Directive does not cover issues such as which tests should be available as over-the-counter self-testing kits, which remains a matter for individual member states (subject to other provisions of EU law) (EU Medical Devices Experts Group 2002).

History

Medical device regulation has only been pursued systematically in Europe since the 1990s which saw the introduction of three Directives which harmonized medical device regulation in the EU. Prior to harmonisation there were highly divergent approaches – in some countries there was no regulation, while in others some devices were regulated as medicines. Such was the case with IVD devices – in the early 1980s only France and Germany regulated some tests, but the advent of AIDS led to increasing concern about test quality and other member states began to develop IVD regulations. As a result of increasing regulatory divergence between member states the European Diagnostic Manufacturers Association (EDMA) asked the European Commission for a harmonizing Directive. The IVD Directive was published in 1998 and came into force in all EU states in 2003.

Responsible Bodies

The medical device directives are administered in the European Commission by the Directorate-General for Enterprise (DG Enterprise), but while the Directive applies throughout the EU, it is implemented by Competent Authorities and Notified Bodies within each individual member state. Some member states have multiple competent authorities and notified bodies. Competent Authorities are responsible for interpretation and enforcement of the regulations but review of devices is carried out by independent, third party organisations known as Notified Bodies.

Implementation issues relating to the medical device directives are dealt with at EU level by a number of working groups and taskforces each dedicated to a specific issue such as compliance and enforcement, clinical evaluation and vigilance. The activities of these groups are co-ordinated and overseen by the Medical Devices Expert Group (MDEG). Membership of MDEG (and most of the constituent subgroups) is drawn from member states, industry (trade groups), standardisation bodies and notified bodies.

The Regulations

The fundamental elements of the regulatory system are registration with the regulatory authority, quality assurance, pre-market review and postmarketing surveillance. Registration requires that manufacturers provide the regulator with basic details of their organisation and also of the products they are placing on the market.

Manufacturers must have a quality assurance system in place to cover the entire life cycle of a product, from initial design through to postmarket vigilance. Manufacturing facilities are subject to periodic inspection by the governments and/or accredited third party agencies. Manufacturers can meet QA requirements through certification to recognized standards, such as those developed by the International Organization for Standards (ISO), in particular ISO 13485 which sets out quality systems standards for use in the regulation of medical devices.

Essential Requirements and the New Approach

All the Devices Directives are based on the EU's New Approach framework which seeks to deal with the problems encountered when regulating a very broad range of products based on rapidly changing technologies. Rather than setting out highly detailed requirements which may be out-of-date by the time they are in force, New Approach legislation establishes broad and general essential requirements for safety and performance. In the case of the IVD Directive there are a series of essential requirements including five general requirements with which all IVDs must comply before being CE marked and placed on the market. Although the requirements are

described as essential, not all tests need to meet all requirements. However, whilst it is the responsibility of manufacturers and laboratories to assess which requirements are appropriate to their product, this is not considered carte blanche to pick and choose – the requirements are deemed to be comprehensive and "all must be satisfied save for those requirements which do not apply to a particular product as a matter of common sense" (Hodges 2003). Of particular interest are the first three requirements.

The first states that the test must not "compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users or, where applicable, other persons". Any risks conferred by the test must be outweighed by the clinical benefits. The second requirement states that the devices must be designed in accordance with latest knowledge; risk should be where possible eliminated, and otherwise protected against, and users must be warned of any residual risks. Requirement three states that devices must meet the manufacturer's specifications, taking into account "the generally acknowledged state of the art". Performance criteria that may be appropriate include "analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection".

Where there may be ambiguity about whether products meet these requirements, and what constitutes state of the art, the legislation requires that this is addressed through harmonised standards – also known as European Norms (ENs) – which are set by European standardization bodies. ENs can be revoked or revised as necessary without recourse to fresh legislation (Stinshoff 2004). For the higher risk IVDs (see below) the regulators are expected to produce Common Technical Specification (CTS) which set out more detailed standards for the types of clinical evidence which will be required to gain pre-market approval.

Before placing a device on the market the manufacturer must ensure that it meets the requirements of the Directive. Manufacturers must prepare technical documentation sufficient to demonstrate the conformity of their product, and premarket review of this technical file is a process known as conformity assessment. Pre-market review is one way to ensure truth-in-labelling i.e. that the manufacturer's intended use for the product is supported by the clinical data on the test's performance as set out in the technical file, and summarised in the product label and in promotional material.

Conformity assessment procedures vary depending on the risks posed by the device. Annex II of the Directive lists a small number of tests which are classed as high risk (List A) or moderate risk (List B). Of interest to genetics, ABO and Rhesus typing are listed in List A, while devices for PKU diagnosis and evaluating the risk of trisomy 21 (but no other genetic tests) are included in List B. Annex II tests have to undergo pre-market assessment by a Notified Body, as do devices for self-testing (i.e. those sold direct-to-consumer) but there is no independent evaluation of any other tests. Manufacturers must still prepare technical documentation, but it is the manufacturer who decides whether they have fulfilled their obligations under the Directive and, having done so, awards themselves the "CE mark".

Postmarketing Controls

Once a device is on the market it is subject to postmarketing controls; regulators can places restrictions on the sale, distribution or use of devices, and remove unsafe products from the market. Manufacturers are required to have a systematic procedure to review experience gained from their devices in the post-production phase. For instance, European guidance indicates the importance of post marketing studies in certain circumstances – such as the severity of the disease, or the novelty of the technology – and indicates the range of approaches to data collection which can include: "extended follow-up of patients enrolled in the pre-market trials, and/or a prospective study of a representative subset of patients after the device is placed on the market. It can also take the form of open registries" (European Commission 2004).

Guidance from the European Association of Notified Bodies indicates that a post-marketing surveillance (PMS) system should be in place to collect data on issues such as "changing performance trends [and] performance in different use populations" (European Association of Notified Bodies for Medical Devices 2000). Another guidance, on clinical evaluation in the post-marketing phase, indicates the importance of what it terms Post Market Clinical Follow-up (PMCF) in certain critical circumstances, which may be the severity of the disease, or the innovative nature of the technology, i.e. when "the design of the device, the material, the principles of operation, the technology, or the medical indication is new".

The suggestion that the novelty of a device may be a trigger for greater emphasis on PMS is also reflected in the Directive. Articles 10 and 11 include certain obligations on manufacturers to inform competent authorities when they are introducing "new products" i.e. if *there has been no such device continuously available on the Community market during the previous 3 years for the relevant analyte or other parameter* or if *the procedure involves analytical technology not continuously used in connection with a given analyte or other parameter on the Community market during the previous 3 years.*

Of relevance to genetic tests is that the Directive makes particular reference to microarrays: *. . . this is true in particular of high-density DNA probe devices (known as micro-chips) used in genetic screening*. Such new products are subject to special vigilance procedures, whereby after registration the competent authority *may at any time within the following 2 years and on justified grounds, require the manufacturer to submit a report relating to the experience gained with the device subsequent to its being placed on the market*. There is no information available on how this provision has been used in practice.

Special Measures

The IVD Directive introduced a new mechanism, not present in the other two device directives, whereby a member state can adopt special measures to prohibit, restrict or place specific requirements on a product or group of products, on the grounds of

public health. Such measures must be reported to the Commission and other member states and where it is felt the measures are justified, then they can be enforced across the EU (Medical Devices Expert Group 2002, p. 37).

Reference Materials

The substances which are used to obtain traceability of test results through time, distances and different measurement procedures are reference materials (RMs). RMs can be used for calibration of values indicated by a measuring system or of another reference material, for validation or control of trueness of measured values in laboratories and for evaluation of the performance of a new measurement procedure.

RMs are covered by the Directive as IVDs. Recital 9 states:

> Whereas, although internationally certified reference materials and materials used for external quality assessment schemes are not covered by this Directive, calibrators and control materials needed by the user to establish or verify performances of devices are in vitro diagnostic medical devices.

And Article 1.2 states:

> (b) 'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material,. . ..

The Directive requires (Annex 1, Essential Requirements) that

> the traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or through available reference materials of higher order.

Section 2 Problems

Having outlined the requirements of the Directive, some issues that might need further clarification in the regulatory framework of genetic and other clinical tests under the Directive are discussed in the second half of this chapter. There has been much concern about both the ethical, legal and social consequences of genetic testing and also about the clinical dangers which arise from the premature commercialisation of tests which have not always been properly evaluated and which enter clinical practice when their predictive power and clinical utility are still unclear. There has been a prolonged policy debate about how best to ensure the safe and appropriate use of clinical genetic tests; a number of committees and task forces have reviewed the oversight of genetic testing and their reports have come to similar conclusions. For the purposes of this chapter, the most important idea which has emerged from this debate is a general consensus that genetic tests should not enter routine clinical practice without thorough independent evaluation. Furthermore, it has become a well-established view that full evaluation requires evidence on four criteria set out in what has become known as the ACCE framework.

Analytic validity – accuracy of test identifying the biomarker
Clinical validity – relationship between the biomarker and clinical status
Clinical utility – likelihood that test will lead to an improved outcome
Ethical, legal and social implications

The reason for the failure of the IVD Directive to deliver robust independent pre-market evaluation of the growing number of commercial genetic tests is analysed in this section.

Purpose of the Directive

Discussion of possible limitations of the Directive often refers to the idea that the purpose of the Directive was free trade, not public health. The *main* purpose is indeed the creation of a single market and the removal of barriers to trade (clearly expressed in the first paragraph of the preamble); however, the preamble also states that "maintenance or improvement of the level of health protection attained in the Member States is one of the main objectives of this Directive". Thus, the Directive has a dual purpose – free trade and health protection – albeit the former may be considered its primary purpose. To put it another way: the Directive creates the structure within which free trade can take place and a central part of that structure is regulations designed to protect the health of patients.

GR Higson has addressed this issue pointing out that the representatives of member states who took part in negotiations were from ministries of health and their chief concern was to ensure that the creation of a single market in devices satisfied "their responsibility for the health and safety of their citizens" (Higson 2002, p. 31). A similar point of view was expressed by John Sale, then Director General of EDMA, who complained in November 1998 (a month after the IVD Directive was agreed) that industry had asked for a harmonized regulation for free trade purposes and had ended up with increased regulation motivated by an over-estimation of the risks posed by IVDs (Sale 1998).

(1) LDTs and medical device regulations
Genetic testing is characterised by a high degree of dependence on laboratory-developed tests (LDTs). Whilst the EU treats commercial LDTs as devices subject to the IVD Directive, clarification is required on which in-house tests are covered by the Directive. Tests which are *manufactured and used only within the same health institution*, are excluded from the scope of the current Directive. These in-house tests are covered by national rather than harmonised community legislation. However, the term *health institution* needs elaboration or definition to clarify that commercial laboratories *are* covered by the Directive. Currently it is believed that many commercial test laboratories wrongly claim to be "health institutions" and thus claim to be excluded from the Directive and that member states vary in their approach to the regulation of these tests with some failing to regulate any LDTs and others granting no exemption for health institutions.

The term *manufactured* is another term which is not defined in the Directive. This creates further ambiguity, as clinical laboratories may purchase groups of reagents which are diagnostic kits in all but name, but which are labelled for research use only. By validating these reagents in-house, they may then claim to have manufactured the resulting device and avail of the exemption.

Furthermore, it is not clear that the Directive applies to LDTs performed by labs outside Europe. For instance, the US companies InterGenetics and Myriad have both made their tests available through third-parties in the UK; others are following suit. These UK third-parties collect the samples and return the results but the test is performed by the company in the US in their own reference laboratory. The regulatory status of such tests is currently unclear. Were such US companies to be exempted from the Directive it may place European LDT companies at a commercial disadvantage (for instance the Dutch company Agendia, whose MammaPrint test is the main competitor of Genomic Health's Oncotype Dx not only needed a CE Mark for their test in Europe, but had to gain FDA approval to market their test in the US).

IVD manufacturers are concerned that the current scope of the health institution exemption from the Directive for LDTs is too broad. Manufacturers of CE-marked devices are subject to stringent standards for the design and manufacture of their reagents and devices, while laboratories are free to assemble devices from general-purpose laboratory reagents. Commercial manufacturers cannot compete with such LDTs on cost, and complain that there is not a "level playing field". Meanwhile, the lack of oversight of the quality of design and manufacture of LDTs gives rise to concerns about the quality of the results produced by these tests. Specialist laboratories, on the other hand, argue that the health institution exemption is essential to enable them to develop highly specialised tests which would never be commercially viable as CE-marked products. They also point out that the availability of alternative assays provides an important "second opinion" in cases where the CE-marked product gives an incorrect or inaccurate result. These concerns could at least partially be addressed by limiting the availability of the health institution exemption to laboratories which are accredited to an appropriate international standard, such as EN ISO 15189. This accreditation standard sets out criteria for the analytical validation of all tests performed by the laboratory, and ensures that a robust system for quality control and improvement is in place. There may be issues of subsidiarity in introducing such a limitation to the exemption. At least in part, the exemption enshrines the notion that tests developed and used in a single institution (in a single country) should be regulated locally or nationally and not at EU level. This idea, however, misses the fact that most specialist laboratories test samples from a broad range of sources. A survey of genetic testing laboratories in 2002 found that 60% of participating laboratories had received samples from outside their own country (McGovern et al. 2007); this traffic will only have increased in the intervening years. This international dimension to the application of LDTs calls for an international dimension to their regulation.

(2) Risk classification
The primary reason that most genetic tests are not subject to independent pre-market review in the European Union is that they are either not listed in Annex II of the Directive 98/79/EC or are not self-tests and therefore the manufacturer is not required to submit their technical documentation to a Notified Body. An international comparison of device regulations shows that the European approach is unique. In the United States, Canada and Australia genetic tests which fall within the medical device regulations are all treated as moderate to high risk – and so are generally subject to pre-market review (in Australia some genetic tests are Class II and exempt from pre-market review). There are a number of reasons for considering that many genetic tests are moderate to high-risk:

1. They are often stand-alone, with no confirmatory test available.
2. They are used for critical clinical purposes, such as pre-implantation genetic diagnosis and selecting treatments (pharmacogenetics, molecular oncology).
3. They may have a serious psychological impact (e.g. Huntington's disease).
4. Many new tests are highly complex involving multiple alleles or multiple genes, making interpretation more difficult.
5. If it is a test which is performed in a single reference laboratory, then it may not undergo external quality assessment or even informal peer-review by the pathology community.
6. New genetic tests carry the risks associated with all novel devices – unproven performance in the field and lack of familiarity on the part of users.

This reflects a wider problem with the European framework. In effect, it lacks a coherent mechanism for classifying the risk profile of new tests. The vast majority are considered low-risk, with only a small number being classed as moderate or high risk. Within this schema there appears to be little consistency as regards what is classified moderate-risk. Thus Chlamydia tests are moderate-risk, but other STD tests are low-risk; PSA is moderate-risk, but other cancer tests are not, and tests for the heritable disorder PKU are moderate risk but all other heritable conditions are low-risk. The prima facie assumption is that all new tests are low-risk. Furthermore, the mechanism for adding tests to the high or moderate-risk category has been used only once in the history of the Directive, and this failure to update the lists has led to greater inconsistency, for instance, Gen-Probe's PCA3 test quantifies the PCA3 mRNA in a patient's urine sample as a marker for prostate cancer and thus performs exactly the same clinical function as the PSA test, yet it has not been added to Annex II, List B despite the fact that PSA is in Annex II, List B.

The Proposed GHTF Model

The European Commission is now considering adoption of an alternative risk classification schema developed by the Global Harmonisation Task Force (GHTF) which

is both more comprehensive and more consistent (GHTF 2008). Largely modelled on the Australian and Canadian models, it is a four-class system running from high- to low-risk. The risk class of a test is assessed using a number of criteria, such as the intended use/indications for use, the skill of the user, the degree of reliance placed on the test result, and the potential impact on public health and the patient. The GHTF model places genetic tests into the moderate-to-high risk (Class C) category, and therefore the tests would be subject to independent pre-market review.

Scope of Review – Analytic and Clinical Validity

Most stakeholders believe that the Directive requires manufacturers to provide evidence of a test's analytic validity, but only requires evidence of a test's clinical validity if clinical claims are made by the manufacturer (Hogarth and Melzer 2007). However, recent discussion with a range of competent authorities has revealed that in fact member states disagree about the scope of the Directive, with some believing that it covers both analytic and clinical validity as minimum requirements. An international comparison of IVD regulations indicates divergence between the US and Canadian systems and those of the European Union and Australia in this regard.

Country/region	Analytic validity	Clinical validity
USA	Yes	Yes
Canada	Yes	Yes
Europe	Yes	Unclear
Australia	Yes	Only if clinical claims made?

Discussion of this issue requires clarity on the terms:

Analytic claim	This test identifies gene X (the biomarker)
Analytic validity	The accuracy of test in identifying the biomarker
Clinical claim	By identifying gene X this test diagnoses disease Y
Clinical validity	The relationship between the biomarker and clinical status

Guidance suggests that once a manufacturer has a stated clinical purpose for a test, then they must provide data on its clinical validity. For instance, the MEDDEV guidance on Research Use Only (RUO) products issued in 2004 highlights the issue of the distinction between research and clinical use. This guidance clearly states that an IVD test with no intended medical purpose is not a test under the IVD Directive, it is simply an RUO product.

> In summary for a product to be categorized as an RUO product it must have no intended medical purpose or objective... When a medical purpose has been established based on

> sufficient and broadly agreed upon scientific, diagnostic and clinical evidence, then the product must comply with the requirements of the Directive before the manufacturer can place it on the market with an intended IVD use. (DG Enterprise 2004)

It might be reasonable to infer that in order to define a medical purpose a manufacturer would have to make a clinical claim, and if they make a clinical claim then they must support it with evidence.

Furthermore, looking at the Directive requirements concerning safety and performance which all IVDs must comply with before bearing CE marking and being placed on the market: Is it possible to fulfil the Directive's essential requirements by only providing data on a test's analytic validity? GR Higson, a UK expert on device regulation closely involved in the development of the medical devices directives, commented on this issue, stating that:

> final confirmation of the safety and performance of a medical device is normally provided by observation of the behaviour of the device in its intended use with patients. . . Essential requirements 1 and 6, and in some cases 3, can only be satisfied by the evaluation of clinical data relating to the use of the device. (Higson 2002, p. 49)

The first essential requirement states that the test must not *compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users or, where applicable, other persons*. Furthermore, it says that *any risks which may be associated with their use must be acceptable when weighed against the benefits to the patient and be compatible with a high level of protection of health and safety.* One could argue that one can only assess the benefits of a device in relation to an intended clinical purpose. Risk assessment also requires knowledge of the clinical purpose for the device. For IVD devices one of the main risks are the clinical consequences of an incorrect result. Since such incorrect results might arise from either poor analytic validity or poor clinical validity, then it would appear logical that a comprehensive risk assessment would include the evaluation of the clinical validity of the test for its intended use.

Requirement three states that *the devices must be designed and manufactured in such a way that they are suitable for the purposes referred to in Article 1(2)(b), as specified by the manufacturer, taking account of the generally acknowledged state of the art. They must achieve the performances, in particular, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer.* Common usage of the terms *analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity* would lead one to understand analytical sensitivity and specificity as referring to analytic validity and diagnostic sensitivity and diagnostic specificity as referring to clinical validity. However, in the Commission Decision 2002/364/EC on common technical specifications for in vitro-diagnostic medical devices, the terms diagnostic sensitivity and analytic sensitivity are defined thus:

(Diagnostic) sensitivity – The probability that the device gives a positive result in the presence of the target marker.

Analytical sensitivity – In the context of the CTS it may be expressed as the limit of detection: i.e. the smallest amount of the target marker that can be precisely detected

To answer the debate on clinical validity, these definitions will need to be revisited in the future.

Reference Materials

DG Enterprise has issued guidance on various scenarios in which reference materials may or may not require CE marking, however, concerns still exist that positive control samples sent from one lab to another in the course of routine medical genetics laboratory practice could be classed as IVDs and require CE marking.

EuroGentest submitted a scenario to DG Enterprise describing the transfer of a positive control sample from one institution to another to verify the performance of the assay being used by the institution receiving the control sample. DG Enterprise was asked to advise whether such a sample should be CE marked. A supplementary question asked if CE-marking would be required if the assay being verified was subject to the in-house exemption.

The motivation for this query was that this is a common scenario in medical genetics, where mutations are either rare or (in many cases) "private" to a single family. Members of a family may be tested in genetics laboratories in different institutions or even different member states. It is recognised best practice to include a positive control in all clinical tests, and the only source of a positive control may be the GT laboratory which first identified the mutation in that family.

The motivation for the supplementary question, asking if CE-marking would be required for such a control sample if the assay being verified was subject to the in-house exemption, stems from the wording of Recital 9 (see above), which refers to "calibrators and control materials needed by the user to establish or verify performances of devices". "Devices" in this context could be taken to mean only devices covered by the Directive, in which case controls for exempt devices (e.g. in-house assays) would themselves be exempt. This interpretation would bring a neat proportionality to the scope of the Directive in this area, as it would clearly be impossible to CE-mark a control reagent for use in a single family, whereas it should be viable to CE-mark controls for CE-marked assays. No opinion on the submitted scenario has yet been received from DG Enterprise.

Sets of control materials such as those developed by the UK National Genetics Reference Laboratories may also be classed as IVDs if distributed beyond the institution that created them. This was the essence of an opinion offered by the MHRA, the Competent Authority in the UK. Again, it may be important whether the reagents

are used to verify the performance of general laboratory technologies (e.g. for mutation scanning) or of CE-marked devices.

Conclusion

The IVD Directive was the last of the three to be implemented and came into force in December 2003. As with many new pieces of legislation there are a number of issues which require clarification. Some stakeholders have expressed concerns that not all EU countries have implemented the Directive as stringently as the others (UK Healthcare Industries Task Force 2003). Some countries have introduced additional regulations. In particular France has been unwilling to give up its right of national authority to approve medical devices and in 1998 passed a law requiring a three-month pre-market notification for Class III and many Class II devices.

There are particular concerns about the performance of Notified Bodies which may lack clinically-trained staff or contract clinicians who are unfamiliar with regulatory processes (Higson 2002, pp. 69/202). France has suggested that weaknesses in the operation of the Directives might be addressed through a European Medical Devices Agency.

MDEG has already completed one study of how the Directives are working, based mainly on the first of the three Directives to be implemented. Amongst the issues MDEG has identified is a need for greater transparency in its assessment activity, particularly for high-risk devices. Clinical evaluation is another area which the study reports needs further development. Manufacturers sometimes lack clinical data and notified bodies do not assess the data sufficiently – a Clinical Evaluation Task Force is working to resolve these issues (MDEG 2002).

In 2008 DG Enterprise began a public consultation on the future of the Medical Device Directives proposing a broad range of significant changes to enhance the protection of human health (European Commission 2008). Revision of the risk classification system and enhancement of the essential requirements are two proposals which could directly affect the regulation of genetic tests. More broadly the Commission has suggested a new role for the European Medicines Agency (EMEA) in premarket evaluation of devices and postmarket surveillance activities. The Commission received 200 responses to the consultation and, at time of writing in March 2009, was preparing for further consultation with stakeholders in anticipation of developing formal proposals in 2010.

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Quality Issues in Genetics Services in the United Kingdom

Peter Farndon

Key Points

- The UK has quality standards for commissioning and delivering clinical and laboratory genetic services and for the education and training of staff
- There are quality standards at national, regional and local levels
- Quality markers for genetic services have generally grown from the experiences of genetic professionals over the last 30 years.
- These have formed the basis of formal quality schemes now in operation, which are increasingly being linked to funding
- There is agreement on measuring processes, but debate continues about how best to measure quality of outcomes (for instance, a genetic consultation)
- The views of users of the services (patients and professionals) are an essential component of the quality schemes

Keywords Clinical governance · UK genetic services · Commissioning genetic services · Delivering genetic services · Training and education · Monitoring quality

Introduction

The UK government has stated that it wants patients to benefit from genetic advances in a timely, appropriate and cost effective manner through the delivery of high quality services. Publicly funded genetic services in the UK are part of the NHS which is the main health care provider.

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Quality markers specifically for genetics services have generally grown from the initiatives of professionals and their organisations during the development of services over the last 30 years. Many of these standards have been adopted as the basis of formal quality schemes or used by patients and service commissioners to assess services. Genetic services must also follow the quality guidelines of the hospital of which they form a part, and those of the NHS (National Health Service), which is currently actively promoting quality across the entire health care system through several new initiatives. Some of these national guidelines will be discussed below.

However, a service cannot be delivered without adequately trained and dedicated staff, so this chapter will also consider quality measures related to the training of staff and continual professional development. Members of staff have to provide the service by undertaking certain procedures and practices; these, too, need quality standards.

Background to the UK National Health Service

The NHS was set up in 1948, is free at the point of delivery and is funded by the UK Government from taxation.

In England, the Department of Health, a government department, sets the overall strategic direction, policy and national standards and targets, and provides funds for the NHS. These inform the work of the Strategic Health Authorities who manage and set the strategic direction of the NHS for populations of about five million. Strategic Health Authorities also commission training places from providers of education in line with manpower predictions.

Because of devolved government in Scotland, Wales and Northern Ireland, there are some differences in the organisation of the NHS, but the fundamental principles are the same throughout all four UK countries.

Clinical services are provided locally. Patients look to their family doctor (general practitioner) for general medical care and treatment in local surgeries where a multi disciplinary team cares for the local population. The Family Practice Service has a key role in preventive medicine identifying patients with or at risk of disease (including genetic conditions) and making appropriate referrals for specialist opinions and hospital care.

In England, Primary Care Trusts (PCTs) are responsible for ensuring that these comprehensive services are available for their local population. They assess local health needs and commission services (such as acute care, primary care and mental health care) from Hospital Trusts and general practitioners. Commissioning is a complex process, and as well as assessing population needs, it involves prioritising health outcomes, procuring (ie buying) products and services, and monitoring their delivery. Specialised services, including genetics, are commissioned by a different mechanism. PCTs in a specified geographical region (covering a population of 1–5 million) pool their commissioning budgets for specialist services, which are then commissioned through specialised teams at Strategic Health Authorities. The regional teams work collaboratively as part of the National Specialised

Commissioning Group. To inform commissioners there are nationally agreed definitions of "specialities", which include a comprehensive description of what would be expected to be provided for "medical genetics" services.

Quality in the NHS

Improving quality throughout the NHS in England has recently been at the forefront of several policy initiatives by the Department of Health, following a report "High Quality Care for All". They include expanding the role of the National Institute for Health and Clinical Excellence (NICE) to set quality standards, and requiring providers of healthcare to the NHS to publish quality reports for the public. There is also a requirement for patients to receive treatment by 18 weeks from referral (www.18weeks.nhs.uk).

Much of the excellence in quality of genetic services has been due to cooperation and collaboration between professionals, patients and service commissioners, but in addition to the general national initiatives outlined in the previous paragraph, more formal mechanisms, often tied to the availability of funding, are also being applied to the genetic services.

For instance, specialised service commissioners will be required to assess and then designate the providers who will undertake and manage services for their population. For genetic services, a reference document setting out the criteria for designation, and outlining a model of care based on a national definition of what should be provided as specialist "medical genetics" (www.nsg.nhs.uk/ssnds.htm) is expected in 2009. This is one example of the evolution of quality requirements, where professional guidelines are subsequently adopted into a formal process.

Organisation of Genetic Services

Specialised genetic services are organised regionally, caring for populations of up to 5 million. Regional genetic services are integrated clinical and laboratory services, working in close collaboration with specialist metabolic biochemical and population genetic screening services. As well as offering general and specialist clinics in the regional centre, regional genetic centres offer clinics in local hospitals throughout their region. They are increasingly working with colleagues in other specialties, for instance through joint clinics or by providing support to nurses in mainstream medical specialties whose role is to support patients with genetic conditions.

Quality in Genetic Services

Quality markers can be encouraged at national, regional and local levels. Examples of drivers which have been used in the UK at each of these levels will now be discussed.

National Drivers to Enhance Quality in Genetic Services

Quality has been a key component in commissioning genetic services. In England, genetic services are commissioned by specialist commissioning groups in the Strategic Health Authorities A few years ago, to advise and assist the commissioning of genetic services, the Department of Health set up a committee –the Genetics Commissioning Advisory Group – to take a strategic national overview of genetics in healthcare delivery. Its members represent, amongst others, patients, providers of genetic services, commissioners and the research community. Quality and equity of access are key themes: the terms of reference include "to enable NHS patients and their families to benefit from advances in genetic technologies shown to be effective and to have clinical utility". With the active involvement of providers and commissioners, GenCAG developed a set of quality markers, again mostly based on the previously published recommendations of professional bodies. Regional genetics centres were asked to submit yearly returns against these markers. The results were published in an anonymous form, but each unit was sent its detailed data so that the reasons for local variations could be discussed with managers and commissioners to find ways to improve the services.

Recent developments in the commissioning of NHS services have been specifically introduced to improve quality. As mentioned above, specialist commissioners have been charged with designating providers to provide particular services – the providers have to provide evidence of meeting a set of standards. The final scheme is expected to be published in 2009. Taking a clinical genetics service as an example, it is anticipated that the evidence which a provider would be expected to produce could include:

How integration of the clinical and laboratory services is achieved
The numbers and location of outpatient clinics
Number of staff per million population
Details of the local care pathway and how the dataset is recorded to follow the patient referral and journey
How often patient surveys are undertaken
Arrangements for professional accountability and training
Guidelines for care of specific diseases/syndromes
Whether written information is sent to patients and relevant health professionals following outpatient attendance
How the service is monitored
Deatils of the annual audit programme and changes to practice

The UK Genetic Testing Network is committed to equitable access throughout the UK to genetic testing. UKGTN developed from an existing informal network of laboratories, and is a collaborative co-operative network of patient representatives, providers of genetic testing and commissioners. To become a member, a laboratory has to demonstrate that it meets a set of quality standards.

Patients and commissioners want to ensure that any new genetic tests are of the highest quality and are of clinical validity and utility. The UKGTN has a procedure for member laboratories wishing to submit new tests for consideration of funding by commissioners, the "gene dossier" process, which includes quality standards (www.ukgtn.nhs.uk).

Regional Genetic Services

Quality has always been a cornerstone of genetic services. When scientists and clinicians developed services in the 1970s and 80s they met regularly to discuss the best ways of providing services and to share clinical experience.

There is now a more formal system of clinical governance (Fig. 1). Overseen locally by the hospital in which the genetics service is based, it is a system through which NHS organisations are accountable for continuously monitoring and improving the quality of their care and services and safeguarding high standards (Scally and Donaldson 1998.) All genetic units take part, especially in clinical audit, which is a review of clinical practice against defined national standards so that care can be continuously improved.

Delivering and Monitoring Quality in a Clinical Genetics Service

Clinical services are generally based on professional guidelines from the Royal College of Physicians and the Clinical Genetics Society. The Clinical Governance sub-committee of the CGS produced a set of useful "clinical standards for a genetics unit" (www.clingensoc.org/docs/standards/clinicalstandards.pdf) which offer standards for multi disciplinary team work, accessibility, confidentiality, the genetic

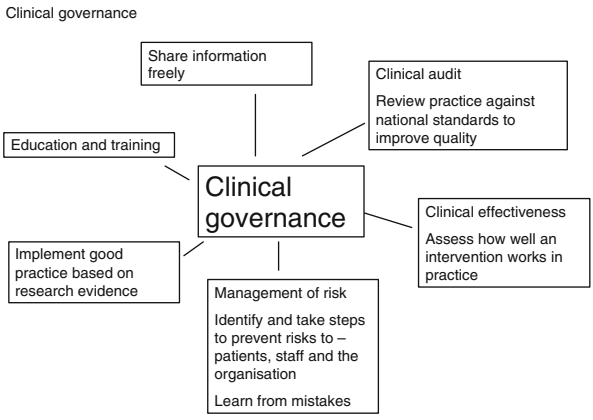

Fig. 1 The components of clinical governance

clinic appointment, pre-clinic consultation and work up, knowledge based practice, counselling skills, correspondence and follow up, documentation and audit.

A working party of the Royal College of Physicians (Royal College of Physicians 1998) had previously highlighted the difficulty of identifying satisfactory measures of outcome and effectiveness in clinical genetics, compared with what could be considered measurable outcomes in some other specialities. They suggested that indicators of quality as a proxy for outcome measures may have to be accepted. They recommended consideration of the scope of the service, accessibility and responsiveness, quality of clinical care, links with the genetics laboratory services and the quality of data collection and handling. In addition, they strongly recommended that the views of organisations representing families with genetic disorders should be actively sought and considered, both by providers of genetic services and also those involved in commissioning the services.

This was echoed in a report from the patients' umbrella group, the Genetic Interest Group, "Guidelines for Genetic Services" (www.gig.org.uk). Although published in 1998, the key requirements are still valid – availability, access and equity, partnership with users, professional collaboration, provision of information, counselling and support, long term follow up and contact of at risk relatives, standards for clinical and laboratory services and monitoring and evaluation.

Clinical genetic units have regular internal clinical audit programmes. As well as auditing specific information about clinical services, data for general outcomes such as waiting times and length from clinic appointment to the post clinic letter being posted are also monitored. Increasingly, quality of care is being assessed through patient satisfaction questionnaires. GIG also produced a list of 20 very useful questions against which clinical genetics services could audit their services (www.gig.org.uk/docs/gig_clinical.pdf). Some regions take part in external quality assurance – such as in the South West of Britain genetic group (comprising the genetic centres in that area of England). One of their initiatives is to audit the quality of clinic letters and their contents by a team of clinicians made up from several centres visiting another centre.

Delivering and Monitoring Quality in a Genetics Laboratory Service

Laboratories providing clinical services to the NHS have to be accredited with the organisation CPA (Clinical Pathology Accreditation (UK) Ltd; www.cpa-uk.co.uk) or equivalent. CPA accreditation involves an external audit of the ability to provide a service of high quality by meeting a defined standard of practice, which is confirmed by peer review. A laboratory has to have a quality management system, including explicit policy objectives and a practical manual. It is expected to undertake user satisfaction surveys and regularly review laboratory procedures and statistics, and undertake clinical audit through a multi disciplinary team. CPA accreditation is

also concerned with competence to practice and has requirements for training and education, including continuing professional development.

Genetic laboratories also take part in external quality assurance (EQA) schemes, follow best practice guidelines, and hold annual management reviews to highlight areas of poor performance and to review objectives. Laboratories have clinical improvement groups with an instant reporting system and analysis of the causes of errors. They must also comply with health and safety legislation.

Laboratory Quality Assessment Schemes

Molecular Genetics

The EQA scheme for molecular genetics was originally set up by the professional body Clinical Molecular Genetics Society (CMGS) in 1991 assessing testing for cystic fibrosis, Duchenne muscular dystrophy and Huntington disease. It is based on collective peer review and includes not only genotyping accuracy but also an assessment of the quality of reporting which measures how understandable the report is for the referring clinician and the patient. The scheme also has an important educational role and may highlight issues in testing which would warrant a best practice meeting, organised by the CMGS to develop or update consensus guidelines.

For the scheme to be recognised by the Department of Health, its administration had to become independent of a professional body. The CMGS EQA subcommittee was therefore re-launched in 1994 as the Steering Committee for Molecular Genetics External Quality Assurance. By 1995 the scheme was offering EQA for eight diseases, and by 1997 the scheme was entirely funded by subscription from participating laboratories. In 1999 the scheme became a full member of UKNEQAS (http://www.ukneqas.org.uk) an umbrella organisation providing a multidisciplinary network of educational EQA schemes across the range of pathology disciplines.

The UK NEQAS for molecular genetics was awarded full accreditation by the authoritative body CPA in January 2001. Its steering committee has members from molecular genetics, clinical genetics, cytogenetics and the private sector and advises on the scientific content and scoring of reports. The scheme reports to the National Quality Assessment Advisory Panel for Clinical Laboratory Genetics, a professional group with executive responsibility for maintaining satisfactory standards of analytical and interpretative work. The panel informs participating laboratories should their performance persistently fall below that considered to be acceptable and offers advice, appropriate assistance, and support to ensure performance returns to an acceptable level.

Cytogenetics

Clinical cytogenetics also has an EQA scheme, (http://www.ccneqas.org.uk) with its own steering group. It assesses three broad inter-linked categories of

performance criteria – technical, analytical and interpretative. It has close links with the UK NEQAS for molecular genetics.

Delivering and Monitoring Quality: The Importance of Education and Training of Staff

Delivering a service of quality depends on individuals and their training so that they are motivated to respond to the expectations of patients and other professionals and achieve the highest standards.

Health professionals must gain a primary qualification (usually via a course of study at a university) and then register with a national statutory regulatory body (such as the General Medical and Health Professions Councils), to be awarded a licence to practice in the NHS. Each member of staff is expected to have a yearly performance review, overseen by their employer. Many professional bodies publish guidance as to what would be expected of a practitioner in their subject to assist in this process.

Clinical Staff

Medical Practitioners

Medical practitioners undertake a specific recognised training programme to become a consultant clinical geneticist. The Specialist Registrar training scheme in genetics, as in all specialties, is overseen nationally by a statutory body. The curriculum is the responsibility of the Joint Royal Colleges of Physicians Training Board (www.jrcptb.org.uk). Following open competition, successful candidates undertake programmes of training in regional genetic centres to meet nationally agreed learning outcomes.

As well as continuous feedback, at the end of each year there is a formal assessment. After successful completion of a 4 year training programme, a certificate of completion of specialty training is awarded, and specialist status noted on the medical register.

Job plans of clinical geneticists recognise a commitment to providing a service of quality and stipulate the taking part in clinical audit and undertaking continuing professional development (CPD). These are assessed yearly in the annual appraisal, undertaken by all consultants in the NHS.

Genetic Counsellors

The Genetics White Paper identified the need to increase the number of genetic counsellors. A structured training scheme, monitored and led by the Association of

Genetic Nurses and Counsellors (AGNC), has been successful with 43 trainees in 17 approved training centres. The Department of Health provided finance for the original scheme; discussions about future funding and organisation are underway.

The AGNC has stated that there is a requirement that genetic counsellors, in training and when registered, should receive supervision in one-to-one or group meetings with a suitably trained and qualified supervisor for purposeful, guided reflection. The definition of "genetic counselling supervision" proposed by the AGNC (www.agnc.org.uk) is: "Focusing on the dynamics between client and genetic counsellor, the aim is to explore the interaction between counsellor and client, the impact of external factors on this, enabling counsellors to learn from experience, improve their practice and maintain competence. The overall intention is to enhance the quality and safety of client care and to promote the ongoing professional development of the genetic counsellor."

Registration for genetic counsellors is currently through the Genetic Counsellor Registration Board, organised through AGNC, whilst an application for statutory recognition of registration is being considered by the Health Professions Council. The Board has set out academic and practical criteria for the experience required. A portfolio (which is assessed at Master's level) of 50 cases also has to be submitted, to demonstrate that 23 competencies have been achieved. One grouping of competency statements is under the general heading "Seek at all times to maintain and improve service delivery and professional standards by promoting evidence-based practice for oneself and others through continual professional development". Registration will have to be renewed every 5 years, when evidence of CPD will be required.

Scientific Staff

Currently, there are separate training programmes for scientists in molecular genetics and in cytogenetics which are overseen by professional bodies. On completion of training and subsequent additional clinical experience, a trainee registers as a clinical scientist with the Health Professions Council. Registered clinical scientists are required to participate in CPD, defined by the HPC as "a range of learning activities through which health professionals maintain and develop throughout their career to ensure they retain their capacity to practice safely, effectively and legally within their evolving scope of practice". Registration has to be renewed every 2 years, when the HPC may ask to see evidence of CPD.

Training for clinical scientists in genetics is well established and regulated, but this is not necessarily the case for some of the other 51 constituent groups of the healthcare scientist workforce. A major review of the organisation of training for healthcare scientists, *Modernising Scientific Careers*, is expected to be published in 2009. It is expected that it will recommend a common training framework, with rotational training leading to registration as a healthcare scientist and an explicit higher specialist training and academic career structure.

Molecular Geneticists

The Training Accreditation Board of the CMGS oversees the structured training which is provided through several laboratories. The first 2 years are typically modular in format with a mix of theory and practical laboratory work, based around acquiring competences in techniques, diseases, management, scientific and clinical knowledge. Assessments are carried out typically after 6, 12 and 24 months. The Postgraduate Certificate of Competence in Clinical Molecular Genetics serves as a foundation for registration as a clinical scientist with the Health Professions Council after a further 2 years of broadening clinical experience.

Clinical Cytogeneticists

The national training programme for clinical scientists in cytogenetics is usually of 2–3 years and available through over 20 accredited laboratories. Overseen by the Education and Training Committee of the Association of Clinical Cytogeneticists, the programme is also modular and competence based, with assessments at the end of each module. Trainees also complete a research project and a secondment to another cytogenetics laboratory. After a final assessment, the Postgraduate Certificate in Clinical Cytogenetics is awarded, after which a period of about another 2 years is spent in training and professional development. To register with the Health Professions Council, a trainee must gain a Certificate of Attainment from the Association of Clinical Scientists. This requires assessment of a portfolio of evidence.

Genetic Technologists

In addition to clinical scientists, genetic technologists (medical technical officers) play vital roles, complementary to those of the clinical scientists. A voluntary register has been set up whilst the process of seeking regulation through the HPC is achieved. A national training programme for genetic technologists has been devised by the Association of Clinical Cytogeneticists Education and Training Committee in collaboration with the Clinical Molecular Genetics Society Training Accreditation Board. The programme will provide a common fundamental training structure in both professions.

On What Should Quality Standards Be Based?

Much debate has taken place over the years about the quality markers to be used and how they should be measured. Examples of recommendations from various bodies

have been mentioned earlier in this chapter, but the debate continues. How can measures be identified that are easy to document and measure not only process but most importantly outcomes? It is relatively easy to identify tangible measurables for a laboratory service – the accuracy and timeliness of a result, for instance – but more difficult for a clinical genetics service. It is possible to count the number of appointments offered and measure waiting times and time to receiving post clinic letters, but how can quality of a consultation be measured? All genetic units use patient satisfaction surveys as one way of gaining some information about this. Regarding the accuracy of diagnosis, clinical genetics services discuss individual cases. In addition there are regional and national meetings where potential diagnoses in people with dysmorphic features are discussed.

Another important consideration in monitoring activity, particularly when comparisons are to be made between services is the need to have a standard set of agreed definitions of clinical activities, and information technology systems which can capture and record the agreed information.

Quality of Information and IT Systems

Quality of electronic information relies on accurate collection, entry and processing. As UK regional genetics services developed, many had to devise their own coding and information management systems. In order to collect and share information, services need to agree not only on database parameters (such as field names and lengths) but how to record information – for instance, what is to be counted as a "referral" to the clinical service.

On a much larger scale than individual genetics units, the NHS is planning to implement a national system of making available patients' clinical records electronically, linked to laboratory test results. The genetics communities have been deeply involved in developing the necessary IT specifications and datasets. A major challenge is the need to link together records of family members, not only from technology considerations, but also taking into account the requirements of ethics and confidentiality. Datasets for genetic laboratory and clinical services have been developed by the National Genetics Reference Laboratory at Manchester (www.ngrl.org.uk/Manchester) following extensive consultation. The *Do Once and Share* project documents a nationally agreed care pathway for the patient journey through the clinical genetics service in England and includes an accompanying dataset to record this and identifies key IT needs (www.bshg.org.uk/documents/official_docs/DOAS_final_printed_report[1].pdf).

Summary

Quality in genetic services in the UK has been driven by the desire of professionals to provide the best service possible. Over the past few years, formal requirements have been introduced by statutory bodies, but these are mostly based on quality

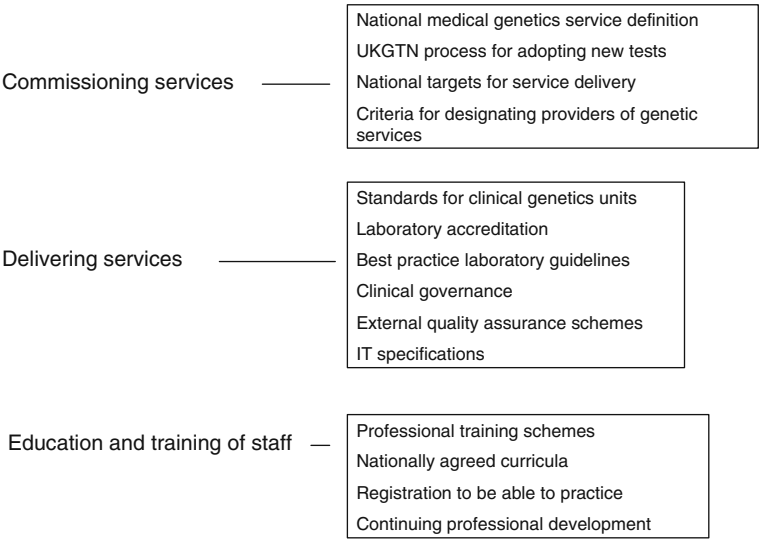

Fig. 2 Components of services which drive or contribute to quality in genetics services in the UK

markers identified by professional bodies. Figure 2 highlights some of the key components of quality in UK genetics services.

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The Primary Care Perspective of Quality in Clinical Genetics Service – United Kingdom as an Example

Hilary J. Harris

Quality is never an accident, it is always the result of intelligent effort

John Ruskin 1819–1900

Key Points

- Quality issues for a genetic service in primary care require further consideration.
- Preconception care needs a framework for delivery in primary care.
- Antenatal care provides many opportunities for delivering genetics in primary care.
- Pharmacogenetics will change prescribing in the future.
- Promote European collaboration to provide education in genetics

Keywords Quality · Primary care · Preconception · Pharmacogenetics · Education

During the past two decades, scientific research has led to a fuller understanding of the contribution made by genes to present and future health. It is acknowledged that genetic information will need to be integrated into all aspects of health care provision, including primary care. How best then can the expectations of patients be realised when advances in genetics outstrip the educational requirements needed to fulfil a quality service? It is unrealistic for general practitioners and their teams to attempt to deliver a comprehensive "genetic" service to their patients. There are however parallels between specialist departments of medical genetics and primary care professionals that provide synergy in the approach to this problem.

Both deliver advice and care to individuals and families, recognising the special importance of family history. Geneticists construct this in a comprehensive and structured way. In primary care knowledge of the family history has sometimes reflected the GPs close association with their patients in providing care often to

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two or three generations. Clinical geneticists may see patients on a limited number of occasions to establish the diagnosis and offer advice and counselling. Primary care will increasingly take on responsibility for co-ordinating care for patients with complex genetic disease where screening, prevention and interventions fall within a range of medical and surgical disciplines. When severe genetic disease leads to increasing morbidity and reduced life expectancy the role of continuing care and terminal care will be undertaken by the GP and their team.

Much of this depends on preserving the strength of general practice, which lies in its system of registration and lifetime records. Retrospective analyses of general practitioner records show ad hoc record keeping and information gaps with sometimes little evidence of family history data. There will need to be a commitment to information technology to process individual genetic data, to link genetic risk factors within families, and to access genetic help lines and current referral protocols. Consultation rates in general practice varying between four and seven a year give many opportunities to reinforce complex genetic information.

Genetic registers, previously the province of departments of medical genetics, are now accessible within disease registers in primary care. There is a deficit of genetic coding for primary care computer systems that needs to be urgently addressed. Despite this most GPs can report on major diagnoses, many with genetic predispositions, examples include cancers, insulin dependent and non-insulin dependent diabetes mellitus, and Alzheimer's disease. The power of this information must be harnessed to increase patients' awareness of their genetic inheritance so that the genetic consultation becomes a standard of care in the next decade. Without this there will be increasing litigation for genetic misinformation.

Taking a family history in primary care is central to both screening and diagnostic opportunities for Mendelian and common complex disease. Many Mendelian conditions are rare and may present to the GP only once or not at all in a clinical lifetime, examples include Huntington's disease [3–7:100,000], Marfans disease [1:5,000], neurofibromatosis [1:3,000]. However collectively they account for a substantial morbidity as the incidence of infectious diseases declines. Family history is recorded at the time when patients join a practice, and can be documented by other members of the practice team, practice nurse, nurse practitioner, health visitor, and midwife. Information on affected members should include age at diagnosis/death. Although three generation family history is the gold standard this is difficult to achieve in a ten-minute consultation. Family history is dynamic, and time should be allowed to update it opportunistically. As a rule of thumb, early age of onset, number of affected relatives and first or second-degree relatedness are pointers to subsets of common complex disease having a genetic basis. Guidelines for the referral and screening of patients with a family history of breast cancer (NICE 2006)/bowel cancer are of great value. Their use ensures that referrals to secondary care for early screening/mutation analyses are appropriate, with the majority of patients able to be managed in primary care. Risk estimation for CHD is carried out in general practice using lipid estimations and lifestyle factors. Individuals likely to be at high risk are those with a family history of premature chd [first degree relative under the age of

55]. The risk factor is increased by a factor of 1.5 if one relative is affected and by 2 if more than one relative is affected. Other genes and constellations of genes yet to be identified will increase the precision of risk estimation allowing for early therapeutic intervention with lipid lowering agents.

Familial hypercholesterolaemia should be considered in patients with lipid levels >7.5 cholesterol >4.9 LDL.As this is an autosomal dominant condition, cascade screening for other family members is advised.

The catalyst for increasing genetic provision in primary care will focus on opportunities in preconception and antenatal care. In the future it is expected that pharmacogenetics will play an important part in health care delivery.

Preconception care is defined as "An organised and comprehensive programme of health care that identifies and reduces a woman's reproductive risks before conception through risk assessment, health promotion, and interventions". Pubmed's MeSH Database 1992.

Preconception counselling provides information and advice at a consultation freed from the time constraints that may pertain in an antenatal setting. This enables choices to be considered and made before pregnancy and for counselling when possible to include both partners. Where further detailed information on family history is needed then this can be ascertained and diagnoses verified from hospital and primary care records. Preconception care (Advisory report 2007) is a package of care that takes account of genetic and non genetic information, family history, medical history [diabetes, epilepsy, sexually transmitted diseases], lifestyle choices, smoking, alcohol, recreational drugs, employment. The majority of care is appropriately undertaken by a generalist and will include such measures as stop smoking advice, reduction of alcohol intake, dietary advice, ascertaining rubella immune status, provision of folic acid [400 mcg] or 5 mg daily for those with a family history of neural tube defect taken for a minimum of 1 month before conception and continuing through the first trimester, and Vitamin D supplementation for women with reduced exposure to sunlight and those with dark skin colour.

Preconception genetic counselling is dependent on accurate family history information ideally from both partners in order to identify any potential risk to a future pregnancy and to give individuals information and choice about screening and the opportunity for referral to a clinical geneticist when there is a possibility of an inherited problem. Carrier screening for haemoglobinopathies, [sickle cell disease and thalassaemia] are offered as early as possible in pregnancy but both can very appropriately be incorporated into a preconception package of care. This will allow for unhurried discussion of results and detailed preparation for the choices available for carrier couples. There is also the opportunity to discuss screening for Downs syndrome which will not take place until the woman is pregnant and ultrasound screening for abnormalities. The present difficulty in providing preconception counselling is that there is little opportunity for this to happen in a busy primary care setting. The majority of women present to their GP for the first time in early pregnancy, however it should be possible to advise about folic acid supplementation to women attending for contraceptive advice, many of whom will be planning a pregnancy in the future.

Preconception care requires service delivery in a programmed and organized way not yet available in most countries. In Hungary where such programmes were piloted and now delivered by specially trained nurses there has been a significant reduction in congenital abnormalities. 6:1,000 newborns previously 35:1,000. There needs to be an attitudinal shift for patients and professionals to recognize the value of preparedness offered by pre-conception care and its positive outcomes for both infant and parent.

The National Institute for Health and Clinical Excellence [NICE] antenatal care guidelines [NICE 2008] state "patients should be given information on antenatal screening at their first contact with a health professional". This first contact will most often be with their GP. Because of the increasing use of sensitive over the counter pregnancy testing kits this consultation will often take place very early in pregnancy [6–8 weeks]. This places responsibility on the GP to provide timely information to enable patients to step on to a screening pathway, if this is their informed choice, in the knowledge that this may lead to further testing and discussion about continuing with an affected pregnancy or considering termination.

Haemoglobinopathies occur in populations originating from Africa, Asia and the Mediterranean and also in many other parts of the world where populations have migrated, UK, Caribbean, North America and Northern Europe. Screening for sickle cell and thalassaemia in England is now offered to all eligible pregnant women and couples. This should take place as early as possible in pregnancy, ideally by 10 weeks. This allows for partners to be tested, where the mother is found to be a carrier, and carrier couples identified to proceed to early prenatal diagnosis by chorion villus sampling from 11 weeks or amniocentesis in the second trimester.

Sickle cell disease affects 1 in every 2,400 births in England, 240,000 are carriers, and about 12,500 have sickle cell disease. It is the commonest recessively inherited disorder in the UK, now overtaking Cystic Fibrosis in frequency. Thalassaemia carriers number 214,000, with 700 people suffering from beta thalassaemia major. A recent Health Technology Assessment trial (Dormandy et al. 2008) reported a delay of 7 weeks between pregnancy confirmation and screening for haemoglobinopathies in primary care, consequently depriving patients of the choice of early prenatal diagnosis. The delay was mostly attributable to organisational difficulties in accessing phlebotomy and referral to midwives and secondary care.

A number of trials of cystic fibrosis carrier screening in antenatal care (Harris et al. 1993) were undertaken in the 1990s looking at the feasibility of early screening and in primary care. To date a programme has not been implemented, although there are cogent reasons for offering this in parallel with sickle and thalassaemia testing. CF testing is carried out as part of the neonatal screening programme that includes phenylketonuria, congenital hypothyroidism, sickle cell disease and MCADD – medium chain acyl CoA dehydrogenase deficiency.

There are considerable benefits to moving antenatal screening into primary care. Patients book early in pregnancy, counselling can take place in a familiar environment with a practitioner who is known to the patient and their family and has responsibility for ongoing care. Computerised health care records provide for recall of patients and recording of genetic data for future health care. However GPs taking

part in CF trials cited considerable time pressures – "It takes 5–10 min to offer the test. I feel rushed and I don't do it well. I worry that I am pushing people into it when I should be unbiased." Other barriers to service delivery in primary care are a fear of genetics due to lack or perceived lack of education and training, ethical and religious constraints. Non-directive counselling is not always a central tenet of the primary care consultation. A National Confidential Enquiry (Harris et al. 1999] into counselling for genetic disorders by non-geneticists in the UK found that clinicians in primary and secondary care overlook the need for recording counselling and data that patients will later need for decisions about reproduction or disease prevention.

Screening for Down's syndrome should be offered to all pregnant women in England regardless of age. Screening uses biochemical markers and/or nuchal translucency measurement, with age and gestation data entered into a computer programme that calculates risk. Where patients book early screening can be completed between 10 and 13 weeks gestation allowing for earlier prenatal diagnosis. It's important that the GP provides the patient with enough information to base a decision on screening and testing. Hospital antenatal clinics may be busy and rushed and blood tests can be seen as "routine" by patients. Risk information is difficult for both patients and professionals and is frequently misinterpreted or over/underestimated. A 43 year old patient with an age risk of Down's 1in 53 had a post serum screening risk of 1in 157. Amniocentesis failed and was not repeated because the obstetrician reassured her on the basis of a lowered serum risk. The subsequent birth of a baby affected by Down's syndrome caused considerable distress for this unprepared couple. A recent report in the UK media describes an increase in the number of babies born with Down's syndrome, which reflects a societal attitudinal shift and improved educational provision for disability.

Advances in the use of Cell-free Fetal DNA [and RNA] for non-invasive prenatal diagnosis will have major implications for patients and primary care providers. Cell free plasma DNA derives from the placenta and can be detected in the mother's blood from 5 weeks gestation (Fan et al. 2008). There are four potential applications, determination of fetal sex in families at risk of a sex-linked disease, for example Duchenne muscular dystrophy. Secondly for detecting specific single gene disorders in high-risk families for example achondroplasia. Thirdly determination of fetal rhesus D blood group status in Rhesus D negative women so that where the fetus is D negative anti D administration is avoided. The fourth application is the detection of fetal aneuploidy particularly Down's syndrome. This is in an early stage of development but may have the potential to replace biochemical screening tests and invasive prenatal diagnosis with its risk of fetal loss. What is certain is that this technology available very early in pregnancy will have educational and administrative challenges for primary care to ensure that patients have informed choice and that ethical issues are fully addressed.

Neural tube defect screening is carried out as part of the fetal anomaly scan at 18–20 weeks. This has replaced maternal serum alpha-fetoprotein estimation [MSAFP] performed alone for screening because of its higher detection rate.

Patients need to be aware that ultrasound scanning may be a diagnostic tool for fetal anomalies and is not simply for dating the pregnancy. Although prevention

of neural tube defect by folic acid medication taken preconception and continuing through early pregnancy has been promoted for many years, less than half the women at the booking visit in primary care are taking folic acid. Linking advice about folic acid supplementation with contraception and with pregnancy testing kits would be helpful, together with computer generated screen prompts.

Pharmacogenetics holds promise for patients in the future and may radically change prescribing in both primary and secondary care. Also referred to as personalised medicines (Royal Society 2005) it aims to identify an individual's genetic makeup, in order to target drugs to improve efficacy and reduce side effects. The benefits could be significant as the NHS drug budget exceeds 11 bn and the financial costs of side effects is over 500 m, not counting the cost in terms of morbidity and misery. At present pharmacogenetic test applications are mostly restricted to oncology. An example is Herceptin available for the treatment of early and advanced breast cancer. The drug targets an abnormal protein [HER 2], which is a tumour growth factor receptor. A subgroup of patients carries a genetic mutation resulting in multiple copies of a gene that causes overproduction of HER2. Herceptin acts at the receptor site so it can only benefit women who have the relevant gene. Approximately 25–30% of breast tumours have high levels of HER2 and for this group Herceptin reduces tumour size and spares healthy cells. Other oncology applications are in colorectal cancer and haematological malignancies. Perhaps of more relevance to the presciber in general practice is research into cytochrome P450 family of genes that produce enzymes in the liver responsible for metabolism of many drugs. CYP450 mutations control the metabolism of widely prescribed proton pump inhibitors identifying three groups of genotypes, rapid, intermediate and poor metaboliser groups. These differences contribute to dose requirements, efficacy and drug interactions. This model is similar for antidepressants, anticonvulsants, anticoagulants and some analgesics. However response to drugs is also dependent on a number of other factors, age, polypharmacy, multiple pathology and compliance. It is likely that pharmacogenetic testing will reclassify some common disease into subsets susceptible to specific treatments, so that the target drug population is refined. This may make it less likely that blockbuster drugs will be developed in the future, a prospect not favourable to drug companies driven by profits and the high cost of drug developments. At present primary care would face challenges in relation to testing and recording genotype data. It would require closer links with pharmacies and laboratories to collate and interpret this information. Technology to perform testing is rapidly becoming more automated and cheaper, with the possibility of near patient testing kits on the primary care consulting room desk. Before this becomes reality there needs to be comprehensive population studies to address cost effectiveness and clinical utility. Further public debate should consider ethical issues of consent to storage and retention of data and concerns that patients may request pharmaceuticals even when test results show non-response or risk of side effects.

The Genetic Education for Nongenetic Health Professionals [GenEd] [Challen et al., 2005] project investigated health professional education at undergraduate, postgraduate, and continuing medical education in terms of genetic content and delivery in 5 countries [France, Germany, Netherlands, Sweden and the UK].

Results showed that health professional education and training differed in structure with wide variation in the content and duration of genetics provided. Many programmes lack any explicit genetics and there is a multiplicity of organisations responsible for setting, assessing, and delivering medical and midwifery education. The strategy adopted by the US National Coalition for Health Professional Education in Genetics is a model that could be adopted in Europe.

As the genetic consultation is integrated within the primary care consultation, quality issues need to be addressed.

In the UK the Quality Outcome Framework [QOF] introduced in 2003 as part of the General Medical Services contract for GPs (NHS Confederation 2003) aims to deliver substantial financial rewards for high-quality care. Standards are delivered in four domains, clinical – management of chronic disease, practice organisation, patient experience, and additional services, which include maternity, child health, contraception and cervical cytology. Notably there is an absence of any genetic component. Criticism of QOF has challenged its mechanistic approach, lack of outcome measures, and inattention to potential harmful effects.

Is it possible to include elements of genetic health care within an updated Quality Outcome Framework? Taking and recording family history, use of referral guidelines, risk assessment and documented information and counselling could be monitored. However the other essential elements of a genetic consultation, empathy, non directive approach, patient choice especially when it includes reproductive decisions, confidentiality and continuing care for patients affected by genetic disease and their families are not appropriate to a tick box framework fuelled by income generation. Raising awareness of genetics in primary care is demanding, and reliant on education programmes tailored to the needs assessment of the workforce. Patients have an expectation and a right to genetic services within primary care to be delivered by an educated primary healthcare team within an equitable and ethical framework.

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Regulation of Genetic Testing/Service in Canada

Martin J. Somerville and Diane J. Allingham-Hawkins

Key Points

- Regulation of genetic testing in Canada is complicated by the unique distribution of responsibilities for health services amongst federal and provincial/territorial ministries of health
- No over-arching regulations or guidelines for quality assurance or delivery of genetic testing services exist in Canada leading to different levels of regulation in each jurisdiction
- Although most provinces offering genetic services voluntarily conform to recommended standards regarding genetic testing services, there is a need for federal guidelines to ensure that minimum standards for quality and patient/consumer protection are met

Keywords Regulation · Quality · Standards · Accreditation

Introduction

Regulation of genetic testing can occur at several levels that may include over-arching issues related to access to services, informed consent, and privacy/confidentiality of health information, as well as service-specific matters such as licensing and/or accreditation of laboratories, training and education of laboratory personnel, proficiency testing, and quality assurance/quality control programs. There are numerous regulatory instruments that can be applied.

Canada's health care system is unique among developed nations. Health care is administered and delivered provincially, although health protection and well-being

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are federal responsibilities. There are ten provincial and three territorial health care systems in Canada. In this context, regulation of health care services is administered provincially/territorially although oversight is a federal responsibility. There are no federal regulations directly applicable to genetic testing (Petit et al. 2008). As a result, the claims or practices of the genetic testing industry are largely unregulated, and governments at all levels receive very limited guidance on whether a specific genetic test should be funded. This is evidenced by a lack of regulation to ensure the clinical validity of genetic tests (Table 1). There are, however, some broad-based federal/provincial regulations that apply to aspects of healthcare including genetic services.

Table 1 Regulated practices within the ten Canadian provinces, listed in geographical order (East to West). The three Canadian Territories (NU, NT, YK) are not included in this assessment. The CCMG is a national professional organization that establishes recommended practices

Issue	NF	NS[b]	NB	PE	QC	ON	MB[c]	SK	AB	BC[c]	CCMG
Laboratory practice											
Definition					*	*	*		*	*	*
Certification/accreditation			*		*	*	*	*	*	*	*
Personnel standards					*	*	*	*	*	*	*
Quality assurance					*	*	*	*	*	*	*
Quality control					*	*	*	*	*	*	*
External quality assessment					*	*		*	*	*	*
Clinical validity											*
Analytic validation					*	*		*	*	*	*
Record retention					*	*	*	*	*	*	*
Report requirements					*	*		*	*	*	*
Follow-up testing					*	*		*	*	*	*
Total issues addressed	0	0	1	0	10	10	6	9	10	10	11
Patient management											
Informed consent[a]	*	*	*	*	*	*	*	*	*	*	*
Genetic counselling					*			*	*	*	*
Use of residual samples					*				*	*	*
Privacy/confidentiality[a]	*	*	*	*	*	*	*	*	*	*	*
Access to services[a]	*	*	*	*	*	*	*	*	*	*	*
Educational component					*	*		*	*	*	*
Total issues addressed	3	3	3	3	6	4	3	5	6	6	6

Provincial Key for Figure and Table: NF = Newfoundland; NS = Nova Scotia; NB = New Brunswick; PE = Prince Edward Island; QC = Quebec; ON = Ontario; MB = Manitoba; SK = Saskatchewan; AB = Alberta; BC = British Columbia; NU = Nunavut; NT = Northwest Territories; YU = Yukon Territories

[a]Federally regulated practices

[b]Izaak Walton Killam Hospital for Children and Queen Elizabeth II Health Sciences Centre are currently preparing for AC accreditation

[c]College of Physicians and Surgeons of Manitoba and College of Physicians and Surgeons of British Columbia Diagnostic Accreditation Program adoption of new comprehensive standards are pending (DAP Annual Report 2006–2007; Manitoba Quality Assurance Program, Annual Report 2008)

Adapted from Cox, et al. 2003.

Access to Services

The *Canada Health Act* is a federal regulatory instrument that defines the criteria and conditions for insured health care services (Canada Health Act 1984). It is based on the principle that continued access to quality health care without financial, or other barriers is critical to maintaining and improving the health and well-being of Canadians. This Act is fairly specifically directed at hospital services, which are considered to include laboratory diagnostic procedures, together with the necessary interpretations of such procedures. This regulation establishes conditions under which the provinces and territories will receive financial contributions from the federal government for healthcare services. This act does not preclude the operation of private clinics or laboratory services that are not hospital-based. In addition, there has been considerable discussion between the federal and provincial/territorial governments about the extent of jurisdictional control based upon how funding of basic healthcare needs should be managed and what constitutes necessary versus elective healthcare services. In this context access to genetic testing varies across Canada, with some provinces offering a broader scope of genetic services than others.

Informed Consent

The legal principles that cover informed consent to medical treatment are grounded in Canadian common law. The same principles can be applied for the purposes of diagnostic or predictive testing for a genetic condition. The Canadian College of Medical Geneticists (CCMG), a national professional organization that adopts policies on which some provincial standards are based, has made recommendations specific to informed consent for genetic testing (Canadian College of Medical Geneticists 2008). In addition, informed consent for research purposes has become integral to ethics review for most research in Canada. The Tri-Council Policy Statement, *Ethical Conduct for Research Involving Humans,* a joint statement prepared by the Medical Research Council (MRC), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC) is the main guidance regarding all human research in Canada and has specific recommendations regarding genetic research (Tri-Council Policy Statement 2008).

Privacy/Confidentiality of Health Information

Consumer privacy in Canada is protected at the federal level by the *Privacy Act* (Canada, Privacy Act 1995) and the *Personal Information Protection and Electronic Documents Act (PIPEDA)* (Canada, Personal Information Protection and Electronic Documents Act 2008). These Acts have no specific provision for genetic test information, but the definition of personal information within the Acts

is generalized to include identifiable information that is recorded in any form. Some Canadian jurisdictions (Alberta, Ontario, Manitoba and Saskatchewan) have legislated Acts that deal with the collection, use and disclosure of health information (Province of Alberta Health Information Act 2001; Government of Ontario, Personal Health Information Protection Act 2004; Province of Manitoba, The Personal Health Information Act 1997; Province of Saskatchewan, The Health Information Protection Act 1999). The province of Alberta, for example, has enacted the *Health Information Act* to protect the privacy of individuals with respect to their health information and to protect the confidentiality of that information (Province of Alberta, Health Information Act 2001). These Acts prevail over the federal Act within the scope of specific areas addressed (eg. health information) within their respective province. Unfortunately, some variation between provinces results in inconsistency in the extent of privacy protection across the country.

Accreditation

Accreditation of genetic services in Canada is administered provincially. Each province has established its own system for accreditation of diagnostic laboratory services. With the exception of Newfoundland, Nova Scotia, and Prince Edward Island, these are mandatory systems. The province of New Brunswick has no specific accreditation program, however, clinical laboratories are operated by the Regional Health Authority and are subjected to accreditation. Accreditation programs specific to genetic services are typically based upon a peer review process, modeled to a varying degree upon American College of Medical Genetics (ACMG) and CCMG policy and guidance statements, and College of American Pathologists (CAP) and International Organization for Standardization (ISO) accreditation programs. These accreditation programs typically evaluate laboratories using a "checklist" of items that vary in scope, but include requirements related to laboratory practice such as qualifications of laboratory personnel, participation in external quality assessment (EQA) programs, quality assurance/quality control measures, and requirements related to patient management such as informed consent, genetic counseling, and access to services (Table 1).

Regulatory Agencies

The Provincial Colleges of Physicians and Surgeons are the Accrediting bodies for laboratories in the western provinces of British Columbia, Alberta, Saskatchewan, and Manitoba. The Quality Management Program-Laboratory Services (QMP-LS) under the auspices of the Ontario Medical Association operates the Accreditation program in Ontario. The Bureau de Normalization du Québec has delegated authority to Accreditation Canada (AC; formerly Canadian Council on Health Services Accreditation) for accreditation of all public laboratories in the province. Hospitals

with genetic services in Nova Scotia have also applied for AC accreditation, although this is not required by the provincial government. The accreditation requirements for the provinces are generally available to the public via their specific websites although Ontario's website is accessible only to participating laboratories.

Jurisdictions

Currently in Canada there are tests available for more than 200 genetic disorders in more than 35 laboratories, 12 of which have CCMG certification as genetics service centres, distributed between seven provinces (Fig. 1). This is known to be an underestimate of genetic testing activity in Canada, since the total laboratory count is based upon voluntary registration of activity on the University of Washington-based GeneTests website (www.genetests.org), and CCMG certification as a genetics service centre is not necessarily a requirement for provincial accreditation. Jurisdictional administration of healthcare in Canada creates impediments to inter-provincial co-operation in the delivery of genetic testing. This has largely precluded the establishment of national reference centres and has led to inter-provincial redundancy of services between publicly funded laboratories. Other specialized inter-provincial medical services do exist in Canada, but genetic testing continues to evolve too rapidly for health administrators to establish recognized coding systems to facilitate reimbursement. As a result, when a specific genetic test is not offered within a province, some provincial health insurers will only approve reimbursement for specimens sent out of country, even though the test may be available in an accredited laboratory in a neighbouring Canadian province.

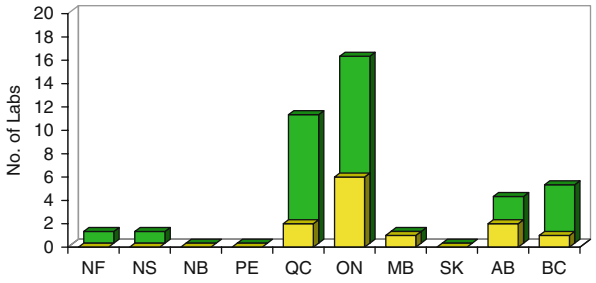

Fig. 1 The number of Laboratories offering genetic testing services on the GeneTests Website (www.genetests.org) in *green*, and certified as a molecular genetic service centres by the CCMG (www.ccmg.medical.org) in *yellow*, listed geographically by province within Canada. Provincial Key for Figure and Table: NF = Newfoundland; NS = Nova Scotia; NB = New Brunswick; PE = Prince Edward Island; QC = Quebec; ON = Ontario; MB = Manitoba; SK = Saskatchewan; AB = Alberta; BC = British Columbia; NU = Nunavut; NT = Northwest Territories; YU = Yukon Territories

Role of Professional Societies

The CCMG establishes and maintains professional and ethical standards of medical genetics services in Canada. The CCMG is not a government agency, but it does inform governments and the public about the importance of medical genetics in the Canadian health care system. The CCMG sets training and certification standards for clinical geneticists and laboratory directors, and provides a national accreditation program for medical genetics training sites (including training for both clinical and laboratory genetics) and clinical and laboratory genetics service centres (Fig. 1). The CCMG has also developed policy statements and guidelines related to various aspects of genetic testing, screening and services including statements on Cytogenetics Retention Guidelines, DNA banking guidelines, Genetic Testing of Children, Guidelines for Retention and Maintenance of Clinical Genetics Records, Patenting of the Human Genome, Prenatal paternity testing, and Cystic fibrosis testing/screening. (www.ccmg.medical.org). In addition, the CCMG has embraced a number of policy statements of the American College of Medical Genetics (ACMG) (www.acmg.net) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) (www.sogc.org). Policies adopted by the CCMG are recommendations that have guided provincial regulatory efforts. Clinical geneticists in Canada are also trained through the residency program in medical genetics of the Royal College of Physicians and Surgeons of Canada (RCPSC) (www.rcpsc.medical.org) and in Quebec, through the Collège des médecins du Québec (CMQ) (www.cmq.org).

Consumer Protection

There are clear challenges that emerge in the design and implementation of a regulatory framework to address the analytical and clinical validity, and utility of genetic tests. According to *Medical Devices Regulations* (Canada, Medical Devices Regulations 1998) In Vitro Diagnostic Devices (IVDD) used for genetic testing are classified as Class III medical devices. As such, they should be subject to stringent regulation requirements before being sold for diagnostic purposes. In practice, however, manufacturers of the reagents and equipment used in molecular genetic testing routinely attach labels specifying, "For Research Purposes Only. Not for Use in Diagnostic Procedures." Labeling in this manner effectively removes the manufacturer from any responsibility with respect to the performance of the reagent or equipment in diagnostic procedures and reduces all molecular genetic testing to "home brew" or laboratory-developed status. If a proprietary in-house assay is shared with another health care facility, this would constitute a "sale" and the regulations would apply. In the majority of cases, however, laboratory assays are either nonproprietary or are not shared. In addition, Medical Devices Regulations only apply to the acquisition of reagents and equipment. The performance of a genetic test as a service within a laboratory falls under provincial jurisdiction, outside the scope of the *Medical Devices Regulations* (Petit et al. 2008).

Regulatory gaps have been identified as a specific concern in the controversial practice of direct-to-consumer (DTC) genetic testing (Hogarth et al. 2008). This type of testing is becoming available on an increasing basis in the United States and Europe. There has been no significant growth in this commercial activity in Canada. The primary concern related to DTC genetic testing stems from a relative lack of international regulation of trans-border commercial activity. There is no protection in Canada for testing that occurs on a sample sent out of country to a DTC service.

Conclusions

Canada has a limited number of federal regulations that are applicable to general medical laboratory practices, and by extension, genetic testing. The extent of regulation specific to genetic testing varies between provincial jurisdictions. National recommendations specific to genetic services are well established within the training and accreditation framework of the CCMG, but the fragmented Canadian regulatory framework has resulted in a considerable lack of consistency in laboratory standards. Most genetics services centres across Canada voluntarily comply with recommended practices. However, a more harmonized approach to the regulation of genetic testing would clearly benefit the Canadian public.

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Quality Issues in Clinical Genetic Services in Australia

Sylvia A. Metcalfe and Agnes Bankier

Key Points

- In Australian genetic services quality assessment processes are recognised to be important
- Consumer input and feedback is also valued but is variable
- Audit of quality related practices is sporadic in the majority of clinical genetic services but occurs to national and international standards in laboratory services
- National protocols, standards and recommendations for clinical genetic services are desired, but developing and implementing these are limited by available resources

Keywords Australia · State-based clinical genetics services · Laboratory services · Consumer input · Accreditation

Background – The Australian Scene

Australia has a population of about 21 million distributed between six states and two territories. There is a socialised healthcare system managed by the federal (Commonwealth) government. Clinical genetic services are publicly funded by state Departments of Health, rather than by the Commonwealth Government, with the model of service provision varying from state to state (Metcalfe et al. 2009). The genetic services work along principles of supporting informed choices and there is a strong commitment to equity of access.

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Clinical Genetic Services

In most states clinical genetic services are centrally administered, providing clinics in metropolitan as well as regional and rural centres – in the interest of equity – usually in hospital outpatient settings. Other models of service provision also exist, i.e multiple independent metropolitan and regional services in the state; the provision of genetic services or the services of clinical geneticists may be contracted from another state.

Clinical genetic services provide genetic risk assessment, diagnosis and testing, counselling and support in the full range of services from pre-implantation genetic diagnosis, prenatal, paediatric and adult genetics. Familial cancer forms a substantial proportion of service delivery in inherited disease; some are part of the centralised clinical genetic service, while in other states familial cancer services operate as distinct entities (Metcalfe et al. 2009). Genetic services are typically multidisciplinary: clinical geneticists, genetic counsellors, nurse coordinators, social workers and administrative support employed by the clinical genetic services, working jointly with related medical specialists. Overall about half the staff members are employed full time in genetic services but the proportion of half and full time employees varies in the different states. Many genetic services include trainees – Fellows in clinical genetics, metabolic medicine and associate genetic counsellors – who work under the direct supervision of senior genetic colleagues. All centres providing training are accredited by the Royal Australasian College of Physicians (RACP), to ensure that they have the resources to provide the learning opportunities and both genetic and counselling supervision for the trainees. The services may also work closely with tertiary educational institutions. Staff members are expected to engage in clinical research, to contribute to undergraduate and postgraduate professional education and give talks to support groups of their patients as requested.

There are few clinical geneticists and genetic counsellors working in private practice, and private laboratories performing genetic tests are increasing in number.

Genetic Laboratory Services

Genetic laboratory services may be part of the centrally administered genetic services or part of hospital pathology services, and include molecular genetics, cytogenetic, newborn screening, maternal serum screening and metabolic screening/diagnosis. As of 2006, over 220 genetic tests were available in Australia, through 56 laboratories, most block-funded through the state Departments of Health and a small number of molecular tests funded by the federal Medicare Benefits Schedule (MBS) (Metcalfe et al. 2009; Suthers 2008 and personal communication). Other tests are available on a fee-for-service basis paid/co-paid for by the client, hospital or genetic service. Tests are also provided by private genetic laboratories, with some

in Australian research laboratories or in overseas centres requiring co-payment or full payment by the client.

The number of genes tested in each laboratory varies from less than ten to over 100 genes, with the majority testing fewer than 50 genes (Suthers 2008 and personal communication). The federal government is investigating ways of rationalising genetic testing in Australia.

Supporting Patients and Their Rights

There are more than 1,000 genetic support organisations in Australia (www.genetics.com.au and www.australasiangeneticalliance.org.au). These groups provide support and information to individuals and families living with a genetic condition. They can be state-based, national or international, and are funded from a variety of sources. Many state Departments of Health fund a state-wide peak body (see www.gpgenetics.edu.au) and these work co-operatively via the Australasian Genetic Alliance (AGA) (www.australasiangeneticalliance.org.au), the Australasian peak body. The AGA and state peak bodies 'facilitate networking between genetic support groups, health professionals and patients and families to improve community and professional knowledge of genetic conditions, their impact and available services'. The AGA is also involved in advocacy and provides written and verbal submissions to Government and others in the field of genetics.

Complaints procedures are core to all clinical genetic services as are requirements for legislative compliance. There are both federal and state privacy legislations and state-based Health Record Acts. Some states have a Charters of Human Rights and Responsibilities and in July 2008, the Australian Health Ministers endorsed the Australian Charter of Healthcare Rights that describes the rights of patients and other people using the Australian health system. The Charter describes seven expectations of rights: equity of access, safety, respect, communication, participation, privacy and comment (www.safetyandquality.gov.au).

Quality Systems in Clinical Genetic Services

The consideration of quality in genetic services needs to include both quality of the services delivered (the content) as well as operations of the service as defined by practice standards, the client's experience, management of operational matters and the processes in place that ensure opportunities for improvement are noted and improvements implemented. Assessment of the content of genetic counselling services is only possible by detailed peer review. Most quality systems in fact assess the *processes* of service delivery, with the aim of having systems and mechanisms for quality management, i.e a quality cycle of audit, identifying opportunities for improvement, developing an action plan, implementing it and auditing the outcome on a cyclical basis.

Setting Standards

The Human Genetics Society of Australasia (HGSA), the peak body for human genetics, has developed Guidelines for the Structure of Clinical Genetics Units in Australasia (HGSA 1999). This categorises 5 levels of services with recommendations on staffing, professional responsibilities, links to laboratories, access to bioinformatics, educational responsibilities and research. Documented practice standards are not available in all genetic centres but are the expectation for training programs. Participation in continuous professional development is a requirement for medical staff.

Assessing Quality

Finding a suitable way of assessing ambulatory genetic services *per se* can be a challenge in a hospital setting, where the focus is more on inpatient services.

Many hospitals use The Australian Council on Healthcare Standards' Evaluation and Quality Improvement Program (EQuIP) (http://www.achs.org.au). This program states it 'is generically designed to provide for all types of organisations which provide healthcare', with mandatory criteria in clinical, support and corporate areas, in a 4-yearly cycle of review (http://www.achs.org.au/pdf/E4A3_poster.mandcriteria.pdf).

The Quality Improvement Council's Health and Community Services Standards has a program (QIC) for assessing ambulatory health services (http://www.qic.org.au/publications.html), which may be considered more suitable for assessing clinical genetic services. It assesses the service against set parameters, recognising that no genetic services are totally separate entities and many of the operational aspects are covered by the host organisation (see Box 1).

Box 1 Parameters accredited through the Quality Improvement Council of Australia program (QIC)

Building Quality Organisations

- Leadership and management
- Management of human resources
- Management of physical resources
- Financial management
- Knowledge management
- Risk management
- Compliance monitoring

Providing Quality Services and Programs

- Community needs
- Planning and provision of services
- Culturally safe and appropriate services and programs
- Consumer rights
- Empowering consumers
- Coordinated services and programs

Sustaining Quality External Relationships

- Service agreements, partnerships and sustainable service
- Collaboration and strategic positioning
- Incorporate and contribute to best practice
- Build capacity

Consumer Input

A consumer survey conducted in one state aimed to identify what clients valued in clinical genetic services around themes of expectations, information, respect, privacy and logistics (Nisselle et al. 2008) and led to a number of conclusions about quality care (see Box 2). The survey highlighted the importance of the post-consultation management of the anxiety people felt whilst waiting for their test results.

Box 2 Recommendations from an Australian consumer satisfaction survey (Nisselle et al. 2008)

Foundations for a Quality Clinical Genetic Service

1. Respectful, supportive and caring approach by health professionals
2. Communication that facilitates knowledge, clarifies expectations and is responsive to clients' concerns
3. Trusting environment that protects privacy and confidentiality
4. Clinical genetic services that conform to Practice Standards
5. Staff who are accredited and able to provide accurate and timely information, conforming to Practice Standards
6. A working environment where staff are supported personally and professionally

Current Status of Quality Processes in Clinical Genetic Services

To gather specific information for this book chapter about the range of quality assessment systems in place throughout Australia, we conducted a survey of clinical genetic services. One author, SM, collected data from medical directors of general clinical genetic services. Data were not collected from stand-alone familial cancer, neurogenetic, metabolic services, etc, where these are not funded through the general clinical genetic service.

The directors of 14 general clinical genetic services were contacted to participate in a telephone interview. They received a question schedule before interviews were held indicating the range of questions. The interviews were audiotaped and the responses to each question were summarised and recorded in a spreadsheet. Each participant was then sent a summary of their individual responses as well as a de-indentified aggregated summary of collated responses so that each could provide feedback and verify the data collected.

Data were obtained from 13 of the 14 directors (or their proxy, such as the office manager) who agreed to be interviewed; services in all states were represented. Further data on a 15th service established at a later date were subsequently collected and added. We categorised services arbitrarily into three groups according to numbers of staff employed by the service: small (< 5 full time equivalent (FTE) staff in total); medium (5 to 15 FTE); large (> 15 FTE). Further details about the range of staff employed are shown in Table 1. Six services were classified as

Table 1 Categories of Australian clinical genetic services according to staff numbers (full time equivalents, FTE, employed by the service)

	Small sized service[a] ($n = 6$)	Medium sized service[b] ($n = 3$)	Large sized service[c] ($n = 5$)
Range of number of FTE medically qualified staff (consultant clinical geneticists and Fellows in training, and other medical specialists)	0.2–1.0 FTE	1.3–4.4 FTE	5.4–14.5 FTE
Range of number of FTE genetic counsellors, nursing and allied health (including associate genetic counsellors in training, nurses, social workers, dieticians)	0–2.2 FTE	2.3–8.0 FTE	4.4–15.5 FTE
Range of number of FTE administrative support staff (managers, clinic coordinators, secretarial, database personnel)	0–1.5 FTE	2.5–4.3 FTE	4.0–9.0 FTE

[a] Small sized service: <5 FTE staff
[b] Medium sized service: 5–15 FTE staff
[c] Large sized service: >15 FTE staff
n = number of services in that size category

small, 3 as medium, and 5 as large, with quite a mix of clinical staff (including clinical geneticist consultants, trainee Fellows and other medical specialists), genetic counsellors and allied health/nursing staff (including those genetic counsellors with Board certification, associate genetic counsellors, specialist nurses, social workers and dieticians), and administrative support staff (including mangers, clinic coordinators, secretarial staff and database personnel). Four services were established before 1990 falling into the medium or large sized service category. All of the small sized services were established after 1993, with 3 of these in the last few years. Current HGSA guidelines recommend one FTE clinical geneticist, one FTE genetic counsellor and one FTE support staff per 300,000 population. It is difficult to determine the population served by each of the clinical centres because of different models of service delivery and overlapping service provision between them. However, if staff numbers are combined in each state where more than one service exists, then it appears that only one state fulfils all the above HGSA staffing requirements and all seem to meet requirements for the genetic counselling criteria in states where we have been given complete information. These recommendations are under review and with the current change in practices it is anticipated that more genetic counsellors will be recommended (ie two per geneticist).

Each participant was initially asked to describe their understanding of quality processes. While the responses were varied, as might be expected, clearly the majority were able to articulate this mirroring our description above. All of the clinical services have a base in one or more public hospitals (with a number having outreach services) and 11 of these use the hospital's formal accreditation process, ie EQuIP. Significantly, 9 out of 11 participants commented that this accreditation process does not actually examine the needs of their clinical genetic service, mostly because the EQuIP program seems to be better suited to accredit inpatient services and tends to focus on aspects such as occupational health and safety, but also because many services tend not to have a voice in the hospital administration. Only four services (two of which were small) have a representative on their hospital quality committee. Interestingly, a participant from one small service felt that that they had good input into this committee because the hospital itself was also small thereby contributing positively to their overall relationship. One large service uses an alternative accreditation process, namely QIC, described above, perhaps more suited for ambulatory care. This clinical genetic service also has its own Quality Committee and a Quality Liaison officer. The majority of services draw on various HGSA guidelines regarding genetic testing (www.hgsa.com.au), as well as the Guidelines for the Structure of Clinical Genetics Units in Australasia described previously (HGSA 1999). These guidelines are adopted directly, or are used to inform their own internal written protocols and standards at five centres, with some input from state Departments of Health Genetic Services Advisory Committees (GSAC) where these exist. Eight of 13 clinical services have not developed their own documentation for protocols and standards. A few participants refer to international guidelines and the literature to inform their practice, especially in regard to standards for genetic testing, but would prefer Australian-based standards.

Responses to questions related to conducting audits of practices were mixed. Almost all centres collect some data but these are not necessarily audited. Regular departmental meetings are held at which practice is reviewed. Roughly one half of the centres conduct some form of audit of practice, and these tend to be mostly *ad hoc*. Examples of areas where audits do occur include: referral data; waiting time for appointments; review of patient file data; correspondence (before appointments and follow-up); the length of time between appointments, results released, and follow-up letters. However, the majority of clinical services do not audit all of these practices and often there is minimal documentation. Four centres conduct audits on a cyclical basis ranging from monthly to 3-yearly. Audits are reported either to higher hospital management or to state Departments of Health. It was typically commented that while it is important and desirable to conduct audits, this is often difficult to carry out in practice because of limited resources, both staff and time. Interestingly, audit patterns appear not to be related to size of the service. One large service that has quality management cycles and detailed documentation uses the QIC process of accreditation every 3 years.

Credentialling staff occurs in all clinical services. Clinical geneticists all undergo continuing professional development (CPD), and are required to follow the process of Maintenance of Professional Standards (MOPS) through the RACP. Ten of the clinical services monitor the MOPS status of their clinical geneticists, usually at the annual performance review. Attendance at national and international conferences is encouraged. Associate genetic counsellors (i.e those in training) undergo Part II qualifications to receive certification from the Board of Censors of the HGSA (HGSA 2002) and this is monitored by the clinical services. However, practice varies between clinical services to what extent CPD of genetic counsellors occurs once they are Board Certified. There is currently a voluntary MOPS-type system under the auspices of the Board of Censors of the HGSA but is under review. Supervision of genetic counsellors is widespread and, where a service is small or where genetic counsellors work in outreach areas, such that supervision cannot occur in-house, external supervision is arranged. Mentoring of clinical staff is also common. Typically human resources and occupational health and safety issues are managed by the hospital or Departments of Health, with one exception where all operations are shared with the associated research institute. Staff at all clinical services undergo annual performance reviews where goal setting occurs and, in about half of the centres, this includes specific key performance indicators.

Participants were asked about any policies they have for legislative compliance and patients rights, with a focus on privacy and confidentiality. Clinical services require their staff to sign confidentiality agreements when they are initially employed, often a requirement of the Departments of Health; further agreements may be signed to access patient databases and files as required. This is a consequence of federal and state legislation regarding privacy, part of hospital policy and is included in staff induction programs. The display of information (flyers or posters) describing patients' rights is more variable. A number of clinical services produce pamphlets that describe their service; this includes what patients might expect when they attend for an appointment. The pamphlet is often sent to the

patient with their appointment letter or is available in the waiting room. Privacy rights may be described in the pamphlet, or is sometimes included in the letter, or discussed during the consultation. Providing information on complaints procedures is typically part of hospital policy and is available in all clinical services.

Consumer input into quality processes in clinical genetic services varies considerably. Only two participants said they have formal consumer input through membership on a committee within their clinical services, while four mentioned indirect consumer input through membership on GSAC, where the consumer is a representative of genetic support group peak bodies. Five participants stated that there is more informal input through feedback forms, telephone calls and email, and 8 mentioned the hospital complaints system as a vehicle for feedback. A consumer satisfaction survey is currently, or has been previously, used by 5 clinical services and a further 5 would support the use of such a survey in the future. More than half of the participants commented that the main obstacle to consumer input is lack of staff and time to coordinate this. In one centre, the genetic support group peak body is co-located: this consumer organisation is involved in strategic planning and together they have a joint quality work plan. This clinical service also has developed a communication strategy with input from the peak body as well as other community consultants.

Finally when asked to comment on how quality issues should be addressed, all participants felt there is a need for an overarching committee to ensure national benchmarking for genetic services and 11 suggested that this could be a committee within HGSA. The HGSA currently has a Genetic Services Committee and there were mixed views about whether quality issues should be a remit of this committee or whether a separate committee would be more beneficial. Again, there were concerns about lack of resources to develop and implement activities of such a committee.

Quality Systems in Laboratory Services

The regulatory frameworks in Australia aim to ensure that genetic testing occurs in a setting that promotes and protects patient safety and wellbeing. Standards and best practice guidelines are determined by National Pathology Accreditation and Advisory Council (NPAAC). The assessment and accreditation against these standards are managed through the National Association of Testing Authorities (NATA/RACP) and certified to ISO/IEC (the International Organization for Standardization/the International Electrotechnical Commission) standards. All laboratory pathology services must be accredited in order to qualify for MBS funding as well as for state funding as required by Federal Health Insurance Acts. These standards must also be met for admissible evidence from forensic laboratories.

The Therapeutic Goods Act (TGA) provides additional oversight for genetic tests used for diagnosis or genetic susceptibilities, known as “in vitro diagnostic medical devices” or IVDs”. These provide pre-market regulatory oversight for kits and registered devices, manufactured commercially or developed within the

laboratories, classified according to their assessed public health risk, based on international guidelines.

The majority of molecular genetic testing laboratories participate in the HGSA Molecular Quality Assurance Programme, which is offered in partnership with the international European Molecular Quality Network (EMQN) and CF Network. All newborn screening laboratories participate in the international Centers for Disease Control and Prevention quality assurance program, while metabolic screening laboratories also participate in an international program, namely European Research Network for Evaluation and Improvement of Screening, Diagnosis and Treatment of Inherited Disorders of Metabolism (ERNDIM). All cytogenetic testing laboratories participate in the HGSA Quality Assessment Programme and some may also engage in international programs such as the UK National External Quality Assessment Service (UKNEQAS).

The potential issues around direct–to-consumer (DTC) genetic testing have been investigated by the National Health and Medical Research Council (NHMRC). The use of DTC for diagnostic and predictive diagnostic testing is not supported. Ongoing work of NHMRC, NPAAC and EuroGentest continue to produce standards that provide benchmarks for quality testing in genetics. HGSA has encouraged a national approach to rationalising genetic testing for rare disorders to national reference laboratories.

Conclusion

Documentation of procedures, standards and protocols and their regular review is time-consuming but an essential component of quality management, together with a well-managed process for complaints, identifying opportunities for improvement and acting on them in a quality cycle that enhances management. While providing client-centred services is everyone's aim it appears that client feedback and critical review are not general practice in Australia and may be resource limited. National guidelines and standards are useful and national recommendations that include quality management are desirable and seen as important, but mechanisms to create and monitor adherence to these standards need to be established.

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Clinical Genetic Testing and Services – The US Perspective

W. Andrew Faucett

Key Points

- Most clinical genetic tests in the US are laboratory developed tests and enter the market with limited oversight.
- The US distinguishes research testing from clinical testing and requires CLIA-certification for the release of patient specific results.
- The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) and the Collaboration, Education and Test Translation Program (CETT) are two US model programs to evaluate genetic tests.

Keywords EGAPP · CETT · Genetic testing oversight · CLIA · Laboratory-developed tests

Introduction

Clinical genetic testing and clinical genetic services in the US have limited national (Federal) oversight or regulation and vary significantly from State to State and community to community. Clinical genetic tests predicted to have significant volume enter the US market quickly with and without controversy and other needed clinical tests with lower anticipated test volumes are not available or require government support for translation (Faucett 2008). As discussed by Boone and Chen in chapter "US Oversight and Regulation of Genetic Testing" most clinical genetic tests in the US are laboratory-developed-tests (LDTs) and oversight of these tests is limited to individual laboratory regulation and quality control and not on test specific

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parameters. The Food and Drug Administration (FDA) provides direct regulation and oversight of the significantly smaller proportion of tests that are developed as in vitro diagnostic test kits to be marketed to multiple laboratories and an emerging category of in vitro diagnostic multivariate index assays (IVDMIAs) which use complicated mathematical algorithms (Gutman 2003). The US makes a legal distinction between research tests and clinical tests and individual patient results of tests performed by research laboratories may not be shared with clinicians or patients (http://www.cms.hhs.gov/clia/). This chapter will discuss:

- The majority of clinical genetic testing (in vitro diagnostics) in the US is offered as laboratory- developed-tests (LDTs) and not subject to direct regulation. Quality assessment standards and programs are provided by professional organizations (SACGHS April 2008).
- Control of access to genetic services and testing in the US serves as a default oversight mechanism and is managed by multiple gatekeepers including clinicians, government and private insurers, and the individual consumer with the increasing use of direct-to-consumer (DTC) genetic testing and DTC marketing.
- EGAPP (Evaluation of Genomic Applications in Practice and Prevention) and the CETT Program (Collaboration, Education and Test Translation) are two model programs developed in the US to evaluate and ensure quality genetic testing (Teutsch 2009; Faucett 2008).
- Clinical genetic services for direct patient diagnosis and care in the US are primarily located in academic medical centers with limited satellite clinics.

In Vitro Diagnostic Testing – Clinical Genetic Testing

Clinical genetic testing in the US is market driven and it is the responsibility of the laboratory director and individual laboratory to decide when there is sufficient evidence to move a genetic test to the clinical arena and the appropriate testing methodology for each new clinical test. Currently most genetic tests are laboratory-developed-tests (LDTs) and are not subject to outside review or evaluation before public release. Under CLIA regulations the laboratory director is required to validate the new test and provide information about analytical validity, sensitivity, prevalence of the condition, and clinical use of the test. CLIA regulations require laboratories to assure that their test results are accurate, timely, reliable, confidential and do not present risk of harm to patients. All laboratories releasing results to US clinicians or patients require CLIA certification with the exception of those analyzing patient samples from New York State and Washington State where CLIA-certification is replaced by State regulatory agencies with additional specific requirements. Release of research results performed in a non-CLIA-certified laboratory to a clinician or patient that could be used in patient management is not allowed under the CLIA regulation. Evidence or proof of clinical validity and clinical utility are not required before a new LDT test is released although information on clinical utility is often requested by insurers to justify payment for testing services. For most genetic tests, proficiency programs do not exist and laboratories must develop internal programs

or work with other laboratories offering the same test to organize sample exchanges (http://www.cms.hhs.gov/clia/) (http://www.wadsworth.org/labcert/clep/clep.html).

Steps to Ensure Quality Testing

Most quality laboratories in the US follow additional guidelines provided by professional organizations and other certification organizations in addition to CLIA-certification. In the US, professional guidelines are provided by the American College of Medical Genetics (ACMG), the Association of Molecular Pathologists (AMP) and the College of American Pathologists (CAP). Laboratories may also participate in accreditation programs which meet the CLIA requirements and include additional requirements. Programs are provided by the Joint Commission at http://www.jointcommission.org, CAP and other voluntary organizations. The ACMG has developed "Standards and Guidelines for Clinical Genetics Laboratories", "Ultra-rare Disease Testing Guidelines" and other guidelines which include requirements, considerations, validation and standards for cytogenetic, biochemical and molecular tests, accessible at their website www.acmg.net (Ledbetter and Faucett 2008; Richards et al. 2008; Hudson et al. 2006; Grody and Richards 2008).

In the US, genetic testing is considered "high complexity" under the CLIA regulations and laboratory directors must have a PhD or MD degree with board certification in an approved specialty.

- ABMM – American Board of Medical Microbiology
- ABCC – American Board of Clinical Chemistry
- ABMLI – American Board of Medical Laboratory Immunology
- ABB – American Board of Bioanalysis
- ABMG – American Board of Medical Genetics (added (2/12/1996)
- ABHI – American Board of Histocompatibility and Immunogenetics (added 2/12/1996)
- ABFT – American Board of Forensic Toxicology (limited to individuals with a doctoral degree) (added 1/13/1997)
- NRCC – National Registry of Certified Chemists (limited to individuals with a doctoral degree) (added 5/28/1997).

Clinical laboratories must have a clinical consultant but the CLIA regulation does not provide specifics regarding training in human genetics. Other laboratory accreditation bodies such as ACMG and CAP do provide guidelines that require genetic expertise and certification (http://www.cms.hhs.gov/clia/) (SACGHS 2008).

Clinical Genetic Testing Educational Materials and Support Services

Clinical laboratories routinely provide educational materials about new tests written for medical geneticists and genetic counselors. Clinical and research tests are

listed on GeneTests http://www.genetests.org and most geneticists and genetic counselors use this resource to find new tests. Often there is limited information available for primary-care clinicians and patients and many are not aware of GeneTests as a resource.

Many clinical genetic laboratories in the US include masters-level trained and certified genetic counselors on staff who serve as the liaison with the clinical community. Genetic counselors often help clinicians determine the appropriate test or tests for their patients and request additional clinical information and family history information needed for test interpretation. Genetic counselors often report and explain test results to clinicians. In general laboratory based genetic counselors do not answer questions from patients and families. (SACGHS 2008)

Controlling Quality of Testing Via Gatekeepers

In the US multiple gatekeepers play a critical role by helping to ensure that genetic testing is used appropriately and that testing is performed by laboratories with high quality standards. Clinicians including medical geneticists and genetic counselors serve as major gatekeepers and are responsible for reviewing the testing claims made by individual laboratories, laboratory CLIA-certification, and laboratory adherence to additional professional guidelines before ordering a clinical test. Medical geneticists and genetic counselors also provide professional guidance to primary-care clinicians (Grody and Richards 2008; Ledbetter and Faucett 2008). Increasingly in the US genetic tests are being ordered by primary-care clinicians and specialty clinicians with limited training in medical genetics. Direct-to-consumer marketing of genetic tests encourages individuals to discuss genetic testing with their primary care physician. Primary care providers often are not aware that most clinical genetic tests are LDTs and may not be aware of the lack of regulation of individual tests (Genetics and Public Policy Center 2007).

Federal, State and Private insurers serve as major gatekeepers by limiting reimbursement for genetic tests and limiting which laboratories may perform testing in some instances. Clinicians must work closely with insurers because most institutions have limited funds to cover the cost of testing that is not reimbursed by insurers. Medicare generally develops policies on coverage for most clinical testing in the US and these policies are used by many private insurers. Few genetic tests have been reviewed by Medicare because the program is focused on healthcare for the elderly and does not include prevention benefits. Medicare has developed coverage guidelines for breast cancer and colon cancer genetic testing in specific situations (http://www.cms.hhs.gov/MedicareGenInfo/).

Medicaid provides medical expense coverage for many individuals with genetic conditions. It is managed by individual States and funded by Federal and State funds. Federal guidelines require a core set of services and States may provide additional services from State funds. State Medicaid programs evaluate and approve laboratories to provide services for residents of a given state (http://www.cms.hhs.gov/MedicaidGenInfo/). Clinicians must work with regulators in each state to obtain

coverage of a specific test. Many clinical genetic laboratories find Medicaid reimbursement rates low and only accept Medicaid payment in their home State. In general if a laboratory accepts Medicaid they may not bill the clinician, institution or patient for the portion of a test not reimbursed by Medicaid. Laboratories often do not accept Medicaid from other States and this limits the availability of clinical genetic tests provided by laboratories located in a different state (Greenstein et al. 2001; SACGHS 2008).

Most private health insurance in the US occurs through employer sponsored group insurance programs. These programs are regulated by Federal guidelines and do not include specific guidelines on coverage of genetic testing and services. Coverage of genetic testing is market driven and based on the cost of the insurance plan and assessment by the insurance company of the value of the test and usually requires evidence of the test's impact on patient management and care – clinical utility. Coverage varies and expensive plans usually cover genetic tests with clinical utility and inexpensive plans may exclude all genetic testing. Many genetic tests do not have proven clinical utility and must be reviewed by the Medical Director of each insurance company for coverage. Individual private health insurance is governed by State regulation. Some states have guidelines on what must be covered in State regulated insurance plans (Teutsch et al. 2009; Haddow and Palomaki 2003).

Currently over thirty laboratories offer genetic tests directly to consumers (DTC) in the US and the number of laboratories using this business model is growing. Often information about testing and the quality of a given test is limited resulting in a consumer not having the necessary information to assume the gatekeeper role. The quality of DTC companies varies greatly with some companies having multiple genetic experts on staff including genetic counselors and other companies having no genetic expertise on staff. Authority to order a test in the US is determined by State law and approximately twenty-five States allow consumers to order all medical tests directly from a laboratory. Insurers generally only provide reimbursement for testing provided based on an order by an approved clinician. Regulations in the twelve States which allow limited use of DTC and the thirteen States which restrict DTC vary greatly and include States that limit test ordering to physicians; States that allow all healthcare providers to order tests; and States that allow clinicians to sign off on a test order without seeing the patient. Routine clinical genetic tests and many of the newer controversial genetic tests in the US are currently offered as DTC tests (Genetics and Public Policy Center 2007).

Model Programs – Genetic Test Evaluation and Translation

Two pilot programs in the US include evaluation of new genetic tests. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) was developed by the Centers for Disease Control and Prevention (CDC) National Office of Public Health Genomics and the Collaboration, Education and Test Translation (CETT) Program was developed by the National Institutes of Health (NIH) Office of Rare Diseases (ORD) and the CDC Division of Laboratory Systems. EGAPP

evaluates test post release and focuses on tests with the potential for broad population use or public health tests. CETT evaluates tests prior to translation and focuses on rare disease genetic tests which have been developed in research and now are ready to move to clinical testing (Teutsch et al. 2009; Faucett et al. 2008).

Evaluation of Genomics Applications in Practice and Prevention (EGAPP)

EGAPP is a pilot project initiated in 2004 consisting of an independent, non-Federal Working Group of thirteen multidisciplinary experts in areas such as evidence-based review, clinical practice, public health, laboratory practice, genomics, epidemiology, economics, ethics, policy, and health technology assessment. The project's goal is to establish and evaluate an evidence-based process for assessing genetic tests that have recently moved from research to clinical practice but have not gained wide use or acceptance among clinicians and public health programs. The panel prioritizes and selects tests, reviews CDC-commissioned evidence reports and other contextual factors, highlights critical knowledge gaps, and provides guidance on appropriate use of genetic tests with the potential for broad public health impact. Tests targeted for review include population-based applications such as carrier identification, predictive testing for inherited risk of common diseases, and pharmacogenetic testing for variation in drug response.

EGAPP aims to integrate:

- Existing recommendations on implementation of genetic tests from professional organizations and advisory committees.
- Knowledge and experience gained from existing processes for evaluation and appraisal (e.g., US Preventive Services Task Force, CDC's Task Force on Community Preventive Services), and the international health technology assessment experience.

The independent EGAPP Working Group has published Recommendations and Evidence Reports which incorporate new approaches for collecting, analyzing and grading evidence on analytic and clinical validity and clinical utility of genetic and genomic tests (Teutsch et al. 2009).

EGAPP was an outgrowth of previous CDC initiatives including the ACCE process for assembling and analyzing data on genetic tests. The ACCE (Analytic validity, Clinical validity, Clinical utility and Associated ethical, legal and social implications) was developed as a model process for evaluating data on emerging genetic tests (Haddow and Palomaki 2003; Sanderson et al. 2005).

Collaboration, Education and Test Translation (CETT) Program

The CETT Program offers a model of test review before translation and requires applicants to meet quality standards for laboratory test methods that are greater

than current US CLIA regulations and professional guidelines. The objectives of the CETT Program include: (1) Development of new genetic tests for rare diseases; (2) Translation of genetic tests from research laboratories to clinical practice; (3) A collaboration model and provision of education about each rare genetic disease, related genetic research and the clinical impact of testing; (4) Collection and storage of genetic test result information in publicly accessible databases to leverage the information into new research and new treatment possibilities.

The CETT Program states that all parties benefit when: (1) the quality of testing for rare disorders meets or exceeds existing standards; (2) clinical laboratories, researchers, clinicians, and disease specific advocates collaborate; and (3) high quality educational materials explain what the test can and cannot do and how best to use the test results.

The CETT Program includes a model process to determine "when a test is ready for prime time" through internal review by CETT Program Staff and external review by an expert Review Board that considers information in the peer-reviewed published literature and what is known about the predicted mutation detection rate. The CETT Program enforces the notion of "truth in advertising" by requiring descriptions of the test and test result reporting that (1) clearly explain what is known about the mutation detection rate of the test; (2) explains the limitations of the test itself; (3) helps the patient and clinician understand the meaning of test results; and (4) places the test results in the context of patient care. Each test in the CETT Program is reviewed by the CETT Program Scientific Advisor for completeness: scientific evidence, methodology and laboratory experience. Simultaneously, the CETT Program Coordinator reviews draft test result report forms, and draft educational materials.

Each application is reviewed by members of the CETT Program Review Board representing the non-geneticist clinician, clinical genetics professional, laboratory geneticist, biochemical genetics, researcher, and patient advocate communities. Each application is reviewed independently by a panel of six members, one from each of the representative groups.

The reviews focus on scientific evidence, proposed methodology, impact on healthcare, laboratory qualifications, data collection, educational materials, and evidence of collaboration.

When looking at scientific evidence, the reviewers consider:

- How many genes cause the disorder?
- What percentage of patients with the disorder have mutations in the gene for which testing is proposed?
- What percentage of patients will be identified using the proposed testing method compared to current testing methods? Are other methods of diagnosis available, which the proposed test would replace or complement?

The proposed test methodology is evaluated for specific goals:

- Is the test translation approach efficient? Do the proposed individual sample fees seem reasonable?

- How will unusual results, such as variants of unknown significance (VUS), be evaluated and reported?
- If mutation screening is used, how will negative results be evaluated?
- How will the test be validated? Are positive and negative control samples available?
- Will testing be available in all formats needed by the community – diagnostic, carrier, prenatal and pre-implantation genetic diagnosis (PGD)?

The test must provide evidence of a potential positive impact on healthcare:

- Will the proposed test change the current diagnostic pathway?

The following laboratory qualifications are reviewed:

- Laboratory Director's certification
- CLIA or other certification of laboratory
- Number of disorders currently tested by the laboratory
- Availability of genetic counselors or physician consultants to provide clinical consultation.

Evaluation of the plan for educational materials includes:

- Plan to develop educational materials about the disease and how the test is used in patient care for two audiences – medical geneticists and non-genetic clinicians and patients.
- Test result report forms for negative, positive, or indeterminate results that clearly explain the results of the test, the implications of the test result for the person tested, and the limitations of the test itself.
- Agreement to write a GeneReview within 1 year or provide suggested updates to a current one to include testing information (Faucett et al. 2008).

Clinical Genetic Services in the US

Most clinical genetic service in the US is provided in academic medical centers with uneven geographic distribution and limited access for a significant proportion of the US population. Locations of genetic healthcare providers can be found at http://www.acmg.net, http://www.genetests.org, and http://www.nsgc.org The type of service provided by academic centers varies greatly due to differences in State funding, the number of certified genetic healthcare professionals, the percentage of the state population with insurance coverage, and the types of insurance coverage. The role of physicians without specialized training offering genetic services and genetic testing has expanded greatly in prenatal and cancer genetics and is beginning to expand in neurology, cardiology and preventive medicine (SACGHS 2008).

Also new models of web-based genetic counseling services are beginning to be funded by private health insurers (Informed Medical Decisions).

Multiple reports indicate that the number of clinical medical geneticists is low and not increasing to meet the predicted future needs. These reports indicate that many training positions in medical genetics go unfilled. The number of masters-trained genetic counselors is growing but the rate of growth is predicted not to be fast enough to meet the population needs with the anticipated expansion in genetic testing (Korf et al. 2008).

Conclusion

The US has historically relied on a combination of laboratory regulation, professional guidelines, and trained genetic healthcare professionals to ensure quality genetic services and genetic testing. Currently most genetic tests are LDTs and have no direct oversight to ensure quality. The Genetics and Public Policy Center and others have called for specific regulation to ensure the quality of genetic testing. New models of test evaluation similar to EGAPP and the CETT Program may provide needed guidance as new oversight programs are considered. Increased education for genetic healthcare professionals, primary-care healthcare professionals and the public about quality parameters of genetic testing will be needed as the volume of testing increases.

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US Oversight and Regulation of Genetic Testing

Bin Chen and D. Joe Boone

Key Points

- The oversight responsibilities for genetic testing in the United States (US) are shared by multiple governmental and non-governmental entities, including federal and state government agencies, healthcare payers, professional associations, and other sectors. This chapter describes:
- The complex array of US oversight mechanisms and responsibilities related to genetic testing and the application of genetic tests and testing information in patient care and health management at the federal, state, and private-sector levels;
- Issues and potential gaps in oversight mechanisms for genetic testing, such as concerns related to analytic validity, clinical validity, external quality assessment, clinical utility, and direct-to-consumer genetic testing; and
- Ongoing efforts to promote quality testing and improve the utilization of genetic testing services in clinical and public health practices

Keywords Genetic testing · Genetic test information · Quality assurance · Laws · Regulations · Mandated and voluntary oversight · Compliance · Direct to consumer genetic testing

Introduction

Genetic testing encompasses a broad range of laboratory tests that are increasingly becoming standard practice for diagnosing and managing disease. Recent scientific and technological advances in genetic testing have challenged existing frameworks

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for regulation and oversight (Secretary's Advisory Committee on Genetics, Health, and Society 2008). The purpose of oversight is to reduce the risk of harm that may accompany testing and test results and to promote appropriate utilization of testing that will maximize health benefits. Therefore, it is critical to monitor and assess the impact of genetic testing applications on individual health care and public health and to adapt oversight processes in the best interest of the public.

The oversight responsibilities for genetic testing in the US are shared by multiple governmental and non-governmental entities, including federal and state government agencies, healthcare payers, professional associations, and other sectors (Secretary's Advisory Committee on Genetics, Health, and Society 2008). These entities contribute to the oversight framework by undertaking information development (data collection, scientific studies, and reporting requirements to identify and measure benefits and risks), standard-setting, compliance mechanisms, or a combination of these essential functions that are necessary in virtually any context. The complex array of US oversight and regulations, including those relevant to genetic testing, relies on three categories of compliance mechanisms: (1) mandatory compliance that is legally enforceable under federal and/or state statutes and regulations, (2) incentive-driven compliance that is not legally mandatory but is supported by concrete financial or liability-related incentives to comply with an otherwise voluntary standard, and (3) informal or voluntary compliance that may help promote implementation of voluntary standards, such as the voluntary certification and self-regulation programs developed by professional bodies and industry groups (Secretary's Advisory Committee on Genetics, Health, and society 2008). In addition, "watchdog" activities by consumer advocacy organizations and fear of adverse publicity can promote compliance with voluntary good practices.

This chapter focuses on the oversight for genetic testing and the application of genetic tests and testing information in patient care and management in the US. While directed to the US processes, the issues may not differ from those of other countries or from those for other complex laboratory tests. To help frame recommendations for policymakers and stakeholders, this chapter describes the US oversight mechanisms and responsibilities related to genetic testing at the federal, state, and professional and industry levels, the oversight issues and potential gaps that have been recognized, and the ongoing efforts to promote quality testing and improve the utilization of genetic testing services in clinical and public health practices.

Current Oversight for Genetic Testing

Current oversight includes federal and state legislatures, federal and state regulatory agencies, state and federal courts, and professional and industry oversight bodies. Table 1 summarizes the key elements of jurisdiction and corresponding systems of oversight for genetic testing that are described below.

Table 1 Key elements of the regulatory oversight framework for genetic testing in the US

Area of jurisdiction	Systems of oversight
Regulation of clinical laboratories and testing services	*Federal:* Clinical Laboratory Improvement Amendments (CLIA) regulations administered by CMS, FDA, and CDC. Other federal agencies may have involvement (e.g., the Federal Trade Commission (FTC) in oversight of marketing). *State*: Regulatory oversight in some states such as New York, Washington, and California.
Medical and diagnostic product regulation	*Federal:* FDA regulation of genetic tests and therapies used in conjunction with genetic tests, with oversight of marketing shared between FDA and FTC.
Regulations affecting reimbursement and access to genetic testing	*Federal:* CMS Medicare. *State:* State health programs and insurance regulations affecting private insurers. *Informal/private sector*: Medical necessity and utilization review practices, contracts.
Regulation of clinical practice (e.g., when, whom to test; physicians' claims and disclosures about tests)	*State law*: Medical practice and pharmacy regulations, consent laws, genetic privacy acts, tort law. *Informal regulation*: Voluntary guidelines and professional standards.
Regulation of specific uses and misuses of test results (e.g., privacy and data security; discrimination in employment and insurance; torts involving inappropriate or mistaken uses of genetic information)	*Federal:* Health Insurance Portability and Accountability Act (HIPAA) of 1996, Americans with Disabilities Act of 1990, Employee Retirement Income Security Act of 1974. *State:* Statutes and tort law.
Standards of patient responsibility	*State tort law:* Delineates when patients are responsible for protecting themselves as opposed to when they are entitled to rely on protection by other parties (e.g., manufacturers, physicians).

Federal Oversight and Responsibilities of Federal Agencies

The US Congress is involved in the oversight for genetic testing through legislations that provide statutory authority to specific government agencies to establish and enforce regulations applicable to genetic testing or address specific aspects related to the use and treatment of genetic information. For example, the Federal Food, Drug, and Cosmetic Act (FFDCA) mandates that laboratory test systems, including genetic tests that are regulated as medical devices, be subject to pre-market clearance or approval by the Food and Drug Administration (FDA) (Federal Food, Drug, and Cosmetic Act, as amended). The Social Security Act mandates that medical services, including laboratory testing, be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformedbody

member" to be considered for Medicare coverage (Social Security Act, as amended). Federal legislations have also been established to address particular uses and misuses of genetic information, such as the Genetic Information Nondiscrimination Act of 2008 that prohibits discrimination in health insurance and employment based on an individual's genetic information (Genetic Information Nondiscrimination Act of 2008).

Federal regulations of testing products. FDA regulates genetic tests that qualify as products developed by industry as medical and IVD devices, including test kits, quality control materials, and analyte-specific reagents (ASRs) (21 CFR Part 820 Quality System Regulation, revised as of April 1 2008; 21 CFR Part 809 In Vitro Diagnostic Products for Human Use, revised as of April 1 2008). In general, genetic testing products pass through the FDA's medical device premarket clearance or approval processes to ensure their safety and effectiveness. Since 2003, several DNA-based genetic tests have been cleared by FDA, including test systems detecting factor V Leiden and prothrombin G20210A thrombophilia, cytochrome P450 genotype, and mutations in the CFTR gene. FDA has made available guidance documents regarding the classification and review criteria of these genetic tests (Food and Drug Administration 2004; 2005; 2007a).

Since September 2006, FDA has issued draft guidance documents clarifying FDA's oversight for analyte-specific reagents (ASRs), which include antibodies, receptor proteins, nucleic acid sequences, or other biological or chemical reagents that are used by laboratories to develop in-house tests (Food and Drug Administration 2007b); and for a subset of laboratory-developed tests known as in vitro diagnostic multivariate index assays (IVDMIAs) (Food and Drug Administration 2007c). The ASR guidance document addresses industry efforts to market more complex combinations of ASR-based products under the less demanding requirements of single ASRs and clarifies products that are not considered as ASRs and thus are not exempt from the FDA premarket review requirements (Food and Drug Administration 2007b). IVDMIAs typically use complex mathematical algorithms, often with the aid of computer software, to interpret large amounts of genetic or protein data to yield results that can be used to guide medical decision-making. Though many laboratory-developed genetic tests do not fall within this category, these tests include some of the complex genetic and proteomic tests, such as gene expression profiles that might predict cancer prognosis and guide the use of chemotherapy (Food and Drug Administration 2007c). In February 2007, FDA cleared the first IVDMIA test that uses gene expression profiling for predicting metastatic risks in women with early-stage breast cancer (Food and Drug Administration 2007d).

Federal regulations for laboratories performing patient testing. At the federal level, laboratories performing genetic testing, whether using FDA-approved or -cleared tests or test systems or laboratory-developed methods, are subject to the Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations (42 CFR Part 493 The Clinical Laboratory Improvement Amendments Regulations, as amended). The CLIA regulations are based on the complexity of testing and include requirements for proficiency testing (PT), laboratory personnel, the total

testing process (including the preanalytic, analytic, and postanalytic phases), and where applicable, more specific requirements for testing specialties and subspecialties. Although clinical cytogenetics is recognized as a CLIA specialty that must meet specific quality assurance and personnel requirements as specified in the regulations, there are no specialty requirements for other genetic tests, such as molecular and biochemical genetic testing. However, as these genetic tests are generally considered high complexity testing, laboratories performing molecular or biochemical genetic testing must comply with applicable general CLIA requirements for non-waived testing and the personnel requirements for high complexity testing.

The Centers for Medicare & Medicaid Services (CMS) oversees the administration and implementation of the CLIA regulations (Centers for Medicare & Medicaid Services 2009). CMS provides guidance and information resources to help laboratories achieve compliance with the regulations and assure accurate and reliable test performance and result reporting (Centers for Medicare & Medicaid Services 2008). CLIA requires laboratories performing non-waived testing to undergo biennial inspections by CLIA surveyors or approved accrediting organizations. If noncompliance is found and substantiated, CMS can impose sanctions that include monetary penalties, ceasing testing until problems are corrected, revocation of the laboratory's CLIA certificate, and suspension of Medicare and Medicaid payments (Centers for Medicare & Medicaid Services 2009).

Other federal agencies such as the National Institutes of Health (NIH), the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC), and the Health Resources and Services Administration (HRSA), do not have direct regulatory authority for genetic testing but contribute to the oversight system by advancing the translation of genetic tests and services into clinical and public health practice, evaluation of the evidence base for making recommendations, providing technical advice to regulatory agencies, and developing guidance for various stakeholders. Examples of the responsibilities of these federal agencies include:

- The *CDC Division of Laboratory Systems* (DLS) provides technical consultation to CMS regarding the CLIA regulations, manages and supports the Clinical Laboratory Improvement Advisory Committee (CLIAC), performs assessment studies on laboratory practices and services, and develops guidance and training materials for promoting the quality of laboratory testing (Centers for Disease Control and Prevention 2009a). The *Evaluation of Genomic Applications in Practice and Prevention* (EGAPP), under the Office of Public Health Genomics at CDC, aims to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to clinical practice and public health (Centers for Disease Control and Prevention 2009b).
- *AHRQ's Evidence-based Practice Centers Program* generates evidence reports in support of the EGAPP initiative and has commissioned a study on monitoring

use and outcomes of gene-based applications in the US health care system in conjunction with CDC (Agency for Healthcare Research and Quality 2009). AHRQ also administers the US Preventive Services Task Force (USPSTF), an independent panel of experts in primary care and prevention that systematically reviews evidence of effectiveness and develops recommendations for clinical preventive services. USPSTF has conducted reviews of relevant genetics topics, including BRCA testing and hereditary hemochromatosis (US Preventive Services Task Force 2005; US Preventive Services Task Force 2006).

- *NIH Office of Rare Diseases* supports the Collaboration, Education, and Test Translation (CETT) Program that promotes the translation of tests for rare genetic diseases into clinical settings and encourages clinical laboratory and research collaborations. The program has active partnerships with federal entities, including CDC, HRSA, and CMS, and many non-federal groups (Collaboration, Education, and Test Translation Program 2009).
- *National Institute of Standards and Technology* (NIST), a non-regulatory federal agency within the US Department of Commerce, supports measurement procedures and reference materials for traditional biomarkers, as well as DNA-based standards for *HER2* testing and fragile X syndrome (National Institute of Standards and Technology 2005). NIST also advances the integration of health information technology (IT) standards to raise the quality of clinical outcomes and lower the costs of health IT implementation (National Institute of Standards and Technology 2009).

Federal advisory committees do not exert governmental oversight but provide recommendations and advice to the federal government. Examples of federal advisory committees that address issues related to genetic testing include:

- *Secretary's Advisory Committee on Genetics, Health, and Society* (SACGHS) was chartered in 2002 to investigate and address a broad range of policy issues raised by the development and use of genetic tests, including specific questions related to the adequacy and transparency of the current oversight system for genetic testing and, as warranted, to provide advice on these issues (Secretary's Advisory Committee on Genetics Health, and Society 2009).
- *Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children* (ACHDGDNC) provides advice and recommendations on appropriate application of universal newborn screening tests, technologies, policies, guidelines, and programs for reducing negative outcomes of heritable disorders (Advisory Committee on Heritable Disorders in Newborns and Children 2009).
- *Clinical Laboratory Improvement Advisory Committee (CLIAC)* provides recommendations and advice regarding the CLIA regulations, their impact on medical and laboratory practices, and the modifications needed to CLIA standards to accommodate technological advances (Clinical Laboratory Improvement Advisory Committee 2009).

Oversight at the State-level

State regulation of testing services. At the state level, 26 states have a certain degree of statutory authority for oversight of the practice of clinical laboratory medicine (Secretary's Advisory Committee on Genetics, Health, and Society 2008). Many states use CLIA requirements to regulate genetic testing laboratories. However, New York and Washington independently operate their own laboratory certification programs, which are exempt from CLIA because CMS has deemed them equivalent to or more stringent than CLIA requirements (Centers for Medicare & Medicaid Services 2009). The New York State Department of Health requires that all laboratories that test specimens obtained from New York state residents be subject to the state's clinical laboratory requirements and obtain preapproval for any genetic test they intend to offer to New York state residents (New York State Department of Health 2009). The Washington State Laboratory Quality Assurance Program regulates laboratories within the state and evaluates the analytic and clinical validity of the tests these laboratories perform (Washington State Office of Laboratory Quality Assurance 2009). California, through its newborn screening and prenatal screening program, has rigorous review of those types of assays, but its oversight does not generally extend to other genetic testing (California Department of Public Health 2009a,b). New Jersey applies some personnel standards to laboratories that perform genetic testing (New Jersey State Department of Health and Senior Services 2009). With the exception of New York, no state requires review of validation data for individual assays other than in the context of an onsite inspection, which for most state programs does not involve peer review (Secretary's Advisory Committee on Genetics, Health, and Society 2008).

State regulation of clinical use of genetic testing. The clinical use of genetic tests is primarily regulated at the state level employing a complex web of state statutes, regulations, and liability rules that influence the extent to which patients benefit from genetic testing and are protected from harms (National Conference of State Legislatures 2009). This includes state medical practice acts, informed consent statutes, pharmacy regulations, state genetic testing statutes and privacy acts, and state tort liability rules that serve to define the physician's standard of care. State laws affect whom to test, when to test, which test to use, and what actions should be taken in response to specific test results. In addition to the regulation of genetic tests in general, states have specific oversight of newborn screening performed by state public health laboratories (National Conference of State Legislatures 2008).

State regulations and liability rules also provide incentives to follow federal standards and other efforts relating to clinical laboratory testing. An example is physician compliance with safety warnings stated in FDA-approved product labeling. While the FDA decides whether medical products can be marketed and approves their labeling, it does not require physicians to comply with the instructions and warnings in product labeling (Food and Drug Administration 1972). States have not embraced a direct regulatory approach to this problem, and tort lawsuits are the main *de facto* compliance mechanism at the state level. The result is a very weak set of incentives for physicians to heed warnings in product labeling, with only

some states treating compliance with labeling as the standard of care. To date FDA has not exercised its authority of characterizing a medical device as "restricted" and imposing stringent limitations on its sale, distribution, or use for the purpose of restricting the clinical uses of genetic tests. Physicians are generally free to use an FDA-approved genetic test either in or out of compliance with its labeling, subject only to state tort liability for uses that prove positively injurious (Secretary's Advisory Committee on Genetics, Health, and Society 2008).

Voluntary Standards, Professional Guidelines, and Other Oversight Mechanisms

Professional societies, industry trade groups, and private-sector accreditation and oversight bodies play important roles in the oversight of genetic testing. They are also involved in the development of guidelines and recommendations regarding the appropriate use of genetic tests. Guidelines may be evidence-based, best practices, or based on expert opinion. Several professional societies contribute to the oversight system by developing standards, position statements, and practice guidelines (American College of Medical Genetics 2009; American Society of Human Genetics 2009; Association of Public Health Laboratories 2009; Clinical and Laboratory Standards Institute 2009; College of American Pathologists 2009; National Society of Genetic Counselors 2009). They are involved in accreditation of laboratories, guideline and standard development, advancement of best practices, PT programs, promotion of health professional education in human genetics, and other efforts that improve health care through laboratory medicine. The term "informal regulation" is sometimes used to refer to these activities. Specific examples include (1) The American College of Medical Genetics that develops clinical practice guidelines and establishes voluntary laboratory standards to help medical geneticists provide accurate and reliable diagnostic genetic laboratory testing consistent with current technologies (American College of Medical Genetics 2009); (2) The Association of Molecular Pathologists supports the development of new technologies in molecular biology (Association for Molecular Pathology 2009); (3) The American Society of Human Genetics provides venues for investigators to share their research findings (American Society of Human Genetics 2009); (4) The Association of Public Health Laboratories promotes policies that support healthy communities, such as state newborn screening programs and the oversight of genetic tests (Association of Public Health Laboratories 2009); (5) The Clinical and Laboratory Standards Institute develops voluntary standards and guidelines (Clinical and Laboratory Standards Institute 2009); (6) The College of American Pathologists offers the most comprehensive genetic testing PT program (College of American Pathologists 2009); and (7) The National Society of Genetic Counselors (NSGC) promotes the recognition of the genetic counseling profession as an integral part of health care delivery, education, research, and public policy (National Society of Genetic Counselors 2009). In addition, advocacy groups, organizations,

and individuals may engage the public in issues pertaining to genetic testing. Other organizations monitor and analyze developments in genetics that affect health care and serve as sources of information for the public, the media, and policymakers. Examples of such organizations include the Genetic Alliance, a coalition of more than 600 advocacy organizations serving 25 million people affected by some 1,000 conditions (Genetic Alliance 2009); and the Genetics and Public Policy Center that helps policy leaders and the public better understand the rapidly evolving field of human genetics and its application to health care (Genetics and Public Policy Center 2009).

Oversight Issues, Efforts to Address Gaps in Current Oversight System, and Considerations for Future Oversight for Genetic Testing

Oversight Issues and Gaps

As advances in genomic research and technology provide promise for rapid development of new genetic tests, concerns have been raised that some genetic tests could become available without adequate assessment of their validity, benefits, and utility (Secretary's Advisory Committee on Genetic Testing 2007; Secretary's Advisory Committee on Genetics, Health, and Society 2008). Consequently, health professionals and consumers may not be able to make a fully informed decision about whether or how to use these tests. In the US the expanded use of genetics and genomics has elevated a wide range of policy issues including: (1) safe and effective translation of research findings into genetic tests and the integration of genetics and genomics into health care and public health; (2) the clinical, public health, ethical, economic, legal, and societal issues raised by genetics and genomics; (3) adequacy of oversight and quality assurance measures for the performance and delivery of genetic testing services; (4) gaps in research, data collection, and analysis; (5) patent policy and licensing practices governing access to genetic and genomic technologies; and (6) use of genetic information in education, employment, insurance, and law (Secretary's Advisory Committee on Genetics, Health, and Society 2008). The increasing complexity of these issues has imposed great challenges in developing approaches to improving the oversight mechanisms that assure the quality, safety, and effectiveness for all, rather than some, genetic tests (Secretary's Advisory Committee on Genetics, Health, and Society 2008).

Analytic validity and clinical validity. Assuring the analytical and clinical validity of genetic testing is paramount. Analytical validity of a genetic test refers to the test's ability to measure the analyte or genotype of interest accurately and reliably, and is commonly determined by establishing or verifying the accuracy, precision, reference range or normal values, reportable range, analytical sensitivity, analytical specificity, and other specifications required for test performance. Clinical validity refers to the accuracy of a test in diagnosing or predicting risk for a health

condition and is measured by clinical (or diagnostic) sensitivity, clinical (or diagnostic) specificity, and predictive values of the test for a given health condition (Secretary's Advisory Committee on Genetics, Health, and Society 2008). The CLIA regulations emphasize the analytical validity of laboratory testing, but do not include specific requirements for laboratories to validate clinical performance specifications of new tests or test systems other than requiring laboratory directors and technical supervisors to ensure the selection of the test methodology is appropriate for the clinical use of the test results and has the capability of providing the quality of results required for patient care (42 CFR Part 493 The Clinical Laboratory Improvement Amendments Regulations, as amended). FDA evaluates clinical validity of genetic tests based on the nature of the test, its intended use, and the amount of existing information about the associations of genetic markers and clinical diagnosis (21 CFR Part 820 Quality System Regulation, revised as of April 1 2008; 21 CFR Part 809 In Vitro Diagnostic Products for Human Use, revised as of April 1 2008). However, since many genetic tests are performed using laboratory-developed methods, laboratories performing these tests must comply with all applicable CLIA requirements, but laboratory-developed tests are not currently subject to the FDA pre-market review.

External quality assessment. The CLIA regulations have not yet included PT requirements for genetic tests. Laboratories performing genetic testing must meet the general CLIA requirement for alternative performance assessment for tests not specified on the list of regulated analytes, to at least twice annually verify the accuracy of the genetic tests they perform (42 CFR Part 493 The Clinical Laboratory Improvement Amendments Regulations, as amended). Laboratories may participate in available PT programs for the genetic tests they perform as a means to meet the CLIA alternative performance assessment requirement (Centers for Medicare & Medicaid Services 2009). In principle, all genetic tests and other high-complexity tests should be required to undergo PT. Thus, gaps in oversight still exist regarding regulation, breadth, costs, and availability of testing materials for existing PT programs (Secretary's Advisory Committee on Genetics, Health, and Society 2008).

Clinical utility. Clinical utility involves identifying the outcomes associated with specific test results. Information on clinical utility is critical for managing patients, developing professional guidelines, and making coverage decisions (Secretary's Advisory Committee on Genetics, Health, and Society 2008). The potential value of a genetic test is realized only when it provides a meaningful benefit to patients, families, or society. However, as is common in medicine, the lack of high-quality evidence of benefit from prevention or treatment interventions has been recognized as the primary gap in identifying the net benefit for individuals who undergo genetic testing (Secretary's Advisory Committee on Genetics, Health, and Society 2008). Only a few studies have been conducted of the clinical utility of specific genetic tests, and there has been insufficient analysis of the standard of evidence on which the clinical utility of genetic tests should be evaluated and on which evidence-based methods applicable to genetic testing should be developed (Centers for Disease Control and Prevention 2009b; US Preventive Services Task Force 2005; US Preventive Services Task Force 2006). Meanwhile**,** publications show that some

genetic tests have been inappropriately offered based on genetic association studies that have not been adequately validated (Haddow and Bradley 1999; Jeffrey and Adams 2000).

Direct-to-consumer (DTC) genetic testing. The increase in direct-to-consumer (DTC) genetic testing has raised concerns about the potential risks or misuses of certain genetic tests (US Government Accountability Office 2006). Based on information available as of October 2008, consumers can directly order laboratory tests in 27 states while in another 10 states, consumer-ordered tests are allowed under defined circumstances (Genetics and Public Policy Center 2009). As DTC genetic tests become increasingly available, a variety of genetic profile tests have been marketed directly to the public that claim to answer questions regarding cardiovascular risks, drug metabolism, dietary arrangements, and life styles (US Government Accountability Office 2006). In addition, DTC advertisements have also caused a significant increase in the demand for molecular genetic tests, such as those for hereditary breast and ovarian cancers (Centers for Disease Control and Prevention 2004; Mouchawar et al. 2005). Though allowing easy access to the testing services, DTC genetic testing has raised concerns about the potential for inadequate pre-test decision-making, misunderstanding of test results, access to tests of questionable clinical value, lack of necessary follow-up, and unexpected burdens on primary care physicians (Federal Trade Commission 2006; Gollust et al., 2003; Wasson et al., 2006; Wolfberg 2006).

Efforts to Address Gaps in Current Oversight System

Since 1997, multiple advisory groups and committees have provided recommendations to the government and other sectors regarding actions and approaches needed to enhance the oversight and ensure the safety and effectiveness of genetic tests (Genomics and Personalized Medicine Act (S.976), introduced in Senate in 2007; Holtzman and Watson 1999; Laboratory Test Improvement Act (S.736), introduced in Senate in 2007; Secretary's Advisory Committee on Genetic Testing 2007; Secretary's Advisory Committee on Genetics, Health, and Society 2008). In an SACGHS report focusing on the oversight of genetic testing and the application of genetic information in patient care and management, upon recognition of the concerns for inadequate or misapplied knowledge of the clinical validity of genetic tests and for applying genetic tests without proper documentation that the clinical validity is adequate for the intended use of the tests, the Committee recommended that the US Department of Health and Human Services (HHS) take the following action steps to address the identified gaps:

- To improve clinical laboratory quality, PT should be required for all non-waived laboratory tests for which PT products are available. HHS should support innovations in PT and ensure funding for the development of reference materials and methods used for quality control, performance assessment and standardization.

- To help close the gaps in oversight related to clinical validity to help assure the appropriate use of laboratory tests, all laboratory tests should undergo FDA premarket review.
- To enhance the transparency of genetic testing and assist efforts in reviewing the clinical validity of laboratory tests, HHS should appoint and fund a lead agency to develop and maintain a mandatory, publicly available, web-based registry for laboratory tests.
- To better understand the usefulness of genetic tests, HHS should create and fund a public-private partnership to evaluate the clinical utility of genetic tests, develop a research agenda to address gaps in knowledge, conduct public health surveillance to assess the health impact of genetic testing, and help advance the appropriate use of electronic health records as a resource for assessing clinical utility and quality of health care.
- To meet the educational needs of health professionals, public health workers, patients, and consumers, HHS should support efforts to identify education or training deficiencies in each of these groups and develop effective clinical decision support systems. In addition, FDA should prepare a guidance document articulating the scope of its regulation of clinical decision support systems (Secretary's Advisory Committee on Genetics, Health, and Society 2008).

Improving education to patients and other consumers along with efforts to guide health care professionals, on DTC genetic testing. Both the government and professional organizations have developed educational materials that provide guidance to consumers, laboratories, genetics professionals, and professional organizations regarding DTC genetic tests (American College of Medical Genetics 2004; Federal Trade Commission 2006; Hudson et al. 2007). In 2006, the Federal Trade Commission (FTC), in conjunction with FDA and CDC, issued an alert to warn consumers to be wary of claims made by at-home genetic tests (Federal Trade Commission 2006).

Enhancing oversight for genetic testing under the current regulatory framework. Since 1997, various groups and legislative efforts have called for increased US government oversight of genetic testing, including the creation of a genetic testing specialty under CLIA (Holtzman and Watson 1999; Secretary's Advisory Committee on Genetic Testing 2007). CLIAC recommended the augmentation of the CLIA regulations governing the quality of clinical laboratories generally and genetic testing laboratories specifically (Clinical Laboratory Improvement Advisory Committee 2009). In May 2000, CDC published a Notice of Intent soliciting public comments on plans to add a genetic testing specialty with specific requirements under CLIA (Centers for Disease Control and Prevention 2000). CMS decided in September 2006 that rather than establishing a CLIA genetic testing specialty with prescriptive requirements, alternative approaches should be pursued including: (1) providing CMS surveyors with guidance on assessing genetic testing laboratories; (2) developing educational materials for and provide education to genetic testing laboratories; (3) maximizing the expertise of CMS-approved accreditation organizations, some of which already have molecular diagnostic standards; (4) explore

creative genetic laboratory surveying alternatives; (5) develop alternative PT mechanisms (e.g., inter-laboratory comparisons) with the assistance of CDC and FDA and encourage laboratories to participate in them; (6) seek assistance from FDA and CDC on the review of complex analytical test validations; (7) collect data on genetic testing laboratory performance; and (8) collaborate with others on oversight concepts/issues. This planned course of action was later supported by SACGHS in its 2008 report providing recommendations regarding future oversight of genetic testing (Secretary's Advisory Committee on Genetics, Health, and Society 2008).

To enhance the oversight of genetic testing under the current CLIA framework, CDC has worked with CLIAC to develop recommendations for good laboratory practices for ensuring the quality of genetic testing. A guidance document providing recommended good laboratory practices for molecular genetic testing for heritable diseases and conditions was published in June 2009 in the *Morbidity and Mortality Weekly Report* (MMWR) as a *Recommendations and Reports* (R&R) publication (Centers for Disease Control and Prevention 2009c). This document provides guidance for good laboratory practices for ensuring the quality of the total genetic testing process (including the preanalytic, analytic, and postanalytic phases of molecular genetic testing), the laboratory's responsibilities regarding authorized persons, confidentiality of patient information, personnel competency, factors to consider before introducing molecular genetic testing or offering new molecular genetic tests, and the quality management system approach in molecular genetic testing. Recommendations for good laboratory practices focusing on other areas of genetic testing, such as biochemical genetic testing, molecular cytogenetic testing, and somatic genetic testing, are planned in future guidance documents. CDC and CMS have also initiated efforts to revise and update the CLIA requirements for PT programs and laboratories, taking into consideration the need for improved performance evaluation for genetic testing. In addition, efforts have been made by professional societies, standard-setting organizations, and other advisory committees to develop voluntary quality standards to promote the quality of genetic testing and to improve the appropriate use of genetic tests in health care.

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Regulatory Issues in Clinical and Laboratory Genetics in Developing Countries; Examples from Latin America

Victor B. Penchaszadeh and Marcos José Burle de Aguiar

Key Points

- Latin America, a region of medium-to-low income countries with a population of 580 million, is experiencing a rise in non communicable diseases coexisting with nutritional and infectious diseases characteristic of poverty and underdevelopment.
- Congenital defects and genetic disorders have increased their share of morbidity and mortality over the last 2 decades of the twentieth century, and tertiary care-based genetic services have developed in academic centers and referral hospitals in the public system of big cities.
- Main problems in genetic services are underfunding, fragmentation of services and access inequities despite the existence of a sizable workforce of about 600 clinical geneticists in the region.
- Clinical and laboratory activities in medical genetics are poorly regulated and concern for the quality of services is not high among health authorities and health professionals. There are no systematic efforts for quality assessment of clinical genetic services, genetic counseling and genetic testing. The few existing regulations are difficult to enforce and most initiatives for quality assessment and improvement are voluntary.
- Quality assessment of genetic services is improving slowly, as ministries of health in some countries of the region are working with professional societies to develop new regulations and mechanisms to enforce them.

Keywords Public health genetics · Genetics services regulation · Genetic testing regulation · Quality improvement · Latin America

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Introduction

In the same way that developing countries vary widely in history, tradition, culture and economic resources, they do differ in their approach to regulation of, and quality assurance of health services in general and of genetic services in particular. Regulation and quality assurance of health services in developing countries are deficient because of several interdependent factors, including deficient governance of health systems, lack of tradition for regulation and quality assurance and lack of resources. This chapter focuses in Latin America, a region of the developing world that is distinct from other regions in culture, tradition and health issues, and with more similarities than differences in genetic services. This said, however, there still remains a wealth of heterogeneity in the approaches that different countries of the region have to regulation and quality assurance of genetic services. Given space limitations, a general overview on these issues is presented as they pertain generally to Latin America, with examples from Argentina, Brazil, Costa Rica and Cuba.

Demographic and Health Indicators

Latin America, with its population of 580 million people, is characterized by an extensive ethnic and cultural diversity, including Amerindians, African Americans, Europeans and Asians, with variable degrees of admixture. Most Latin American countries have medium-low annual incomes (regional average $5,000 per capita). Industrialization and urbanization is occurring at a fast pace, albeit with marked disparities between and within countries. The degree of socioeconomic inequality in the region is one of the highest in the world: in 2006 over half the population was living in poverty and 27.6% was earning less than $2 per day (World Bank 2006). Average life expectancy is 73.4 years, infant mortality rate 20.2 per 1,000 and maternal mortality 89.4 per 100,000 (with wide ranges according to country median income and social class) (PAHO 2007).

The prevalence of genetic diseases and congenital defects in Latin America is similar to other regions of the world (Penchaszadeh 2004), with hemoglobinopathies posing a significant public health burden in countries with a high proportion of African ancestry (Brazil and the Caribbean). Due to epidemiological transition, the main burden of disease is comprised by non communicable diseases with genetic contribution, particularly cardiovascular diseases, cancer, hypertension, diabetes and mental illness, while congenital anomalies are high in the rank of causes of infant mortality (PAHO 2007).

Health Systems

Most Latin American countries organized their health services in the mid-twentieth century under the responsibility of the state, with three main coexisting health subsystems. The *public system*, run directly by the state and funded from general

revenues, comprises national, provincial and municipal networks of health care services at primary, secondary and tertiary levels, with largely free access (albeit with a number of deficiencies that require out-of-pocket expenses by patients). Although in theory any citizen can access the public system, in practice it covers 50–60% of the population. A second subsystem is funded by employer-employee contributions, usually administered by the *social security system*, providing health services to employees and retired persons, either directly or through contracts with the private or the public sector, and covering about 35% of the population. The private sector caters to the 10% of the population with the highest income and is based in private-for profit-insurance. The average annual per capita health expenditure in Latin America in 2006 was only $262 (PAHO 2007), with wide variations by social class and marked inequities in distribution and favoring high technology medicine in tertiary centers rather than primary care-centered health care.

In Argentina (population 40 million, GNP per capita USD 5,150), the annual total expenditure in health is 7.8% of GNP (PAHO 2007). Twenty-two percent of the latter is spent by the public system to serve 48% of the population, mostly the poor and those without insurance; the social security system spends 29% of total health expenditures to serve 44.5% of the population, largely blue-collar workers, employees and retired persons, mostly contracting with the private sector. The for-profit private sector spends 49% of total health expenditures to serve only 7.5% of the population (the upper classes). Although the Argentine health system has an overall good level of spending and counts with good human and structural resources, it suffers from significant segmentation, fragmentation and inefficiency, leading to inequities in access and quality of care (PAHO 2007). The assessment of new health technologies regarding their analytical validity, risk for the public's health, and quality assessment issues is under the purview of the ANMAT (National Administration of Drugs, Food and Medical Technology), which has a limited mandate and very scarce resources (www.anmat.gov.ar).

In Brazil (population 200 million, GNP per capita USD 4,710), the 1988 Constitution defines health as every citizen's right and a duty of the State and the annual total health expenditure is 7.4% of GNP (PAHO 2007). The Brazilian Health System, called Single Health System (Sistema Único de Saúde – SUS), is run and financed by the state and comprises a regionalized and hierarchic network according to principles of decentralization, comprehensive health care and prevention, and community participation. (Marquez-de-Faria et al. 2004). Services that SUS cannot provide are contracted with the private sector, which is regulated by the National Agency of Supplementary Health (*Agência Nacional de Saúde Suplementar – ANS).* In turn, the National Agency for Sanitary Control (*Agência Nacional de Vigilância Sanitária* – ANVISA) is the agency responsible for regulating all the health care institutions in Brazil, be they hospitals, laboratories or private practices. This agency establishes general rules, criteria, parameters and methods for quality control and has local branches in states and cities called Sanitary Inspection (*Vigilância Sanitária)*, which are the local authorities responsible for executing the regulations and control determined at the national level. ANVISA accredits external quality control systems for health services, and gives incentives

to institutions that use such programs and encourages participation and certification by ISO (International Organization for Standardization). The National Certification Organization (*Organização Nacional de Acreditação* – ONA) is a national non-profit non-governmental organization, which promotes voluntary evaluation by medical institutions and issues certification of quality in health care.

Genetic Services

Health services for the diagnosis, treatment, follow-up and counseling of patients and families with, or at risk for genetic conditions, have had a fragmentary and uneven development in Latin America, being largely concentrated in urban and wealthy areas. The public sector continues to be the largest provider of genetic services in the region, but under-financing, poor planning and coordination, and lack of regulations and quality assurance have hindered their efficiency and quality of care. The social security system and the private sectors' main goal is cost containment and profit, at the expense of quality of care. Departments of health of the public sector at city, provincial, and national levels rarely have explicit policies or programs in genetic services, except for newborn screening (see below) which tend to be mandated by law (Penchaszadeh 2004). Exceptions to this state of affairs are offered by Cuba and Costa Rica, which have socialized health care systems of which genetic services are an integral component (Heredero-Baute 2004; de Cespedes et al. 2004).

Access to family planning services and contraception is limited and although induced abortion is largely illegal in almost all countries of the region, it is practiced extensively. Recently, national or local legislation in some countries began to allow pregnancy termination for severe fetal anomalies (Colombia, Argentina) and, exceptionally, outright elective abortion (Mexico City). In November 2008, the Uruguayan congress passed a law allowing elective abortion but was vetoed by the president.

Latin America counts with a skilled, well-trained and sizable workforce in clinical genetics. There are approximately 600 physicians trained as clinical geneticists, mostly in Argentina, Brazil, Cuba and Mexico. Virtually all countries count with national professional societies of human or medical genetics, which oversee the requirements to become a clinical geneticist, which usually involve completing a 3–4 year residence in clinical genetics or spending a variable amount of time in a genetic service after graduation. Most clinical geneticists work part-time in the public sector as well as in private practice. The specialty of clinical genetics (for physicians) has been recognized in several countries, usually involving the ministry of health and the professional associations of clinical geneticists. Genetic counseling is largely performed by clinical geneticists, as there are no training programs in genetic counseling for non-physicians.

In Argentina, the specialty of medical genetics is recognized by the ministry of health and the Argentine Society of Genetics has certified about 80 clinical geneticists who staff approximately 40 clinical genetics units throughout the country,

providing genetic consultations and counseling. Efficiency and quality of care are hindered by concentration in a few major cities, understaffing and long waiting lists in the public sector. Cytogenetic testing is available in about half of genetic units, while DNA testing is available for diagnosis only in a very small number of public hospitals and academic centers, only for a handful of conditions. A few private laboratories offer DNA tests on a fee-for-service basis and samples are frequently sent abroad for analysis. Pre-test informed consent is discretionary (Penchaszadeh 2008).

In Brazil, medical genetics developed in the 1970s in university hospitals, most of which are part of public universities and constitute the backbone of genetic services in the country. Clinical genetics was recognized as a medical specialty in 1983 by the Federal Council of Medicine, requiring the completion of an accredited residency or proving on-going practice in the specialty for a minimum of 6 years and passing an exam set by the Brazilian Society of Medical Genetics (*Sociedade Brasileira de Genética Médica – SBGM)*. There are currently 160 certified clinical geneticists, who work part time in university hospitals or in the SUS, as well as in private practice However, there are no positions of clinical geneticists in public non-university hospitals, and geneticists fill positions under other specialties (Marques-de-Faria et al. 2004; Gandelman-Horovitz et al. 2006). Recently, the Ministry of Health, in partnership with the Brazilian Society of Medical Genetics, developed an initiative to integrate genetic consultations, genetic counseling and genetic testing within the Unified Health System (www.sbgclin.org.br/infuteis.asp?=8 and www.conass.org.br).

The care for genetic conditions in most countries of the region is clearly deficient as the public sector tends to be under-funded and under-staffed and the health insurance plans (whether "social" or private) tend to reject claims for genetic diseases with the argument of "preexisting conditions". This unjust state of affairs is receding slowly, thanks to legislation in several countries that is forcing health insurance plans to cover genetic conditions. Notably, in 2008, the Brazilian government agency that regulates private health insurance (ANS) determined that they must pay for molecular tests for diagnosis of genetic diseases.

Newborn Screening

Newborn screening for PKU and congenital hypothyroidism (CH) began in several countries of the region in the 1980s and 1990s, usually mandated by law. Generally, the national ministries of health are in charge of implementation and regulation. However, in some countries, each state or province organizes newborn screening on its own, relying on several private and public labs, without much regulation or control of analytical validity, confirmation of results and follow-up of affected infants. Coverage has marked geographic and social class differentials.

In Argentina, newborn screening for PKU was mandated by law in 1986, congenital hypothyroidism (CH) was added in 1990 and cystic fibrosis (CF) in 1995. Tests are performed in several public and private laboratories, with little quality control.

By 2007, 74% of the provinces were testing for PKU and CH. Of those, 40% were also screening for CF and 10% for galactosemia. Population coverage correlates with resources, political will and degree of development and organization of health services. In one third of jurisdictions providing newborn screening, coverage was less than 50% with the highest coverage (close to 100%) occurring in the City of Buenos Aires (http://www.msal.gov.ar/htm/Site/promin/UCMISALUD/index.htm). Laboratories providing tests must submit to external quality control programs. In 2007 a new law was passed by Congress mandating newborn screening in all the territory of the country for: PKU, CH, CF, galactosemia, congenital adrenal hyperplasia, biotinidase deficiency, retinopathy of prematurity, Chagas disease and syphilis. The law states that the public sector and social security insurance must cover the expenses of screening and treatment for these disorders http://test.e-legis-ar.msal.gov.ar/leisref/public/showAct.php?id=6601.

In Brazil, the National Program for Neonatal Screening (*Programa Nacional de Triagem Neonatal* – PNTN) is a public program of the Ministry of Health through the 822/2001 law. It is currently active in all states and includes approximately 80% of liveborns in the country, that is about 2,500,000 newborns/year. Fourteen states screen for congenital hypothyroidism and PKU, ten states add sickle cell, and three states add sickle cell and cystic fibrosis. The Ministry of Health coordinates the PNTN and each state has its own administration, responsible for local execution. The program is regulated by rules elaborated by the Ministry of Health and state administrations submit monthly reports. Laboratories providing tests must submit to external quality control programs and many are linked to the Quality Control Programs at CDC in Atlanta, USA.

Cuba and Costa Rica have well established centralized newborn screening programs with quality control mandated as part of the regulations. Cuba screens for PKU, CH, galactosemia, biotinidase deficiency and congenital adrenal hyperplasia (CAH), with a locally developed methodology and a strong internal quality control system mandated by executive order of the ministry of health (Heredero-Baute 2004). Costa Rica started its newborn screening program in 1990 for PKU, CH and maple syrup disease (MSD), to which it added CAH and galactosemias in 2002. There is single central Laboratory affiliated to the Program of Quality Assurance of the CDC in Atlanta and recently tandem mass spectrometry was added, expanding the number of conditions tested (de Cespedes 2004).

Prenatal Genetics

Prenatal diagnosis of genetic diseases has developed primarily in the private sector, under a fee-for-service basis that only a small proportion of the population can afford. In contrast, there is very little prenatal diagnosis activities in the public and social security sectors. This is probably due to the fact that, with few exceptions, in most countries of Latin America there are no legal provisions for pregnancy termination for fetal reasons. While prenatal ultrasound is widely available, couples

with fetal abnormalities do not have the option of legal termination of pregnancy, except for anencephaly and other "non-viable" fetal defects in selected countries or cities (Colombia, Argentina, Cuba, Mexico City). In contrast, prenatal diagnosis is widely practiced in the private sector for middle-upper class couples, for whom legal restrictions don't seem to apply. Thus, what is one of the widest applications of genetics to health, is only available to the well off and completely unregulated by the state or by professional associations.

Regulations and Quality Assessment in Laboratory Genetics

Clinical laboratories are accredited by special agencies of the ministries of health. Accreditation requirements revolve around proper training of the director, physical space, equipment, handling of hazardous materials and safety matters. Except for laboratories that perform newborn screening, there are no official agencies that control or monitor the analytical validity of tests. Quality assessment of laboratory results rely mostly on the voluntary decision of the lab directors to participate in a quality control program, usually of an international agency.

Chromosome and DNA studies are performed in the laboratories of public hospitals, mostly teaching hospitals, or by private laboratories. Genetic tests are usually under the responsibility of professionals with a degree equivalent to a Ph.D., who perform cytogenetic, biochemical and molecular genetic testing, assisted by technical staff. DNA tests are performed locally only for a handful of conditions, the remainder are sent abroad on a fee-for-service basis. While these laboratories are certified by a state agency, participation in quality assessment programs is voluntary and regulation very lax. Further, while in theory most of these labs must have in-house and external quality control programs, there is little government oversight on these issues. Brazil probably is the country of the region where the oversight is more efficient. The main institutions that provide this control are the National Certification Organization (ONA), ISO, and the Clinical Laboratory Certification Program (PALC) of the Brazilian Society of Pathology and Laboratory Medicine. In addition, laboratories must submit to the ABNT guidelines (Brazilian Association for Technical Rules – *Associação Brasileira de Normas Técnicas).*

Concluding Remarks

In conclusion, there have been significant developments in the provision of clinical genetic services, genetic counseling and genetic testing in Latin America over the last 2 decades. However, a number of problems remain, namely, inequity in the access and coverage of available services, lax regulations on the quality of health services in general and of genetic services in particular, and deficient regulations of the performance of laboratories involved in genetic testing. It is expected that the

continued work of national societies of medical genetics in conjunction with state agencies will lead to an improvement in the access and quality of genetic services in the region.

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Assuring Quality When Establishing Medical Genetic Services in Middle- and Low-Income Nations

Arnold Christianson and Ron L. Zimmern

Key Points

- Quality assurance encompasses all actions taken to establish, protect, promote and improve the quality of health care.
- Medical genetics services aim to help people with a genetic disadvantage to live and reproduce as normally as possible.
- Health transition has resulted in many middle- and low-income nations developing medical genetic services appropriate to their needs and circumstances.
- Health needs assessment is an objective, epidemiological evidence-based approach to commissioning and planning health services to improve population health.
- To assure quality in establishing of medical genetic services, middle- and low-income nations should consider undertaking health needs assessments.

Keywords Medical genetic services · Congenital disorders · Middle- and low-income nations · Health needs assessment

Introduction

Quality assurance has been defined as all actions taken to establish, protect, promote and improve the quality of health care. Health care encompasses all services provided by health care practitioners to patients for diagnosis, treatment, including continuing, rehabilitation and palliative care, counselling, prevention and health

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education. Quality assurance of these health care services applies to two components, their infrastructure and resources, their structure, and the monitoring of their performance and readjustment to enable continuing maintenance and improvement of health care (Donnabedian 2003; Wright el al. 1998).

Medical genetics services aim to help people with a genetic disadvantage to live and reproduce as normally as possible. The definition embraces people with a congenital[1] or a complex disorder[2], and people at increased reproductive risk for having children with such disorders, including patients, parents, other relatives, and those identified by medical genetic screening. It establishes that patient care and prevention are not alternatives, but are complementary and inseparable aspects of the services for affected individuals, their families and communities (Christianson et al., 2006; Christianson and Modell 2004; WHO 1985).

Medical genetics services are a relatively recent addition to the range of services for health care. Achievements in cytogenetics, biochemical and molecular genetics stimulated Victor McKusick to propose in 1959 the birth of clinical genetics (McKusick 1975). Five years later the World Health Organisation (WHO) recognised the significance of human genetics for public health in industrialised nations. This arose because of health transition, the change in demography and pattern of diseases of a country or region, consequent on socio-economic, education, infrastructure and health care development (WHO 1964). By 1960 almost all of the industrialised nations had overcome their health problems from infectious diseases and malnutrition, resulting in congenital disorders achieving public health significance (Christianson and Modell 2004).

In industrialized countries medical genetic services were initially situated in specialties, including paediatrics, obstetrics, haematology, neurology. Then the need for specialised clinical, counselling and laboratory services prompted the development of medical genetic services, as recognised today, in tertiary, mainly academic, centres. The initial focus was congenital disorders and their development was driven largely by the translation of rapidly developing medical genetic knowledge and technology into health care (Christianson and Modell 2004). Complex disorders were incorporated with continuing health transition and impetus from the Human Genome Project. As processes for the maintenance and improvement of health care developed, like health needs assessment and quality assurance and management, these were also applied to medical genetic services.

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[1] A congenital disorder is defined as any abnormality of structure or function, including metabolism, which is present from birth. It is synonymous, and can be used interchangeably, with the term birth defect. Serious congenital disorders are those that are life threatening or have the potential to cause disability.[3]

[2] Complex disorders develop after birth, manifesting in childhood but mostly in mid and later life. They are complex because their aetiology is multifactorial, with the environmental component being mostly postnatal. By comparison with multifactorial congenital disorders (congenital malformations) they are clinically complex, being systemic and involving different organs and systems. They include a wide range of diseases including common disorders like cancer, diabetes, hypertension, mental disorders and stroke.

Medical genetics started in middle- and low-income nations[3] as academic research endeavours in the 1970s. A WHO Advisory Group, in 1985, recognised many middle-income nations were achieving significant health transition and would require medical genetic services in the foreseeable future. As with industrialised nations these services would initially be for the control[4] of congenital disorders (Christianson and Modell 2004; WHO 1985).

The Advisory Group recognised the medical genetic services model of industrialised counties was not suitable for middle-and low-income nations. The latter required that the general principles of the tertiary care-, basic science-, individual- and family-based practice of medical genetics of industrialised nations be adapted to the public health and primary health care based systems of middle- and low-income countries (WHO 1985).

Informed by the history and progress of industrialised countries a holistic approach, coordinating effective interventions in woman, reproductive, maternal, infant and child health for the care and prevention of common congenital disorders was developed between 1997 and 2007. This involved the integration between primary, secondary and tertiary health care of involved services including family planning/contraception, pre-conception care, obstetrics, paediatrics and medical genetic clinical and diagnostic laboratory services (Christianson et al., 2006; Alwan and Model 1997; WHO 1999).

However, to-date, only Cuba has initiated and developed universal, comprehensive medical genetic services (Heredero 1992). The I R Iran is progressing in achieving this for a selected group of disorders. Several other middle- income countries including Argentina, Brazil, Chile, China, Egypt, India, Jordan, Malaysia, Mexico, Oman, Philippines, Saudi Arabia, South Africa and Thailand have nascent medical genetic services they are expanding to meet their needs and circumstances.

Recent developments suggest that medical genetic services for the care and prevention of congenital disorders may soon be prioritised by the WHO as a means to assist governments meet their health Millennium Development Goals (WHO 2009). If this occurs it will promote the development of medical genetic services in many middle- and a few low-income nations. Previously documented literature can advise governments of the components their services should comprise and how to integrate them (Christianson et al., 2006; Christianson and Modell 2004; Alwan and Model 1997; WHO 1999; WHO 2000). To assure quality in the establishment of their medical genetic services they should consider undertaking Health Needs Assessment (HNA) (Christianson and Zimmern 2009).

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[3] Middle- and low-income nations is the term preferred for so-called "developing" nations. Middle- and low-income nations are defined by the World Bank.

[4] The WHO defines a control programme for congenital disorders as encompassing best possible care (diagnosis, treatment and genetic counselling with psychosocial support) available with prevention by community education, *preconception care*, medical genetic screening, genetic counselling, prenatal diagnosis and associated services. *Preconception care*, has recently been added to the original definition.

Health Needs Assessment for Medical Genetic Services in Middle-and Low-Income Nations

Health care systems continually face challenges from health transition, technological advances, public expectations and demands, resource limitations and the rising cost of health care. Health care needs assessment was introduced in the 1970s to plan, introduce and improve health care services. By the 1990s it had evolved beyond the medical model centred only on health care services into Health Needs Assessment (HNA), an objective epidemiological, qualitative and comparative evidence-based approach to commissioning and planning health services to improve population health (Wright el al. 1998; Smith and Haggard 1982; Stevens et al. 2004; NICE 2005).

A *need* is a population's ability to benefit from an intervention or service. It is a function of both the prevalence of a problem and the effectiveness of the intervention(s) or services- health care, social, legal and policy development- available for the health need. Problems and disorders with no effective remedies have no need, whilst low prevalence problems and disorders with available effective interventions are problems of lesser need.

Health care needs are those that benefit from health care interventions, whilst *health needs* additionally include changes to social & environmental factors that influence health, including socioeconomic status, education, pollution, diet, employment and behaviour. *Needs* must be distinguished from *demands,* which are what patients want and ask for (Wright el al. 1998; Stevens et al. 2004).

Only in the last decade has HNA for medical genetic services in industrialised nations been used. The Oregon's Strategic Plan for Genetics and Public Health is a good example (Silvey and Newell 2002). The formal use of HNA for developing services for the care and prevention of congenital disorders in middle- and low-income nations has not been documented. Possible barriers to its use include limited knowledge and understanding of the process involved in HNA; a assumed lack of epidemiological data; insufficient comprehension of the scope and availability of effective interventions for congenital disorders; and a perceived limitation of human and financial resources (Christianson and Zimmern 2009).

The main objective of HNA for congenital disorders in middle- and low-income countries would be to identify programmes, services, activities, opportunities and resources to plan and implement medical genetic services, and extend those available, for the benefit of countries' populations. This would optimise the infrastructure and resource allocation, the structure, of these services from their establishment or early stages of their development. In 2000 the WHO envisioned such an approach suggesting countries should form a multidisciplinary task team to undertake the work (WHO 2000). The approach to HNA delineated below could be used (Fig. 1) (Christianson and Zimmern 2009). The HNA comprises a set of steps that all need to be completed, though not necessarily in a linear manner.

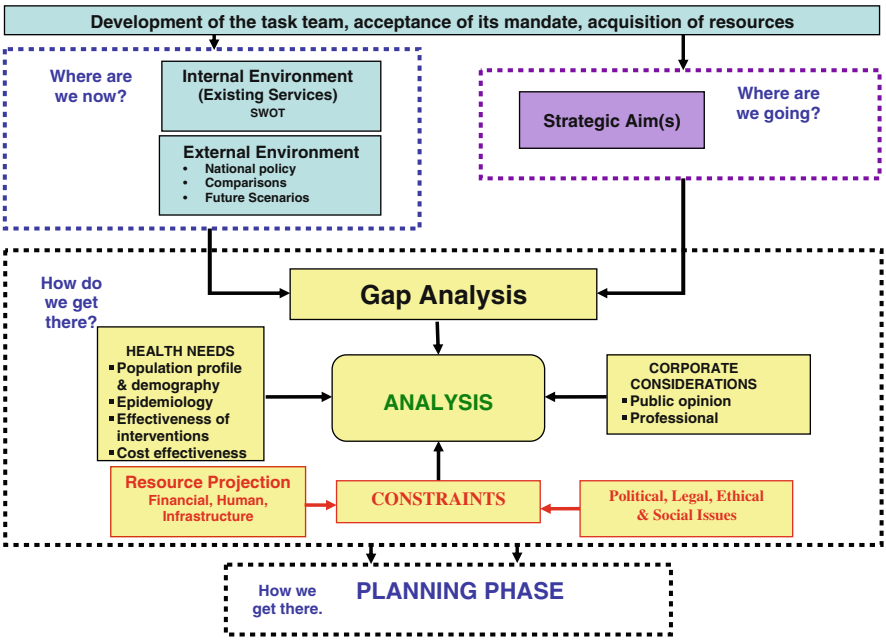

Fig. 1 Schematic approach to health needs assessment

1. Strategic aim(s)

The HNA task team should include appropriate professionals, including senior health managers, policy makers and planners, and public representatives. It could include the services of experts from other countries who have experience in either or both of HNA or developing medical genetic services in middle- and low-income nations. Its first undertaking would be to consider and clearly establish the strategic aim(s) of the HNA. They need to be developed with consideration of the country's internal and external environment.

2. The national internal and external environment

The internal environment is an objective profile of existing health, including health care, services. Baseline knowledge of these services details the current situation in order to consider what to develop, what to change to and how this can be achieved (Christianson and Zimmern 2009; Stevens and Gillam 1998).

Middle- and some low-income nations will have components of medical genetic services which with expansion or re-orientation can be mobilised for the universal care and prevention of common congenital disorders. These include, apart from clinical and laboratory diagnostic services, family planning, antenatal care, infant and child health (paediatrics), surgery, especially paediatric surgery, and neuro-developmental therapies.

The external environment is an appraisal of those issues that have moulded the internal environment and which might further impact it in the future (Christianson and Zimmern 2009).

National laws, policies and guidelines need to be carefully considered. They should be easily accessible in all countries (Christianson and Zimmern 2009; Stevens and Gillam 1998).

The "comparative approach" of comparing and contrasting services offered in different places clarifies what services are available and how they meet health, including health care needs, elsewhere. The differences that exist between them and local existing service levels helps identify deficiencies in provision of services (Stevens et al. 2004; Stevens and Gillam 1998). In industrialised countries the comparison is between well developed services to identify service "gaps". In developing medical genetic services in middle- and low-income nations the comparison would be between industrialised nation services and existing middle-income nation's services to evaluate what might be possible in local circumstances to reduce the obviously existing disparity. Comparisons of components of medical genetic services between middle- and low-income nations with similar levels of service delivery are to a limited extent also now possible (Christianson and Zimmern 2009).

Current medical genetic knowledge and technology can advise on the development of present health services. However, human and medical genetics is advancing rapidly and political, economic and social changes are constant features of middle- and low-income nations. These need to be understood to anticipate and incorporate the range of future scenarios that might affect the provision of medical genetic services for the care and prevention of congenital and, in time, complex disorders (Christianson and Zimmern 2009; Stevens and Gillam 1998).

Comparing the strategic aims and the internal and external environment facilitates an estimation of the "gap" between them, leading into the next phase of collection of information for analysis and prioritisation. This assists with plotting the way forward, i.e. "how do we get there (Christianson and Zimmern 2009)?"

3. Health needs

The health problems in a country or population need to be determined for HNA. This is accomplished by consideration of the population's profile, demography and the epidemiology of the disorders under consideration. Epidemiology includes incidence, prevalence, mortality and morbidity, including subcategories of severity, which may require different interventions or services. This quantifies the number of individuals that could benefit from an intervention or service. It is then necessary to establish the effectiveness[5] of available interventions or services for the disorders or health issues identified. If possible cost-effectiveness of interventions or services, the cost per unit benefit, should also be determined. The assessment of epidemiological, effectiveness and cost- effectiveness data then enables the assembly of the

[5] Effectiveness is the degree to which possible improvements in health are actually attained (Donnabedian 2003).

relative priorities of the health needs of the population (NICE 2005; Stevens and Gillam 1998).

Most middle- and low-income countries have limited empiric data on the epidemiology of congenital disorders, but that which is available should be used to assist them in determining their health need for congenital disorders. A lack or deficiency of epidemiological data need not delay HNA for the implementation of medical genetic services. Recently, modelled global congenital disorder birth prevalence data, presented on a country by country basis, has been published in the Modell Birth Defects Database. This can be used unit empiric data becomes available (Christianson et al., 2006; Christianson and Zimmern 2009).

A range of effective interventions and services for the care and prevention of common congenital disorders that are appropriate for middle- and low-income nations has been documented (Christianson et al., 2006). Many others that may not presently have priority are available for when their health need arises.

The cost of care for congenital disorders can be high and thus not considered cost-effective. This is especially true for treatment of chronic disorders that saves lives and prolongs it, the cost thus remaining through that prolong life. Considered nationally, the cumulative cost of care for such disorders increases rapidly year on year as more people with the disorder are born and live. In circumstances of limited resources this can affect the sustainability of the care service. To ensure sustainability it is necessary to successfully implement comprehensive prevention services. This is in line with the aims of medical genetic services in which patient care and prevention are not alternatives, but are complementary and inseparable aspects of the service. Combined, effective care and prevention for a particular disorder can be cost-effective (Christianson et al., 2006; Christianson and Modell 2004; WHO, 1985).

4. Professional and public opinion

The structured collection of knowledge and opinions of stakeholders including health professionals (doctors, nurses, managers, policy makers, planners, service providers, experts) and the public (patients, their families, the public, politicians and the press) is important to augment the objective assessment of existing services. Called the “corporative approach”, it can access the knowledge and experience of participating individuals that would otherwise be overlooked. The comparative approach is subjective and open to personal, political and financial agendas but is essential to democratise the process to justify decisions taken (Stevens et al. 2004; NICE 2005; Stevens and Gillam 1998).

Professional opinion needs to be obtained from two groups, medical and paramedical professionals and senior health policy makers, planners and managers. The latter are necessary as they will be able to assess what actually is possible in the health care system and be responsible for implementing what is finally planned. To ignore them is to invite failure (NICE 2005; Stevens and Gillam 1998).

Public opinion should include consumers and the community at large. Consumers can be accessed through patient/parent support groups, if these are available and user

consultation panels. The community can be reached with a range of tools including citizen's juries, focus groups, questionnaire surveys and particularly in middle- and low-income nations, community appraisals (NICE 2005; Stevens and Gillam 1998; Jordan et al. 1998).

5. Constraints

Proposed new health services, or changes to the current services, require resources, human, infrastructural and financial, to ensure they are possible and sustainable. Those tasked with the work will also require training appropriate to the work expected of them. These resources, in conjunction with other issues, political, legal, ethical, social and possibly others, raised by the HNA process may comprise constraints that require careful consideration before analysis.

6. Design

The information gathered can now be analysed to prioritise those disorders and factors that impact health and the effective, and if possible cost-effective, interventions and services available that will assure health benefit. Then a rational plan with a clear set of objectives and interventions and services to achieve these can be formulated to accomplish the project's strategic aim(s). This includes an audit processes to evaluate and monitor both the ongoing progress and the outcome of the HNA (Wright el al. 1998; Smith and Haggard 1982; NICE 2005; Stevens and Gillam 1998).

Conclusion

Middle-and low-income nations face numerous challenges and barriers when developing medical genetic services. The experience of developing these services in industrialised nations provides a template that can be adapted by middle- and low-income nations to help them accomplish their purpose efficiently and expeditiously. HNA is part of the template and its use can assist them establish well organised and structured medical genetic services that are appropriate to their needs and resources.

Successful establishment of a medical genetic service using HNA as described above, should not be seen as an endpoint, but rather the first step in the continuing development, maintenance and improvement of these services. In this HNA and quality assurance would have overlapping goals. HNA is about the planning of effective health services and interventions, that are measured by their effectiveness or the extent to which meet their objectives or purposes. Quality assurance is about setting standards for those services and interventions, and is measured by the extent to which they meet those standards. Both call for an on-going cycle of structural and performance monitoring and re-evaluation leading to corrective action (Donnabedian 2003; Wright el al. 1998). In this manner the quality of the services is improved and maintained ensuring better population health.

For middle- and low-income nations in the nascent phase of the establishment of their medical genetic services HNA could be staring point, with a quality assurance in the objectives and programmes to achieve this included in the planning phase. This would facilitate the development of medical genetic services appropriate to their needs and circumstance, assuring quality from their inception.

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Clinical Validity and Utility of Genetic Testing in Heritable Disorders

Poupak Javaher and Jörg Schmidtke

Key Points

- Many genetic tests are not sufficiently evaluated because of limited knowledge and resources.
- The development of standards and guidelines for analytic and clinical validity and clinical utility of genetic tests is thus still in its infancy.
- It will not be possible to achieve universal or comprehensive consensus on such standards, but rather only in a general form.
- It is foreseeable that evaluation standards for more common diseases will be easier to develop than for very rare disorders.

Keywords Genetic testing · Analytical validity · Clinical validity · Clinical utility

Test Definitions and Applications

The term "genetic tests" refers here to quantitative and qualitative analyses of human genetic material with the purpose of diagnosing hereditary (Mendelian) diseases or specifying the risk of such a disease occurring. For a more detailed discussion of the definition of "genetic tests", see Chapter 18 "The Use of Principles in Allocating Scarce Health Care Resources for Genetic Tests".

Genetic tests can be useful in the following contexts and the evaluation of genetic tests must take account of the objectives which apply in each case.

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- *Diagnostic tests:* Diagnosing or ruling out a suspected disease in a symptomatic person
- *Predictive tests:* Risk assessment in asymptomatic individuals (as a rule from families known to be affected by a disease)
- *Preimplantation and prenatal tests:* Diagnosing or ruling out a genotype or a disease in an embryo or foetus
- *Carrier test:* Identification of heterozygous carriers of autosomal- or X-linked recessively inherited diseases
- *Screening tests:* Systematic testing of individuals in the general population or population groups for the presence or absence of disease-relevant mutations
- *Pharmacogenetic tests:* Tests for genetic differences in response to drugs (dose-dependency, side-effects)

Evaluation of Genetic Tests

An evaluation of genetic tests should examine both the characteristics of the tests themselves and their efficacy in clinical contexts. The validity (efficacy) of genetic tests is determined using the parameters of sensitivity, specificity, positive predictive value and negative predictive value.

Analytic Validity

The "analytic validity" of a genetic test measures its ability to determine a specific genotype exactly and reliably (Kroese et al. 2004). It is discussed in chapters "Quality in Cytogenetics", "Fluorescence In Situ Hybridization (FISH) – Quality Issues in Molecular Cytogenetics", "Quality Issues in Biochemical Genetic Testing", "Emerging Technologies, Need for Quality Assessment."

Clinical Validity

The "clinical validity" of genetic tests is a measure of the accuracy (sensitivity, specificity and predictive values) with which a test identifies or predicts a clinical state (Kroese et al. 2004).

The key to assessing the clinical validity of a genetic test is definition of the phenotype with regard to specified criteria (e.g., use of agreed symptom catalogues or biochemical markers). The aim of the tests is to identify those individuals who have or will develop the defined phenotype (Sanderson et al. 2005). The rate of false positive and false negative results can be assessed when evaluating a test comparing the results in individuals who have a known disease with individuals who do not. Determining the positive predictive value and the negative predictive value in the case of rare diseases can pose a special challenge because the number of healthy

controls required in order to determine the true prevalence (a priori probability) may be very large.

Clinical Utility

The term "clinical utility" refers to the ability of a genetic test to provide information that is significant in the clinical context (Kroese et al. 2004).

Although clinical utility is the most important aspect for the evaluation of any medical test, including genetic tests, it is difficult to define. Relevant questions are:

- Will the test result change the clinical management?
- Will the test subjects receive a "net gain" from the test?
- Will the cost-benefit ratio be acceptable?

If the answer to these questions is "No", then even a test with the highest analytic and clinical validity will not survive in practice.

On the other hand, tests with low analytic and clinical sensitivity or predictive power can be of considerable clinical utility for the management of patients or family planning – provided that limitations of informative value are explicitly described and explained. It is therefore important that the requirements to be met by a test in terms of clinical and analytic validity are considered in the overall clinical and social context in which the test is to be applied. As described below, analysis of the clinical utility of a test comprises not only clinical aspects but also economic and psychological factors.

Dimensions of clinical utility of genetic tests (Sanderson et al. 2005):

1. Evidence of efficacy and effectiveness (efficacy refers to controlled settings; effectiveness refers to true settings)
   - Improvement of the outcome: positive health effect in the totality of persons eligible for the test,
   - The test should be regarded as part of a complex intervention in patient care, and not be evaluated in isolation
2. Economy
   - Cost-effectiveness analysis (comparison of costs and health effects in natural units so as to estimate the value of the intervention)
   - Cost-benefit analysis (analysis of expenditure in relation to the possible medical benefit in monetary units)
3. Psychosocial consequences
   - Consequences for individuals, including perceived personal empowerment
   - Consequences for families
   - Consequences for society

Validity and Utility of Genetic Tests in Clinical Settings

Decisions for or against performing a genetic test depend to a high degree on the clinical context and frequently require examination of the test objective and the a priori probability of a positive test result. The latter is always dependent on the familial and demographic context in which the test person finds himself/herself.

The clinical validity of genetic tests can be very variable. In particular, the test sensitivity can be influenced by allelic and/or locus heterogeneity. The positive predictive value depends to a large degree on the a priori probability of a positive result (age dependency, familial history, ethnicity).

The clinical utility is closely linked to the aim of the test in so far as the extent of its usefulness is determined by the extent to which its aim is fulfilled. A test may be very useful with regard to a specific aim, e.g., diagnosis, but of little use with regard to another aim, e.g., population screening. The a priori probability that is used to decide for or against conducting a test depends greatly on the context; e.g., for Down syndrome a 0.5% risk is almost universally applied as the lower limit for justifying invasive prenatal diagnostics, while a prior probability of 8–20% e.g. for breast cancer is regarded as the lower limit for searching for a predisposing mutation in at-risk persons (NHS guideline, familial breast cancer).

Diagnostic Tests

A "diagnostic test" is always performed on a patient with manifest clinical symptoms with a possibly genetic cause. In this case, the test serves to rule out or confirm a certain clinical diagnosis or it helps to differentiate between two or more clinical alternatives ("differential diagnosis"). Sometimes a diagnostic test is merely used to rule out a certain, rather rare manifestation in a relatively large group of diseases or disabilities because such elimination is of particularly interest in the person's family (e.g., in the case of fragile X syndrome in children with delayed development).

A correct diagnosis based on a genetic test can:

- spare the patient other diagnostic measures which may entail risks and/or costs;
- guide clinical management and therapy;
- have a significant psychological effect, even in the absence of a specific therapy;
- also be helpful for life planning and family planning beyond a directly medical context;
- avoid "medical odysseys".

Predictive Tests in Asymptomatic Persons

Predictive genetic tests investigate whether people who present no manifest clinical symptoms are carrying one (or more) gene variants associated with a certain disease. Such tests are occasionally offered as part of population screening, but are generally reserved for people with a specific positive family history. Predictive genetic tests

increase the probability of a correct prognosis of whether a healthy person with a hereditary disease in the family will develop the condition or not. The availability of genetic tests which predict a future disease permit interventions to alleviate, cure and/or prevent the illness in persons who are at increased risk. Even if such interventions do not (yet) exist ("therapeutic gap"), predictive tests can still be useful in a variety of ways, including the possibility of informed family planning and life planning, reducing uncertainty and – in the case of people with negative test results – alleviation of worry and avoidance of otherwise indicated medical interventions (regular clinical monitoring or invasive preventive measures). A balance between benefits and risks of tests with regard to positive and negative consequences must be evaluated on a case-by-case basis so that every test subject can make an informed personal decision (Kroese et al. 2004).

The utility of predictive genetic tests is dependent on the severity of the disorder, the predictive values, the available options for risk reduction, the individual's own previous experience of the condition and the information requirement of other family members. Thus the utility of a predictive genetic test is rarely static; rather it changes with time as knowledge grows, new prevention strategies are developed and personal and family circumstances change.

Predictive genetic tests for asymptomatic persons can essentially be applied individually or collectively. An individual approach is the test for a specific person with a high a priori risk of a specific disease in the family history. A collective approach can either be diversified (e.g., newborn screening for metabolic diseases) or can refer to a selected sub-group with risk factors dependent on origin. An intermediate approach – not uncontroversial in terms of social ethics – is "cascade screening", in which relatives of the person affected are actively approached concerning their genetic risks.

Genetic tests for healthy people at high familial risk are offered in the case of late-manifesting illnesses, especially familial cancer (including breast, colorectal and thyroid cancers) and neurodegenerative diseases (Huntington's disease, spinocerebellar ataxia). If informed consent cannot be obtained from children, predictive genetic tests should only be carried out if there is a proven clinical utility in infancy Ibarreta et al. 2004. The predictive value of genetic tests is generally high if all the persons with a particular phenotype carry the same mutation (genetic homogeneity) or if – in the case of allelic and/or locus heterogeneity – the relevant disease-correlated mutation is known from studies of affected relatives. If it is possible to prevent an illness (e.g., selective thyroidectomy in the asymptomatic phase of thyroid cancer) reliably, the utility of a positive test result is obvious. If the benefit of early disease detection is proven, positively identified genetic carriers can undergo particularly closely meshed clinical monitoring. Even if no clinical interventions are available, a minority of at-risk persons opt for predictive tests; the resulting psychological reactions range from gained certainty (even if the test is positive) through to feelings of guilt (if the test result is negative) (Skirton 2001).

Predictive (presymptomatic) tests that are offered to the public should generally be implemented in accordance with the WHO guidelines (American College of Medical Genetics).

Genetic Tests as an Aid to Reproductive Decision-Making

Tests for Asymptomatic Carrier Status

A "carrier test" looks for gene mutations that are associated with recessively inheritable disorders. Here it is not the person tested who is clinically at risk, but rather their offspring. The test result can therefore be significant for reproductive decision-making by the person tested. Carrier tests on children are generally refused and should be postponed to an age at which informed consent can be given (Ibarreta et al. 2004).

Carrier tests for autosomal recessive diseases are usually offered to people with an increased a priori carrier risk due to their family history or ethnicity. The latter pertains, for example, to the populations in the Mediterranean countries at increased risk for ß-thalassaemia, or Ashkenazi Jews at risk for Tay-Sachs disease. Such tests mostly take the form of formal programmes within the social health care system. The high level of acceptance of such tests has produced a major decrease in the prevalence of these disorders in these populations. In the USA, all pregnant women are offered carrier tests for cystic fibrosis.

If a carrier test for a recessive disease is requested by persons with regard to reproductive decision-making a dilemma my arise: if assistance with family planning is regarded as a private matter not covered by health insurance, yet a prenatal test for the same disease during pregnancy is treated as a "medical act" paid for by the health insurer. This dilemma is linked with the moral debate surrounding "tentative pregnancy" (i.e., enabling parents to terminate a pregnancy if tests indicate that the foetus is not healthy). Most clinical geneticists would argue that genetic tests as an aid to reproductive decision-making before pregnancy are a "medical act" with clinical utility.

Prenatal Diagnosis

Prenatal genetic tests are intended to clarify whether a foetus carries any disease-related mutations. Prenatal tests for chromosomal abnormalities are usually conducted on account of a known increased genetic risk, e.g., due to family history (chromosomal translocations), on account of abnormal ultrasound findings and/or biochemical parameters in the maternal serum as well as advanced maternal age (increased risk of trisomy 21 and other numerical chromosomal aberrations). Prenatal tests for monogenic disorders are less frequently applied. As a rule, they are only requested if the parents are (possible) mutation carriers (e.g., if a child of these parents is already affected or if other increased familial risks exist).

Prenatal tests can be either diagnostic or predictive/prognostic. A range of aspects of test evaluation have therefore been discussed in previous sections of this chapter. In the prenatal context there is the additional challenge of giving due regard to the interests of both the developing child and the pregnant mother. These interests may – depending on medical and psychological circumstances, and also social and moral values and standards – coincide or conflict; and the clinical utility of these tests can thus be judged in very different ways.

Prenatal diagnosis can contribute to specific therapeutic interventions during pregnancy and/or medical management of the newborn baby shortly after birth. Some of these measures are of proven benefit for the child (e.g., corticoid therapy for the pregnant mother to prevent masculinisation of the female foetus in cases of adrenogenital syndrome). Conversely, prognosis of a serious disorder in the child gives rise to the option of abortion. Although this prevents the birth of a child with a certain disease, it is not appropriate to talk of disease prevention in this context. If – as in many countries, including Germany – in such situations, abortion can be medically indicated in the interest of the life and well-being of the mother, a justifiable clinical utility must also be ascribed to prenatal diagnostics and its consequences.

Summary of Some Systematic Evaluation Processes of Clinical Validity und Clinical Utility of Genetic Tests

Centres for Disease Control and Prevention (CDC), ACCE model

While criteria for assessing clinical validity and utility of genetic testing had already been developed by the US Task Force on Genetic Testing in 1997 (Holtzman and Watson 1997), the world's first systematic approach to a model process for evaluating genetic tests was developed in the ACCE project (*A*nalytic validity, *Clinical* validity, *Clinical* utility and *E*thical, Legal and Social Issues), which was initiated in collaboration with the CDC (Centres for Disease Control and Prevention, Office of Genomics and Disease Prevention) and the Foundation of Blood Research (ACCE). This project comprises the collection, evaluation, interpretation and processing of data concerning (essentially) DNA-based tests for hereditary diseases. The objective of the project consisted in providing current and reliable data in a meaningful form for health policy decision-making. An important by-product of this process was the identification of gaps in knowledge.

The ACCE wheel (Fig. 1) shows the relationship between the four components of the evaluation and the respective elements of these components. In the centre are the evaluated disorders themselves, taking into account the settings in which the test takes place. With a total of 44 targeted questions, all the components and elements of the ACCE wheel are systematically measured (ACCE).

The ACCE project formed the basis of all the systematic evaluation processes of genetic tests also in the UK (UKGTN) and Germany (GfH), among other countries.

EGAPP, Centres for Disease Control and Prevention (CDC)

EGAPP (Evaluation of Genomic Applications in Practice and Prevention) is a further development of the ACCE project in the CDC, USA. The objective of EGAPP consists in supporting the first phases of a coordinated process for evaluating genetic tests that are at the threshold between research and clinical practice. The EGAPP project incorporates existing specialised guidelines and recommendations.

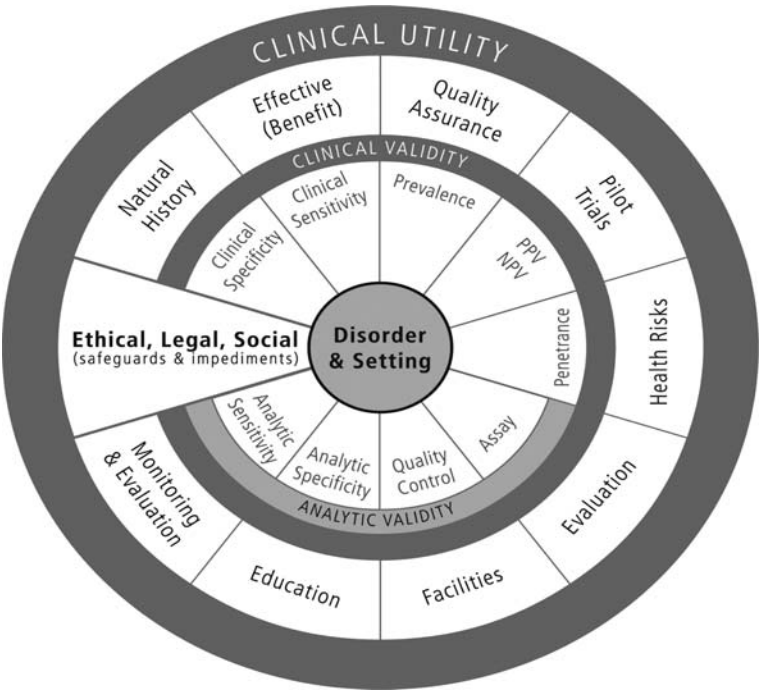

Fig. 1 The ACCE evaluation process for genetic tests. Source: Centres for Disease Control and Prevention (CDC); PPV: Positive predictive value; NPV: Negative predictive value; For further explanations see text (p. #)

The EGAPP project integrates not only ACCE but also the experience gained from other processes for evaluating and assessing medical tests (e.g., Agency for Healthcare Research and Quality/US Preventive Services Task Force, CDC's Task Force on Community Preventive Services) and incorporates HTA (health technology assessment) processes in order to establish a systematic mechanism for the evaluation of genomic applications in American health care practice.

The Eurogentest Gene Cards Initiative

Based on its own recommendations (Javaher et al. 2008) and the German Society of Human Genetics initiative (GfH), Eurogentest, a EU-funded Network of Excellence, has begun to issue disease-specific guidelines ("gene cards") for assessing clinical validity and utility of genetic tests (EuroGentest). The expectation is that such guidelines can be established for the more frequent hereditary conditions which also form the bulk of the workload of genetic testing services. For the rarer conditions, Eurogentest suggests to follow a simplified spreadsheet, which nevertheless addresses the key components of the ACCE framework (Fig. 2).

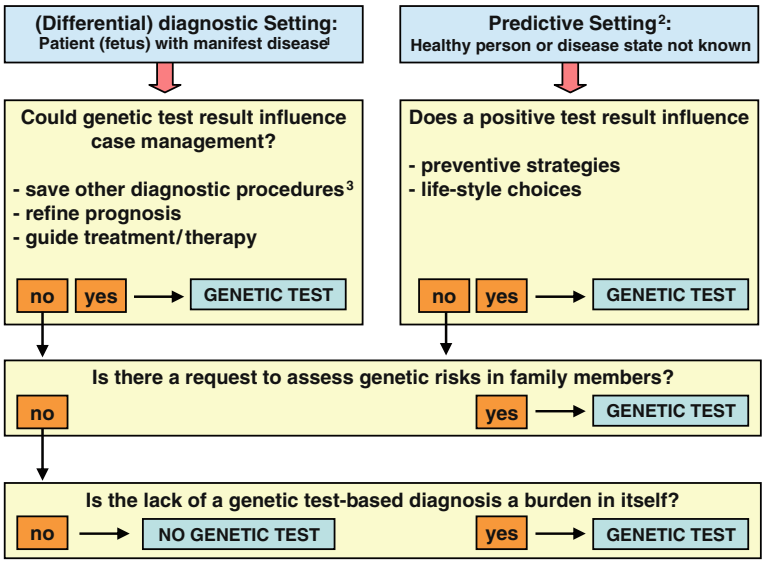

Fig. 2 Assessing clinical utility of genetic testing in very rare disorders. [1]It is assumed here that the patient has been clinically examined. [2]The predictive prenatal setting is included. [3]Includes particularly procedures which are encumbering or hazardous to the patient (from Javaher et al. 2008; reprinted with permission from S. Karger AG, Basel, Swizerland)

Outlook

Limited knowledge and technical resources restrict the extent to which evaluation of many genetic tests is possible at present. In particular, assessing clinical validity is complicated by the fact that for many disorders the mutation spectrum is only incompletely understood. The need to rapidly translate new knowledge and technologies into clinical practice has to be weighed against the time-consuming processes involved in test evaluation. While the range of diseases that can be covered by genetic tests is constantly growing, the number of samples per disease that can be evaluated is extremely small in most cases. That should not, however, be a reason for bypassing an evaluation process as such. Even incomplete evaluations which do not consider all aspects as desired contribute to quality assurance (Ibarreta et al. 2004).

Although it is increasingly recognised that analytic and clinical validity and clinical utility are important criteria for deciding whether to employ a genetic test, the development of standards and guidelines in science and in practice is still in its infancy and achieving consensus concerning appropriate procedures and standards is a gradual process. It is to be expected that, depending on the type of disease, clinical setting, prevalence of the disease and financial limitations, and in view of ethical, legal and social considerations, it will not be possible to achieve either universal or comprehensive consensus on such standards, but rather only in a general

form. It is foreseeable that evaluation standards for more common diseases will be easier to develop than for very rare disorders; for the former, the evidence base will be larger; for the latter the scope of discretion will have to remain wider.

One of the unsolved, and possibly insoluble, problems is to define a risk level below which genetic tests (in a jointly financed health care system) cannot be defended. The particular difficulty is due to the fact that risks always have two components: probability of occurrence and severity of the event. Probabilities of occurrence can be defined with increasing precision as knowledge in the field of human genetics and epidemiology advances. Severities of diseases, on the other hand, will only ever be amenable to imperfect mapping. Another unsolved problem (possibly also insoluble) is the question of whether, and to what extent, the psychological and social dimensions of the heredity of a disorder should be considered when evaluating the utility of genetic tests.

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Clinical Validity and Utility of Genetic Testing in Common Multifactorial Diseases

Michael Krawczak

Key Points

- All commercial providers of genetic tests for common multifactorial diseases (CMD), and most, if not all, large scale genetic epidemiological projects on CMD, claim a potential diagnostic impact of the currently available information on the respective disease-gene association.
- A genetic susceptibility test for a CMD may be useful in a public health context, i.e. trigger one or more preventive measures at an economically sensible level, if the (relative) risk of a sufficiently frequent genotype is sufficiently high and if carriers of that risk genotype benefit enough from the available preventions.
- The relative risks of genetic susceptibility factors for CMD must be quantified in large studies before their clinical utility can be valuated. Currently, such information is either scanty or discouraging. The vast majority of known relative genetic risks for CMD are smaller than 1.5 and are therefore unlikely to trigger preventive measures.
- The most promising candidates for CMD causation are mildly deleterious mutations, which are inherently likely to occur at sub-polymorphic frequency owing to selection. These variants will therefore be inefficient to screen for at a population-wide level.
- Information about interaction between genetic risk factors for CMD is a prerequisite for risk profiling, i.e. the joint assessment of multiple risk factors at a time, to be appropriate and advantageous. Currently, however, such information is lacking for most if not all CMD for which genetic tests are being offered.

Keywords Genetic epidemiology · Risk profiling · Multifactorial diseases · Decision making · Predictive test

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Background

Over the last 10 years, genetic epidemiology has gone through a substantial change of paradigm. While the major achievements in this research area were made in the 1980s and 1990s, leading to the elucidation of the genetic basis of many rare monogenic diseases by means of family-based linkage studies, the focus is now on common multifactorial (so-called "complex") disorders (CMD). Most of the patient-based projects undertaken on CMD entail large-scale retrospective association analyses of unrelated cases and controls. Owing to the small impact that the genetic susceptibility variants for CMD are likely to have, and the large samples sizes required to detect them, significant progress regarding the detection and characterisation of complex genotype-phenotype relationships was soon realized to be possible only through comprehensive collaborative efforts. To a good part, this insight has been responsible for the establishment of consortia like the WTCCC (Wellcome Trust Case Control Consortium) in the UK, the GAIN (Genetic Association Information Network) in the US, and the NGFN (National Genome Research Network) in Germany, to name but a few.

While the major purpose of these and other research activities has been to gain a better insight into the molecular aetiology of the diseases in question, most projects nevertheless also claimed a potential diagnostic or preventive impact (see, for example, www.wtccc.org.uk, www.ngfn.de). Not surprisingly, the potential diagnostic utility of the genetic associations emerging for CMD has been emphasized most strongly by private companies who were trying to market genetic susceptibility tests for such diseases. For example, deCODE Diagnostics said on their website that "a better and more personalized understanding of risk" had become possible for CMD and that the available information would "empower individuals and their doctors to implement more rigorous and potentially more effective prevention strategies" to combat these diseases (www.decodediagnostics.com). Similarly, the US-based company 23andme has declared that they can use genetic association data from the scientific literature "to develop qualitative estimates and definite explanations of what they mean for you", i.e. the individual customer (www.23andme.com). The question arises however whether the currently available scientific evidence justifies such claims of diagnostic utility, and whether a use of research-based disease-gene associations for diagnostic purposes is indeed meaningful.

It must be pointed out of course that, in a free society, entrepreneurs are allowed to pursue their businesses, and consumers to spend their money, in any way they wish as long as they do not infringe upon other people's rights and dignity. Therefore, if attempts to judge the clinical validity and utility of genetic testing for CMD are to be viable, they are best confined to a public health perspective. In other words, if individual preferences are not an issue, a major concern still remains whether currently known genetic associations with CMD are strong and reliable enough for a society to invest resources into their diagnostic use.

Resource Allocation and Health-Related Needs

Resource allocation in public health systems must follow certain principles for it to be accountable and transparent. These principles, if sensibly defined, will be based upon the shared values and believes of a society. Nevertheless, while the dependency of priority settings upon the respective societal background may lead to subtle differences in the way public health resources are distributed in different countries, a common denominator in most instances is that resource allocation should be according to health-related needs. In the context of genetic tests, it may be argued that there is something like "a need to know", which reflects the widespread and often deeply held belief in genetic determinism. However, such a metaphysical definition of "need" appears problematic for public health purposes not the least because it would render inter-individual comparisons of needs very difficult. Thus, the Swedish National Centre of Priority Setting in Health Care (2008) recently emphasized that "a need as internal tension can not be applied to health services since, e.g., even unconscious people have needs". Instead, need is defined by the same group as "something instrumental or goal-related". For diagnostic genetic tests, this leads to the conclusion that they can only be of public health relevance if the test results potentially change the decision making of those involved, i.e. of the individual proband, their family, or the respective health care environment.

Clinical Validity and Utility: A Decision-Theoretical Framework

Adoption of an instrumental view of "need" allows the public health relevance of a genetic test for a CMD to be assessed in a decision-theoretical framework (Fig. 1). Decision making in the face of uncertainty can be formalized as a choice between several possible actions A_i, each of which can lead to one of several outcomes O_j. For the probability $r_{i,j}$ with which A_i leads to O_j, we will henceforth use the term "risk" despite the fact that some of the O_j may in fact be favourable. Every individual is then regarded as having their own decision function Δ by which they choose an

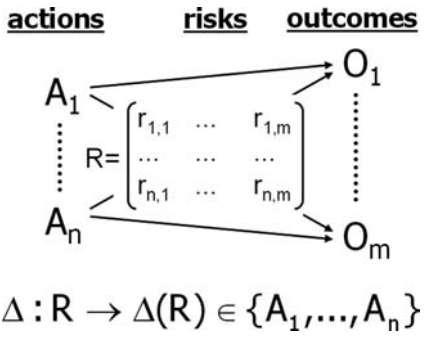

Fig. 1 A decision-theoretical framework for genetic test evaluation

action depending upon the actual risk matrix R. Under this premise, a diagnostic test can only be of public health relevance if the decision making before the test and after the test is considerably different, i.e. if

$$\Delta(R_{\text{pre-test}}) \neq \Delta(R_{\text{post-test}}) \quad (1)$$

for a sufficiently large number of individuals.

In the context of genetic testing, these considerations can be simplified to the choice between two actions that can loosely be termed "prevention" and "no prevention", each of which can result either in the development or the non-appearance of disease. The standard scenario will be that a large number of people choose not to prevent before the test, but that the risk difference $r_{no,g}$-$r_{yes,g}$ of no prevention associated with a particularly susceptibility genotype, g, is substantially higher than the average risk difference r_{no}-r_{yes} in the population, i.e.

$$r_{no,g} - r_{yes,g} \gg r_{no} - r_{yes}. \quad (2)$$

A second possible scenario is that most people choose to prevent before the test, but that there is a protective genotype for which

$$r_{no,g} - r_{yes,g} \ll r_{no} - r_{yes} \quad (3)$$

so that many carriers knowing about their protective genotype may avoid prevention.

Scenario 2 is comparatively rare and depends upon the presence of a strong gene-environment interaction. Nevertheless, an example is provided by the association between serum HDL level and a diallelic promoter polymorphism (with alleles A and G) in the *APOE1* gene. The inconsistent findings published on the respective genotype-phenotype relationship led Ordovas et al. (2002) to adjust their own analysis for polyunsaturated fatty acid (PUFA) intake (Fig. 2). It turned out that the A allele of the polymorphism lowers HDL only in individuals with a PUFA intake of 4% or less. In other people, the A allele has the opposite effect and increases HDL. These results can also be interpreted as signifying that a reduction in PUFA intake increases HDL only in GG homozygotes. In carriers of the A allele, which make up approximately 30% of the white US American population, reduction of PUFA decreases HDL. Thus, if HDL reduction were the only effect of increased PUFA intake that matters, then the current advice of reducing PUFA, which is sensible for the majority of people, would be counterproductive in those with a GA or AA genotype.

In the vast majority of cases, individuals taking a genetic test for a CMD will face scenario 1 because known CMD-specific gene-environment interactions are rare. It can be shown mathematically[1] that scenario 1 can only arise under two conditions:

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[1] Since r_{no}-$r_{yes} = f \cdot (r_{no,g}$-$r_{yes,g}) + (1\text{-}f) \cdot (r_{no,ng}$-$r_{yes,ng})$, where f denotes the population frequency of susceptibility genotype g, formula 2 can only apply if (1) f is not too large and (2) $r_{no,g}$-$r_{yes,g} >> r_{no,ng}$-$r_{yes,ng}$. The second condition can be rearranged to read $r_{no,g}$-$r_{no,ng} >> r_{yes,g}$-$r_{yes,ng}$, which implies that $r_{no,g}$-$r_{no,ng}$, but not $r_{yes,g}$-$r_{yes,ng}$, must be substantially larger than zero.

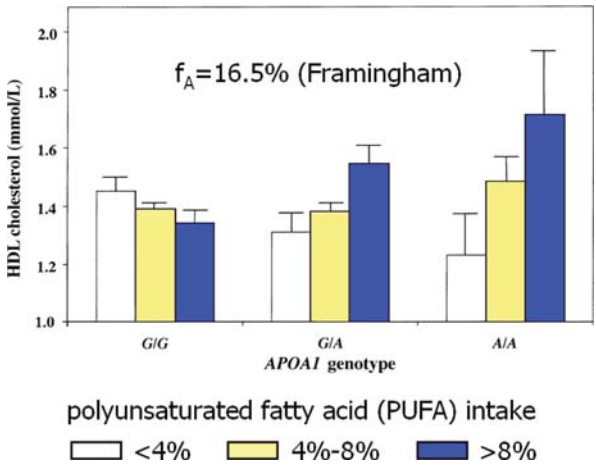

Fig. 2 Relationship between serum HDL, PUFA intake and APOA1 genotype. After Ordovas et al. (2002) © 2002 American Society for Clinical Nutrition

- among those who do not prevent, the (absolute) disease risk of carriers is substantially larger than that of non-carriers (i.e., $r_{no,g} >> r_{no,ng}$), which is equivalent to a large relative genotypic risk in this group (i.e., $r_{no,g}/r_{no,ng} >> 1$),
- among those who do choose to prevent, the (absolute) disease risk of non-carriers is not substantially lower than that of carriers (i.e., $r_{yes,g}$-$r_{yes,ng}$ is either small and positive, or negative), which means that carriers benefit to a large extend from the intervention.

Similar results are obtained when formula 2 is formulated in terms of relative risks instead of risk differences. The two conditions listed above are equivalent to requiring a high predictive value, i.e. clinical validity, and a sufficient benefit, i.e. clinical utility, of the genetic test in question. Not surprisingly, formal decision-theoretical considerations therefore lead to the same quality criteria for genetic tests as laid down in the ACCE framework, devised by the Centres for Disease Control and Prevention (Zimmern and Kroese 2007). This notwithstanding, it has to be emphasised that, while any coincidence of high clinical validity and utility would be sufficient for formula 2 to apply, the only necessary condition is that the two risk differences $r_{no,g}$-$r_{no,ng}$ and $r_{yes,g}$-$r_{yes,ng}$ differ considerably.

Clinical Validity of Currently Offered Genetic Tests for CMD

If, under the supposition of rational decision-making, a genetic test is required to have clinical validity (and utility) before it can attain public health relevance, the question arises whether clinical validity in the form of sufficiently high genotypic relative risks has been demonstrated for currently known CMD susceptibility

factors. A recent survey by Janssens et al. (2008) of meta-analyses that addressed this issue comes to the conclusion that the answer is obviously "No". These authors scrutinized 260 meta-analyses of polymorphisms in 56 genes which are associated with one or more CMD, and for which genetic tests are currently being offered by private companies. All significant odds ratios were found to range between 0.45 and 0.88 for protective alleles or genotypes, and from 1.04 to 1.50 for risk alleles or genotypes. The only exceptions were the risk for systemic lupus erythematosus associated with a promoter polymorphism of the *TNF* gene (OR 2.1) and the risk for Alzheimer disease associated with Apo E4 (OR 3.2).

These results sharply contrast with the hopes and expectations expressed by the proponents of large-scale genetic epidemiological studies and particularly by private companies who are marketing genetic susceptibility tests for CMD. One of the reasons why their initial claims may not have stood the test of time is the general experience in medical research that initial reports of given effects, which are often based upon comparatively small sample sizes, are overly optimistic owing to publication bias and chance effects. This phenomenon has been highlighted several times (see, for example, Ioannidis 2005) and particularly so in the context of genetic association studies. Thus, in an analysis of 370 studies addressing 36 genetic associations, Ioannidis et al. (2001) observed significant inter-study heterogeneity and a poor correlation between the results of the first report of an association and the results of subsequent research on it. In virtually all instances, the first study suggested a stronger susceptibility than was found in subsequent studies (Fig. 3). This effect is also exemplified by a recent study by Carlsten et al. (2008) of the glutathione S transferase M1 (*GSTM1*) "null" genotype and lung cancer. The underlying deletion polymorphism, homozygotes of which have no enzymatic

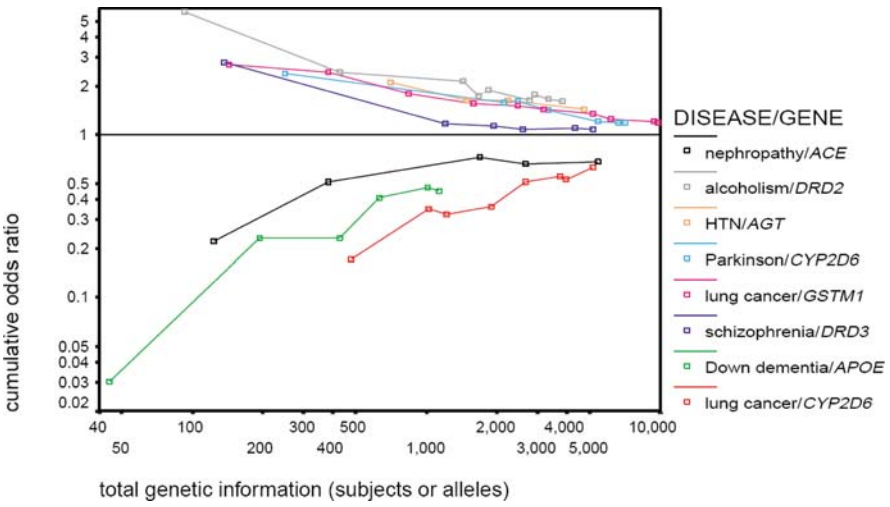

Fig. 3 Evolution of effect size estimates in genetic association studies of CMD. From Ioannidis et al. (2001) ©2001 Nature Publishing Group

function at all, has been examined extensively in epidemiological studies of lung cancer. Originally, odds ratios were estimated to be as high as 1.5, on average, and larger than 2.0 for squamous cell carcinoma. The meta-analysis by Carlsten et al. (2008) shows, however, that the true odds ratios are likely to be in the range of 1.1–1.2, depending on ethnicity, and that the association with lung cancer becomes completely insignificant when only the large studies (>500 cases) are considered.

Low Clinical Validity of CDM Genetic Tests: A Possible Explanation

Why are the relative risks of common susceptibility variants for CMD so low? Based upon a comparison between the rate of synonymous and non-synonymous substitutions among single base-pair changes in gene coding regions, Kryokov et al. (2007) came to the conclusion that the fraction of deleterious amino acid changes among common SNPs (minor allele frequency >25%) is very small. In sharp contrast, rare missense SNPs (allele frequency <1%) appear to comprise a large fraction of deleterious mutations. These findings clearly indicate that – contrary to previous believes – selection has been sufficiently efficient in removing disadvantageous genetic variants from the human population even if their disease-causing potential only became effective later in life. The genetic architecture of CMD therefore appears to be bipartite, with common variants of small overall effects on the one hand, and a large number of rare variants that are functionally relevant and therefore associated with substantially higher disease risks on the other. However, as was pointed out by Bodmer and Bonilla (2008), rare disease susceptibility variants will not be detectable by population based-association studies and can only be identified through extensive DNA re-sequencing of many candidate genes in large numbers of individuals. Their validation also requires an assessment of their likely functional consequences. Therefore, it will be a long time before routine testing of rare susceptibility variants will become a realistic option.

Is "Risk Profiling" a Solution?

If genetic risk factors for CMD have insufficiently small effects when taken on their own, would it not be possible to aggregate these effects in so-called "risk profiles" in order to obtain higher predictive values? In principle, this may be feasible. However, relative risks or odds ratios can not simply be multiplied in order to obtain joint risk figures. This is only valid if the individual risk factors taken into consideration are known not to interact on the respective scale (i.e., logarithmic for relative risks or logit for odds ratios). For the genetic risk variants currently considered suitable for CMD susceptibility testing, such information is simply not available. What is more, large sample sizes would be required to quantify the interaction of genetic risk factors with sufficient accuracy, and with more than two or three risk factors

included at a time, the numbers of patients required would become prohibitively large. There is therefore currently no way in which to calculate the true disease risk associated with a given multi-marker profile. Any claim to the contrary would not be scientifically justified.

Conclusion

Currently known genetic susceptibility variants for common multifactorial diseases are either too rare or have too small effects upon risk to justify testing in a public health setting. Additional research is required to determine how the joint assessment of these variants could lead to more informative risk profiles.

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The Quality of Genetic Screening: An Integral Approach

Wybo Dondorp, Guido de Wert, and Martina C. Cornel

Key Points

- Genetic screening, as opposed to diagnosis, is offered to persons not known to have an indication for testing based on symptoms or increased risk.
- Several frameworks of criteria are available to evaluate whether the benefits of genetic screening outweigh the drawbacks that it always also entails.
- A reliable and valid screening method has a high analytic and clinical validity, implying a high sensitivity and specificity; the clinical utility of a screening method reflects whether screening helps to prevent or reduce the burden of disease, and whether the benefits to participants outweigh the drawbacks.
- Advantages to participants may go beyond treatment and prevention; especially when genetic screening is applied for reproductive reasons and for untreatable conditions.
- Ethical and economical aspects have to be integrated in a comprehensive approach to the evaluation of the quality of genetic screening programmes.

Keywords Genetic screening · Screening criteria · Clinical utility · Autonomy · Cost-effectiveness

Introduction

Many chapters in this book concern genetic testing for diagnostic purposes. Genetic diagnosis is offered to patients who have symptoms of disease, to family members of patients already diagnosed, or (in prenatal or pre-implantation genetic diagnosis) to prospective parents with a known elevated risk of having a child with a

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particular disease. Genetic screening, by contrast, is offered to persons not known to have an indication for testing based on either symptoms, family history or the outcome of prior pregnancies. This chapter concerns the quality of genetic screening programmes. We propose an integral approach in which quality refers not only to test characteristics and laboratory standards, but also to organisational issues and to the ethical, legal, and social (ELSI) aspects of genetic screening (De Wert and Dondorp 2006; Health Council of the Netherlands 2008).

Genetic screening can be either reproductive (aiming at enlarging reproductive choice for would be parents) or non-reproductive (aiming at providing opportunities for treatment or prevention). Reproductive genetic screening can be performed either prior to pregnancy (preconceptional screening for carrier status of autosomal recessive disease) or during pregnancy (such as prenatal aneuploidy screening). Genetic screening of IVF-embryos has until now mainly been done in view of deselecting embryos with chromosomal defects that would limit their chances of succesful implantation. However, the current approach to this is not evidence based (Fritz 2008).

Neonatal screening aims at reducing the burden of metabolic and other usually autosomal recessive childhood diseases by providing opportunities for timely treatment (e.g. dietary measures). However, the recurrence risk of 1:4 entails that parents of an affected child may also have a reproductive interest in neonatal screening that is not limited to finding treatable disease. Genetic screening later in life usually takes the form of screening within families affected by dominant disorders or monogenic subtypes of common disorders, such as familial hypercholesterolemia or colon cancer ("cascade screening"). Whereas neonatal screening is offered as population screening to all newborns, cascade screening is a systematic offer to family members at risk of a dominant disorder (sometimes with reduced penetrance) or a recessive disorder (hemochromatosis in brothers/sisters; fragile X carriership in female relatives). Finally in families with chromosomal translocations a systematic offer of karyotyping is often made.

A future development is genetic profiling of a person's risk of a larger or smaller range of multifactorial diseases. Although genetic susceptability tests for this purpose are already on sale, the scientific foundation of most of these tests is still inadequate (Janssens et al. 2008). Although the commercial provision of such tests to the general public falls under the definition of screening as understood in this chapter, readers are referred to chapter "US Oversight and Regulation of Genetic Testing" for a more detailed discussion of direct-to-consumer testing. Nor will we deal with genetic screening for non-health related purposes (e.g. forensic screening), as that field is outside the scope of this book.

Integral Approach to Quality

Contrary to popular belief, screening is not always beneficial. Whether the benefits that screening may have (in terms of health gains or the provision of reproductive choice) outweigh the drawbacks it always also entails (impact of false-positive or

negative outcomes, overdiagnosis, burdening of the health care system, stigmatization of vulnerable groups), very much depends on the quality of the whole chain of elements that together make up a screening programme. This approach fits in with a tradition of evaluating screening programmes using a framework of criteria the first version of which was drawn up by Wilson and Jungner for the World Health Organisation in 1968, but which has been continuously refined and adapted to new developments ever since. Important contributions to this tradition were made by the Council of Europe, the European Society for Human Genetics and, on a national level, by advisory bodies such as the British National Screening Committee, the French National Agency for Accreditation and Evaluation in Health Care (ANAES) or the Health Council of the Netherlands. A notable contribution to enhancing the implemention of this framework with respect to the evaluation of new genetic tests was made by the international ACCE project (Analytical validity, Clinical validity, Clinical utility and ELSI aspects) at the initiative of the American Centers for Disease Control and Prevention (CDC). In this chapter, we will present some crucial elements of this widely supported normative framework as discussed in a recent report from the Health Council of the Netherlands (2008). We were involved in drawing up this report.

Methods of Genetic Screening

Screening has to be simple, fast and cheap. Initial tests usually give information about an increased risk, but no certainty. A positive (or unfavourable) screening result will often be followed by a diagnostic test. The initial tests used in genetic screening programmes often measure proteins or metabolites and only rarely involve DNA technology. In prenatal screening for Down syndrome in the first trimester free beta human chorionic gonadotropin and pregnancy-associated plasma protein-A are assessed in maternal serum. In neonatal screening analysis of the metabolite octanoylcarnitine on newborn screening blood spot cards by tandem mass spectrometry is used to identify medium chain acyl Co-A dehydrogenase deficiency. A combination of two metabolites is used in phenylketonuria screening (phenylalanine and tyrosine). The combination of a metabolite and an enzyme are assessed in galactosemia screening (total galactose and galactose-1-phosphate uridyltransferase). Also imaging techniques can be used in screening programmes. In Down syndrome screening fetal nuchal translucency thickness can be assessed by ultrasound. Finally questionnaires are sometimes used. In colon cancer screening programmes the question whether first degree relatives had colon cancer at a young age can identify persons that should be advised to undergo colonoscopy instead of fecal occult blood testing. DNA technology is nowadays used as a second step in some neonatal cystic fibrosis screening programmes after an increased immunoreactive trypsinogen was found. For many screening purposes DNA technology is still too expensive and may lead to a high proportion of false positives (mild or unknown mutations).

Quality of Method

Test-methods used for screening must be reliable and valid. The former means that repetition of the test gives the same outcome (reproducibility). The latter means that the test measures what it is supposed to measure.

Analytical validity refers to how a test performs in a laboratory setting, for example how often it produces a positive (or negative) result in the presence (or absence) of the targeted mutation (genotype). Clinical (or diagnostic) validity goes a step further: how often does the test give a positive result for individuals who have or develop the condition in question (phenotype) and how often does it produce a negative result for people without that phenotype? A test can accurately indicate the presence or absence of a genetic mutation, for example, but if people with that mutation hardly ever develop the disease (the penetrance is low), the test serves no purpose.

The validity of a test is determined by its sensitivity and specificity. The (clinical or diagnostic) sensitivity of a test is its ability to identify all individuals with the disease in question; its (clinical or diagnostic) specificity is the ability to identify those who do not have the disease in question. A highly sensitive test produces few false-negative outcomes; a highly specific test few false-positives. The sensitivity and specificity also depend on the clinical spectrum of the disease among the individuals being tested. As compared to patients who are referred to a hospital, it is much harder to distinguish between those who do and those who do not have the disease in question in people with an earlier stage of the disease in the general population. Finally, the most important factor in deciding whether a particular screening method is useful in practice, is the predictive value of the test result. This depends not just on the validity of the test but also on the disease prevalence. A test that performs well in a group with many cases of disease may be unsuitable for use in the general population.

Clinical Utility

It is not enough for screening to lead to early detection of disease or to information about carrier status or risk factors. The purpose of screening is not the outcome of the test, but the ensuing health gain or other benefit to the person being tested. This is often referred to as "clinical utility" (Grosse and Khoury 2006). In a more limited sense, clinical utility is the extent to which the use of a screening method can help prevent or reduce the burden of disease in terms of mortality, morbidity or quality of life. In a broader sense, it refers to whether, all things considered, the benefits that screening can offer to participants outweigh the drawbacks that always exist as well.

In the orginal account of the criteria by Wilson and Junger (1968), the benefits of screening were framed in terms of the availability of "acceptable treatment" leading to a better prognosis than would have existed without early intervention. Without

this, Wilson and Jungner argued, "there can be no advantage to the patient and, in fact, (....) actual harm may be done". The subsequent introduction of genetic screening has not only led to a rephrasing of these conditions so as to include the preventive benefits that timely genetic information may sometimes have, but also to questioning the categorical rejection of screening for diseases not amenable to treatment or prevention.

This latter development was driven by the acknowledgement that prenatal screening for foetal conditions such as Down's syndrome and neural tube defects could not without moral problems be accounted for in the prevention paradigm underlying the original Wilson and Jungner framework. If reducing the birth prevalence of specific disorders is seen as the reason for offering this screening, the danger is indeed that expectant parents are put under pressure to regard selective abortion as an obvious and socially desirable choice. It might also be thought as implicit in presenting them with this choice that people with those conditions have no place in society. In order to steer clear from these moral pitfalls, there is a broad international consensus that prenatal screening for fetal abnormalities has the different aim of providing pregnant women and their partners with an opportunity for reproductive choice and should be presented, conducted and evaluated accordingly. Not only is informed decision making the central quality concern for this type of screening, it also means that its yield should be perceived in terms of choices provided rather than births prevented. However, measures to evaluate informed decision making have rarely been used in the assessment of prenatal screening programmes (Michie et al. 2002).

The break that screening for other purposes than early identification of treatable conditions signifies with Wilson and Jungner's initial criteria need not necessarily be limited to reproductive screening. It could be argued also in other contexts that screening may have benefits beyond treatment or prevention. The findings of the REVEAL study (a study into the psychosocial aspects of screening for genetic sensitivity to Alzheimer's disease) suggest that one might think here of the potential significance of benefits like being given the time to settle personal affairs, achieving certain life plans when one still can do so, or emotional preparation (Hurley et al. 2005). Of course, this does not settle the acceptability of screening for (genetic sensitivity to) serious late onset diseases that are not amenable to treatment or prevention. Potential benefits must be weighed against the obvious risks involved in offering screening for such diseases.

Pros and cons of screening do not only relate to the goal of the screening, also non-intentional findings should be considered. In neonatal screening for sickle cell disease, carriers of hemoglobinopathies will be identified for instance. Whether this is a pro or con depends on the perspective. Parents may consider it an advantage to be aware of their positive carrierstatus in view of future reproductive choices. Others, however, may find this additional information burdening. Moreover, if the child is found to be a carrier, this information will only be useful to him or her at a much later stage of life.

Among the potential drawbacks of genetic screening are furthermore the psychosocial implications of a positive test-result, including the (mis)use of information

by third parties (insurers or employers) and straining of family relations. These concerns would appear in the first instance to arise mainly in the context of screening for a hereditary predisposition to a monogenic disease (including the "Mendelian variants of common diseases") and less so in the case of screening for genetic "sensitivity" to common diseases ("susceptibility testing"). The predictive value of the results of this type of screening is generally low, and the likelihood that relatives will have exactly the same genetic profile is very small (Janssens and Khoury 2006). However, this type of testing may still have the potential of confronting some individuals with high risks of serious conditions with the potential risk of stigmatization or discrimination. If integrated risk profiling would be performed, testing for a number of genetic and non-genetic conditions and risk factors at the same time, it is conceivable that people will not be sufficiently prepared for such an outcome.

Recently, there is much debate about the scope of neonatal screening. Should this, following the classical account of the aim of neonatal screening, be limited to conditions the early detection of which is clearly in the health interest of the children screened? Or is it acceptable to use the same method to also screen for conditions where this would not be the case, given the interest of the parents to be able to also take the recurrence risk of non-treatable recessive diseases into account when making further reproductive plans? First of all, this conflict will in practice be mitigated by the fact that screening for non-treatable disease may still confer benefits to the child (eg. avoid the diagnostic long-haul through the health-care system and enable optimum care to be given as soon as the first symptoms appear). From an ethical point of view, the bottom line should be that screening of neonates in the interest of the parents or the family as a whole is unacceptable if the child would suffer disadvantages as a result. The recent draft additional protocol to the Convention on Human Rights and Biomedicine concerning genetic testing for health purposes drawn up by the Council of Europe does leave somewhat more space for this: the expected benefit to the parents must "significantly outweigh" the risk to the child associated with collecting, processing or sharing the information.

Respect for Autonomy

Participation in screening must be voluntary, and provision must be accompanied by balanced, adequate information that can be understood by the target group. This information must relate to all aspects that are of importance in allowing individuals to reach a well-considered decision on whether or not to take part. It must always include: information about the condition for which the screening would be performed, the nature and design of the screening test, the reliability of the test and the predictive value of a normal or abnormal result, possible implications for relatives and other (different) advantages and disadvantages of participation for those concerned.

In the case of escalated screening, providers and counsellors should be aware that the often "innocent" nature of the first step can conceal the sometimes risky or otherwise invasive nature of follow-up testing or of the options available if a definitive diagnosis is established. Moreover, little if any empirical research has been done into the feasibility of actual informed consent for multiplex screening including the use of imaging techniques such as prenatal ultrasound or body scans using CT or MRI. It has been argued, by the European Society of Human Genetics among other groups, that "screening packages" should be available only for conditions that are sufficiently similar in terms of their nature, severity and implications. In the context of neonatal screening, this would mean for example that screening for treatable conditions would be clearly separated from screening for untreatable conditions.

A related observation is that the notion of respect for autonomy has divergent implications where different forms of screening are concerned. As the aim of prenatal screening is the provision of reproductive choice, this means that in this context non-directive counseling must be the norm. On the other hand, to the extent that neonatal screening is offered in the clear interest of the child, directive counseling of parents reluctant to give their consent is not only acceptable but morally desirable. Respecting parental autonomy does not entail that parents may not be reminded of their responsibilities.

Approriate Use of Resources

Contrary to what many people think, screening does not usually save on the healthcare budget. Therefore, screening that is funded from public or collective resources must address a significant health problem. That does not mean that the condition in question must always have a high prevalence. Wilson and Jungner (1968) already mentioned that phenylketonuria (PKU) is "extremely uncommon but warrants screening on account of the very serious consequences if not discovered and treated very early in life".

The so-called "opportunity costs" must also be taken into consideration: introducing an expensive screening programme might mean that other forms of screening cannot be carried out, or that health care services will have to be cut. In this context, it is important that the balance between the proceeds of a screening programme, in terms of health gain or other benefits for participants, and the costs incurred comes down on the positive side. These must also cover the net costs of follow-up tests and ensuing interventions, ie. after deducting any savings made. A screening method that produces a high proportion of false-positive results soon generates considerable unnecessary cost down the line, and therefore the cost-effectiveness profile of the entire screening process becomes unfavourable.

It is incorrect to think that these considerations are irrelevant to screening offered in the private sector because people pay for it themselves. After all, what they pay for themselves is only the initial screening test and not the subsequent steps of diagnosis and intervention.

An Integral Approach

Quality is determined by the weakest link in a chain. An effective screening programme needs to be properly planned in terms of design, implementation and evaluation. Key components in this are a centralised system for inviting target groups for screening, providing clear, standardised information and reports, quality monitoring and assessment. Systematic investigation of the functioning of screening programmes shows that there is much room for improvement in this area (Antilla et al. 2004). The evaluation of genetic screening programmes has often focussed on laboratory quality and public health impact. A broader assessment integrating all elements of screening is needed.

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The Use of Principles in Allocating Scarce Health Care Resources for Genetic Tests

Wolf Rogowski, Per Carlsson, and Ulf Kristoffersson

Key Points

- Given limited health care resources also for genetic tests, it needs to be considered how we can meet health needs fairly if we cannot meet them all.
- Frequently, health care decision making involves the explicit or implicit use of principles. The four basic principles for ethical decision making autonomy, non-maleficience, beneficience and justice provide an example of an elaborated bioethical framework by Beauchamp and Childress.
- The qualitative use of such principles for allocating health resources within genetic testing is a fruitful starting point, but it should be complemented by health economic techniques and procedural fairness in a pragmatic manner.

Keywords Allocation of health resources · Medical ethics · Health economics · Genetic testing

In industrialized countries as well as in many other countries throughout the world, health care payers are faced with the challenge of including medical innovation into existing reimbursement schemes to improve medical care, ensuring fair allocation of health resources across the affected population and keeping health care spending at a sustainable and affordable level. Therefore, inevitably, difficult decisions have to be made by private, social health insurance-based or tax-funded payers as to which technologies should be covered within the reimbursement scheme and which ones should not.

Which health technologies can be funded by third party payers depends on a number of issues, e.g. the overall resources available for health care. In developing countries with high neonatal and infant mortality rate the greatest needs may be

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to address poverty, malnutrition and infectious diseases, and given a low national income, the perceived need of childhood health care may outweigh other needs including topics of clinical genetics such as neonatal screening. During the last 30 years there has been a successful addressing of these burdens so that many middle income countries now have reached the same level of neonatal and infant mortality as had the Western high income countries in the 1960s. With newborn and infant mortality from infectious disease falling, the burden of genetic disease becomes evident in the society, and several middle income countries who have reached this level have taken initiatives to develop genetic care programmes (Christianson and Modell 2004). However, given the high number of options available e.g. for screening programmes, numerous decisions remain to be made concerning which needs to address first and by which technology. This holds true also in high income countries: due to continuous medical innovation and an ageing society, the costs of all technically possible options for prevention and treatment of disease typically exceed the existing resources. In situations where health care resources are insufficient to fund all desirable services there is a high risk for unfair and inefficient allocation of health care resources. It has been suggested that, therefore, explicit prioritization is warranted to ensure that the necessary and difficult decisions of how to allocate the scarce resources are based on ethical considerations rather than on contingency (PrioriteringsCentrum 2008).

This chapter provides an overview of principles that can be used in decisions about the use of scarce health care resources devoted to genetic tests and different approaches of using these principles are discussed. In the concluding part of this chapter, implications for decision making about genetic tests are discussed.

Principles for the Prioritization of Genetic Tests

Beauchamp and Childress recommend addressing ethical questions in health care by four general ethical principles which have become a leading framework in the field of medical ethics: Respect for autonomy (the obligation to respect the decision making capacities of autonomous persons); Non-maleficence (the obligation to avoid causing harm); Beneficence (obligations to provide benefits and to balance benefits against risks), and Justice (obligations of fairness in the distribution of benefits and risks).

Autonomy

Autonomy refers to the principle of self-determination. This confers personal freedom and free will in decision-making. It is important to note that self determination carries an implicit assumption that the individual has sufficient information and capacity to be able to exercise that self-determination. Autonomy is a fundamental principle in secular democracies. As an individual right it may have to be balanced against the rights of others and is therefore not an absolute (Burnett et al. 2007).

Genetic tests may have implications for patient autonomy in a variety of ways – enhancing patient autonomy may be the sole purpose of conducting a genetic test. Typically, health technologies aim at achieving health benefit and, thus, methods for the evaluation of health technologies frequently focus on the establishment of health benefit the technology aims at. However, many genetic tests may be beneficial without any measurable health benefit, e.g. preconception tests to enhance the decisions of young couples about family planning.

The principle of autonomy implies that an individual has the right to decline to receive information. Yet to a large part, genetic information is shared within a family. Genetic testing may thus also infringe autonomy – for example, if a young woman conducts a presymptomatic DNA-test for a BRCA1/2 mutation which has been found in her grandmother. Finding the grand-maternal mutation implies that the mother also must be a mutation carrier, even if she declined undergoing the genetic test.

Autonomy involves informed consent, which is another important issue in genetic testing. Consent implies more than just a patient agreeing or not refusing a medical intervention. Beauchamp and Childress propose an elaborated concept of informed consent which is composed of seven elements: Preconditions for consent are (1) competence (to understand and decide) and (2) voluntariness (in deciding). Information elements are (3) disclosure (of material information), (4) recommendation (of a plan) and (5) understanding of (3) and (4). The consent then is comprised of (6) decision (in favour of a plan) and (7) authorization (of the plan) (Beauchamp and Childress 2009 p. 120). Informed consent through lengthy genetic counseling may be difficult to obtain, e.g., if parents make decisions on behalf of their children as in the case of newborn screening, in the case of family disclosure, or in a mass screening program (Potter et al. 2008).

Non-maleficence

The principle of non-maleficence imposes an obligation not to inflict harm on others. In medical ethics it has been associated with the rule of "primum non nocere" (first, do not harm) which is frequently invoked by health care professionals despite its obscure origin and implications (Beauchamp and Childress 2009 p. 149).

While genetic tests provide information which may enhance patients' autonomy, they may also impose harms on patients (Potter et al. 2008). Regardless of the potential positive health impact associated with prevention, individuals who test positive may first of all experience a decrease in psychological health in terms of increased anxiety and distress.

Yet the potential harms may also extend to other than medical contexts – there have been strong concerns about potential stigmatization and discrimination, e.g. on the labor or insurance market. Currently, a number of countries, as well as international organizations establish guidelines, recommendations, regulations and/or laws for genetic testing which frequently address these issues (Javaher et al. 2008). The benefit and harms from testing may thus depend on the legal context within a country.

The principle of non-maleficence becomes highly relevant and controversial in its interpretation related to preconception and prenatal screening which may eventually lead to early termination of pregnancy. Depending on when human life and dignity is assumed to start, an abortion can be considered not only potentially harmful for the mother, but unacceptably harmful for the human fetus. Also, difficult decisions have to be made to define when a health problem is sufficiently "serious" to be screened for – and under which conditions severity may justify an abortion.

Beneficence

Morality does not only require that we treat persons autonomously and refrain from harming them, but also that we contribute to their welfare. Principles of beneficence potentially demand much more than the principle of nonmaleficence, because agents have to take positive steps to help others, not merely refrain from harmful acts. The principle of positive beneficence requires agents to provide benefits to others. For decisions on the macro level of health care coverage, the related principle of utility may be of higher relevance. It requires that agents balance benefits, risks, and costs to produce the best overall results (Beauchamp and Childress 2009 p. 197). Establishing the utility of genetic tests raises a number of challenging issues (Rogowski 2007).

For example, due to a lack of trial-based evidence, the estimate of benefit frequently must rely on evidence relating to separate components of a program (e.g., evidence relating to the effectiveness of screening for early disease detection; and evidence on the health impact of early treatment) which frequently is uncertain as well (Rogowski 2007 Potter et al. 2008). Decision analytic modeling techniques provide a set of tools to synthesize the evidence about the separate components of the program in a coherent manner.

It has to be noted that positive beneficence relates to individuals and must not be misunderstood as principles of societal benefit which may imply eugenic discrimination. Therefore, it is crucial that the principles of non-maleficience and autonomy are given high weight in the appraisal of community genetic interventions which include the individual's own possibility to a unbiased and free choice of using offered testing or investigations.

If benefits are balanced with costs, modeling techniques may be needed as well. From a health care system perspective, the analysis of genetic tests needs to account for the total costs of care associated with genetic testing. This includes the costs of counseling, follow-up testing, treatment and prevention, avoided costs of prevented medical conditions or, in the case of screening programs, the costs of achieving test uptake (Rogowski 2007). While the costs of DNA tests are falling at a high rate, the total costs associated with genetic testing might increase rather than to fall over time because of increasing options for follow-up testing and treatment and need for specialist genetic counseling.

Justice

The terms fairness, desert (what is deserved), and entitlement have been used by philosophers in attempts to explicate "justice". These accounts interpret justice as fair, equitable, and appropriate treatment in light of what is due or owed to persons because of their particular properties or circumstances (Beauchamp and Childress 2009 p. 241).

Theories of distributive justice try to connect properties of persons with morally justifiable distributions of benefits and burdens. In discussions about the allocation of health care resources, several types of theory have been influential: Utilitarian theories emphasize a mixture of criteria for the purpose of maximizing public utility; libertarian theories emphasize rights to social and economic liberty, and egalitarian theories emphasize equal access to the goods in life that every rational person values, often invoking material criteria of need and equality (Beauchamp and Childress 2009 p. 244).

Genetic tests consume resources which could also have been allocated elsewhere, either within the health care system or elsewhere for public or private spending. Also public and private spending has impact on health – a number of studies have established a much stronger link between socioeconomic indicators and health than between health care and health (Nolte and McKee 2004). Therefore, while the positive impact of funding a health technology from public budgets is not always clear, there is always a negative effect in terms of opportunity costs (health forgone) by not using scarce resources for alternative purposes like other health technologies or education. Cost-utility analysis (CUA) provides a set of quantitative tools to assess whether the costs per health gain of a new technology are below or above the costs of a technology elsewhere in the health care system which it potentially replaces (Claxton et al. 2008). Cost-benefit analysis compares the benefit from a new technology in terms of willingness to pay with its costs to provide an estimate of whether or not the benefits exceed the opportunity costs also outside the health care sector (Grosse et al. 2008). While both techniques provide helpful information for optimizing the amount of health or societal value from a given health care budget, their use typically conflicts with other principles of distributive justice like equity concerns. This is because typically, the cost-effectiveness of genetic testing strongly depends on a number of characteristics of the target individuals, e.g. prevalence (which depends on ethnic or family background) or gender (in case disease expression differs according to sex like in the case of hereditary hemochromatosis) (Rogowski 2007).

Procedural Principles

Inevitably, conflicts about value judgments or interpretations of the existing evidence will remain in prioritizing decisions. Therefore, it has been proposed that, besides substantive ethical criteria and decision support tools, also procedural

criteria are important to ensure that the decision process achieves a fair and balanced allocation of scarce health care resources.

Most well known are the four criteria of "accountability for reasonableness" proposed by Daniels and Sabin (Daniels and Sabin 1998): (1) Decisions regarding coverage for new technologies and their rationales must be publicly accessible (publicity condition); (2) These rationales must rest on evidence, reasons, and principles that all fair-minded parties can agree are relevant to deciding how to meet the diverse needs of a covered population under necessary resource constraints (relevance condition); (3) There must be a mechanism for challenge and dispute resolution regarding limit-setting decisions (appeals condition); and (4) There is regulation of the process to ensure that the first three conditions are met (enforcement condition).

Case Study: Prioritization in Sweden

A wide range of substantive and procedural principles has been used in decision making about health services. Frequently, these principles are derived from or are converted into national regulations. Sweden provides an example of countries that have address the issue of prioritisation in a highly transparent and explicit manner by a Parliament decision upon an ethical platform in 1997. To support the implementation and to develop methodology the National Centre for Priority Setting in Health Care was established in Linköping year 2000 (http://e.lio.se/prioriteringscentrum/).

The Swedish ethical platform incorporates different aspects of principles and their application outlined above which partly overlap with the principles by Beauchamp and Childress outlined above. In setting up prioritization principles, the Swedish government has formulated three overriding principles:

1. *The principle of human dignity.* All humans have equal value and rights irrespective of their personal characteristics and functions in the society
2. *The needs and solidarity principle.* Resources should be allocated based on need
3. *Cost-effectiveness principle.* In selecting among different activities or interventions, there should be reasonable relationship between costs and effect, measured in terms of improved health and quality of life.

These three principles that are rather basic and rational from the view point of Western philosophy appear in rank order, with the human dignity principle ahead of needs and solidarity principle, followed by the cost-effectiveness principle (Ministry of Health and Social Affairs 1995, http://www.regeringen.se/sb/d/108/a/25124). They overlap with the four principles above. Human dignity relates to the principle of autonomy because treating a individuals as ends in themselves also implies respecting their liberty and thus autonomy of choices. The cost-effectiveness principle on the one hand incorporates the utility (beneficence) principle because cost-effectiveness incorporates an estimate of the net utility or benefit provided by a medical treatment. Additionally, decision making based on cost-effectiveness

analysis can maximize the utility derived from a health care budget. On the other hand, together with the needs and solidarity principle, it relates to the principle of justice as it provides guidance as to how scarce resources should be allocated across treatments.

These principles can in general be applied in clinical genetics both on the level of a health care system as a whole or for policy decisions upon whether or not a single test should be offered in the health care system. As an example from the field of genetic testing, evaluation of genetic risk for breast cancer has received a high priority in the national guidelines for cancer diseases including a priority ranking, whereas for other conditions such as Diabetes, evaluation of genetic risk is not mentioned.

In order to make the ethical principles useful in a day to day care setting they have been interpreted and operationalised in a common model for vertical priority setting (Carlsson et al. 2007). The National Board for Health and Welfare who is responsible for issuing the national guidelines is using these in the day-to-day work on prioritization in the assessment of genetic tests, the Swedish process of priority setting on the national level does not look into details, such as which genes should be tested for where or when. Instead, it only assesses what priority a combination of medical procedure (e.g. genetic testing) and condition (e.g. breast cancer or diabetes) should be given to. These evaluations are done on basis of existing scientific knowledge in open priority setting process involving medical professionals. As it takes more than 1 year to agree on these principles most arguments have been openly discussed so that a consensus in the medical society about its use can be assumed. However, even if a majority of health care workers accept the priorities and follows them, and even if they are used by policy makers in their resource allocation, they have little legal standing. Therefore, opposition from single individual health care providers or groups of stakeholders are possible. An ongoing debate thus remains on how these guidelines should be implemented in day-to-day health care. Moreover, as discussed in the chapter "Quality Issues in Clinical Genetic Services: Ethical Aspects" of this book by Hermerén ethical conflicts between different stakeholders may arise due to different basic standpoints and interests, which may lead to different conclusions on what is warranted from an ethical perspective. While the three principles are typically accepted as starting points, disagreement thus arises as to how they are to be operationalised and applied in needs assessment and prioritisation. They thus guide rather than determine the discussion on prioritization.

International Guidelines as Ground for Priority-setting

There are other examples of guidelines which explicitly have taken resource limitations into account. For example, the guidelines of the European Molecular Genetics Quality Network recommend breast cancer genetic testing for BRCA1 and 2 genes not in all women with a first degree relative with breast cancer due to the still rather high costs for genetic testing. Instead, a number of more or less complex selection

models are proposed to select the women at highest risk women for mutation analysis. This selection process is one the few where medical geneticists have tried to develop a model for prioritisation to be used in every day health care situations.

Other valuable schemes for the evaluation of genetic tests have been developed, such as ACCE (Sanderson et al. 2005) and EGAPP in the USA (Teutsch et al. 2009), gene dossiers in UK (http://guidance.nice.org.uk/), and most recently the gene cards from the Germans Society of Human Genetics (http://www.gfhev.de/index.php) and the EuroGentest network of excellence (www.eurogentest.org). However, these schemes typically only assess whether or not a test can be considered beneficial. They do not address its priority among all available genetic tests in the face of limited resources.

Nonetheless, most of the day to day prioritisation in heath care is not systematic, and often lacks not only thorough reflection of the range of principles outlined in this book chapter but also an evidence-based establishment of benefit.

Discussion

Like in the Swedish example, difficult decisions in the prioritization of health technologies frequently involve contingent normative conflict. Therefore, typically further analysis is necessary which involves weighting these principles according to the specific situation (Beauchamp 2003). The framework of the four principles by Beauchamp and Childress can help identifying important issues to consider in these decisions.

Even if the four principles are a widely used framework for ethical analysis in health care, their usefulness and theoretical basis has been challenged as they do not provide a hierarchy of values and a clear recommendation – which is the ultimate goal of raising the ethical question. They may therefore rather provide a useful checklist and cannot replace other ethical approaches (Callahan 2003). Particularly in the field of genetic screening, there is a strong need for a hierarchy of principles so that the four principles have been argued not to be appropriate (Mallia and ten Have 2003).

In the case one principle or a weighted mix of principles can be specified in terms of a quantifiable objective function, an alternative methodological approach would be the use of quantitative decision analytic models. These allow for a systematic consideration of the different costs and benefits of decision options which is susceptible to rigorous scientific challenge. Such an objective function can for example be the maximization of health outcomes like quality-adjusted life years, or a clearly defined balance between health maximization and specified equity concerns (Olsen 1997 Bleichrodt et al. 2008). Decision analytic modeling has been applied for a variety of technologies including genetic testing in the scientific literature (Rogowski 2009). However, their explicit use in decision practice is restricted, also because some decision makers are reluctant to explicitly considering costs as a criterion in prioritization.

The use of procedural standards has been proposed as a way out of the difficulties associated with qualitative or quantitative weighting of the extent to which a technology meets substantive criteria. Yet also the use of procedural approaches has limitations because frequently, consent about the appropriateness of the established process for deciding upon controversial issues cannot be achieved. Also, the choice of a particular procedure implies value judgments which may be controversial as well (Sabik and Lie 2008).

Conclusions

As new genetic tests are evolving from bench to clinical use, inevitably, decisions about whether or not they should be funded by third party payers have to be made. In a situation with competition for scarce resources, such prioritization will inevitably involve conflicts between different stakeholders, which may also be based on different interpretations of the existing evidence and different perception of needs, e.g. due to individual experiences.

This chapter outlined ethical principles that can be useful to support such prioritization decisions for genetic tests as well as pitfalls they have encountered. None of the aspects outlined above can provide the silver bullet or be the golden standard to tackle all of these issues. However, the reflection and systematic attempts to arrive at economically and ethically sound and manageable criteria for prioritization practice can improve decision making and guide discussions in an environment of increasing financial pressure on funding schemes for health technologies. To enhance the acceptability of any prioritization scheme, it is important that any criteria of prioritization are based on a process which involves generally accepted decision criteria, exhibits sufficient transparency and includes stakeholder involvement.

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Outcome Measures in Clinical Genetics Services

Marion McAllister

Key Points

- Biomedical research has dominated research in clinical genetics.
- Health services research (HSR) and how it can contribute to improving service quality in clinical genetics.
- How healthcare is evaluated in HSR and why there is little robust evidence of patient benefits from using clinical genetics services.
- What are the attributes of a good outcome measure?
- What outcome measures can be used to evaluate clinical genetics services?

Keywords Health services research · Evaluation · Outcome measures · Complex interventions

Introduction

Biomedical research applies the principles of the natural sciences, especially biology, to develop the body of knowledge in clinical medicine. Biomedical research serves us very well in clinical genetics, with the identification of more and more genes, and the elucidation of more and more genotype-phenotype correlations. Such laboratory breakthroughs are very exciting, and have facilitated the exponential growth of clinical genetics services and the options available to affected families. But in healthcare in the twenty-first century, we must increasingly provide evidence that these breakthroughs have been translated into cost-effective interventions that reduce the burden of disease.

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Health services research (HSR) is a newer branch of health research that is complementary to biomedical research. HSR aims to evaluate the effectiveness of healthcare in providing for the needs of the population it serves, and constitutes one important mechanism through which we can improve the quality of the services we provide. The evidence generated by HSR can be used by clinical or policy decision-makers to improve the quality, organisation and management of health services to maximise effective use of resources (Bowling 2002). HSR concerns itself with many aspects of healthcare including patient outcomes, institutional structure, process of care, access to services and cost-effectiveness (Bowling 2002). So, HSR aims to provide evidence about how well the achievements of biomedical research are being translated into patient benefits. Like other areas of healthcare, clinical genetics has historically been dominated by biomedical research, but the turn of the century has been accompanied by mandates from research funding bodies to provide evidence of the effectiveness of healthcare interventions in providing benefits to patients. Furthermore, the World Health Organisation report 2008 calls for "service delivery reforms that re-organize health services around people's needs and expectations, so as to make them more socially relevant and more responsive to the changing world, while producing better outcomes" (p. IX). This is the realm of HSR.

Evidence of patient benefits cannot be collected without effective instruments to measure those benefits; such instruments are known as outcome measures. For health services without a strong tradition of HSR, such as clinical genetics services, assessing the quality of existing or new interventions may be very difficult in the absence of agreement about appropriate outcome measures. Patients may be benefiting greatly from use of those services, but this may not be consistently demonstrable. Are there measures that we can rely on to capture the benefits that patients may derive from using clinical genetics services? In this chapter, I will summarise (1) how service evaluation is approached in HSR (2) the properties of a "good" outcome measure and (3) some recent research on outcome measurement in clinical genetics.

Evaluation

The methods used in HSR include intervention studies (e.g. randomised controlled trials (RCTs)), systematic literature reviews, economic evaluations, as well as qualitative methods and survey research (Bowling 2002). Many of these methods have their roots in the social sciences, rather than in biomedical science, and so they may be unfamiliar to clinicians. The "gold standard" approach to assessment of interventions in healthcare is, of course, the randomised controlled trial (RCT). Historically, it has been difficult to design good intervention studies in clinical genetics for two main reasons (1) the interventions offered in clinical genetics can be difficult to specify and (2) the patient benefits are difficult to measure.

The traditional RCT approach randomises cases to receive either a single drug or a placebo, and then assesses which intervention provides the greatest patient benefit at follow-up, as measured by a set of outcomes. There have been few RCTs in clinical genetics, and most of these have been done in cancer genetics. An examination of some of these studies highlights two important issues. Firstly, there is little agreement across studies about appropriate outcome measures (McAllister et al. 2008a). Secondly, the theoretical frameworks informing the design of the interventions have not been clearly specified, resulting in interventions that have not been clearly described (McAllister et al. 2008a). These issues may go some way towards explaining the paucity of RCTs in clinical genetics, and why, to date, those RCTs that have been done are not providing persuasive evidence of significant patient benefits.

Furthermore, in clinical genetics, we rarely offer simple interventions that can improve health in the traditional sense of a drug or a surgical intervention that can provide a "cure". This may change with time, as evidence accumulates that drugs like losartan may have some benefit in alleviating the symptoms of genetic diseases such as Marfan syndrome. However, for the forseeable future, it is likely that clinical genetics services will continue to provide varying combinations of information, counselling and in some cases, genetic testing for conditions which are, for the most part, incurable. It could be argued that in cancer genetics, and increasingly cardiac genetics, options for surgical, pharmaceutical and screening interventions can be discussed with patients that may reduce mortality and morbidity. However, it is usually genetic testing, counselling about the risks and options, and referral to other specialties that are offered by a clinical genetics service, although joint clinics are becoming more common. The surgical, pharmaceutical and screening interventions themselves are usually offered by those other specialties, which significantly complicates attribution of the benefits resulting from those interventions to clinical genetics. There is also an argument for focussing attention in clinical genetics on those benefits that can be directly attributable to the interventions offered by our services.

However, despite these significant difficulties, developments in HSR may be able to facilitate better intervention studies in clinical genetics. There is increasing recognition in HSR that not all aspects of healthcare are amenable to the traditional RCT approach that assesses a single simple intervention. Clinical genetics services may constitute what the Medical Research Council (MRC) defines as a complex intervention, where the "active ingredient" is difficult to specify, and may involve several interacting components (Craig et al. 2008). A framework has been built for developing, evaluating and implementing complex interventions that may provide very useful guidance to those designing intervention studies in clinical genetics (Craig et al. 2008). Successful applications of the framework have drawn heavily on social science research methods.

With regards to the problem of outcome measurement in clinical genetics, it has long been recognised that patient benefits from using clinical genetics services are difficult to measure. The benefits to patients have rarely been explicitly stated,

and where they have, it has been difficult to match those benefits with appropriate outcome measures. Before moving on to discuss what outcome measures are available to evaluate clinical genetics services, the attributes of a good outcome measure will be described.

Outcome Measures

Patient outcomes in intervention studies are usually measured using a combination of health status measures (mortality, morbidity, clinical change, functional recovery) and health-related quality of life measures. Any instrument used as an outcome measure in healthcare, whether it takes the form of a health status measure (such as an instrument to measure blood pressure) or a health-related quality of life measure (such as a questionnaire) must be shown to be valid, reliable and sensitive to change (Streiner and Norman 2008).

The validity of an instrument refers to whether the instrument actually measures the attribute (e.g. blood pressure, anxiety) that it is intended to measure. There are many ways to assess validity of an instrument, and a good instrument will have had validity demonstrated in a variety of ways. Content validity refers to whether the instrument measures all relevant facets of the attribute. Concurrent validity refers to whether scores or readings on the instrument correlate highly with scores or readings on a "gold standard" measure of the same attribute; of course, this can only be assessed if there is a "gold standard" measure available. Construct validity is perhaps the most important type of validity, particularly of health-related quality of life measures, and it refers to whether measurements using the instrument form the kinds of patterns predicted by theory – are the measurements related to the things we expect them to be related to (convergent validity), and unrelated to the things we expect them to be unrelated to (discriminant validity)? An approach called the Multitrait-Multimethod matrix can test convergent and discriminant validity at the same time. Construct validity, can also be tested by setting up hypotheses that can be tested experimentally. Another way is to see whether group scores on the instrument can predict, or be predicted by, group scores on another measure in the theoretically expected direction (predictive validity). Face validity refers to whether, on the face of it, the instrument appears to measure what it is intended to measure i.e. whether it looks plausible. This is usually assessed by discussion with a group of people (often patients) for whom the attribute to be measured is relevant, and is considered to be perhaps the weakest form of validity. However, it is worth remembering that patients are unlikely to complete a questionnaire that seems irrelevant to them.

Reliability refers to whether or not repeated measurements using the instrument give similar results if the underlying attribute (e.g. blood pressure, anxiety) has not changed. A reliability study can define the reliability of a given instrument for a given population, and is estimated using various forms of correlation coefficient, for continuous data (e.g. blood pressure, anxiety), or using Cohen's kappa for categorical data (e.g. presence/absence of a symptom or behaviour) (Streiner and Norman

2008). Internal consistency reliability provides an assessment of whether items (questions) within a questionnaire, intended to measure, say, anxiety, are correlated with each other and to the total score.

Responsiveness or sensitivity to change over time refers to whether an instrument, which has been shown to be valid and reliable, can detect clinically important changes in the theoretically expected direction following an intervention (Streiner and Norman 2008). Testing sensitivity to change usually involves a before-and-after approach, and can be confirmed in intervention studies. Outcome measures that have been shown to be valid, reliable, and sensitive to change are referred to as "validated" measures. Validated outcome measures are required to provide robust evidence of patient benefit in healthcare.

Outcome Measures in Clinical Genetics Services

As mentioned above, clinical genetics is a rapidly evolving specialty. Change drivers include exponential increases in knowledge about the genetic basis of disease, and associated changes in technologies that have increased options for patient decision-making. Many approaches to outcome measurement have been attempted over the last 20 years; however none has yet proved adequate to take full account of patient benefits. Because of the nature of the problems for which patients seek referral to a clinical genetics service, clinicians have argued that traditional approaches to outcome measurement in healthcare, such as health status measures, are neither relevant nor appropriate. For the purposes of commissioning clinical genetics services in the UK, process indicators (e.g. scope of service, accessibility/responsiveness, links with genetic laboratory services, quality of data collection/handling) as proxies for outcome measures were advocated in 1998 until more robust evidence was available (Clinical Genetics Committee of the Royal College of Physicians of London 1998). Interviews with UK service commissioners, conducted by the author in 2008, confirmed that this continues to be the approach taken by commissioners of clinical genetics services in England to assess service quality.

Returning to the problem of outcome measures, this was tackled in a recent programme of research at Nowgen, A Centre for Genetics in Healthcare (formerly The North West Genetics Knowledge Park) in Manchester funded by the UK Department of Health. A systematic review of the literature on outcome measures used to evaluate clinical genetics services identified the range of existing validated outcome measures used and the key domains (attributes) captured by these measures (Payne et al. 2008). Thirty seven non-genetics-specific (generic) and 30 genetics-specific measures were identified in the review, but little consensus emerged across studies about which are most relevant. 46 of the 67 measures were used and reported in just one paper. The other 21 measures identified were used more than once. These findings highlight the lack of agreement about what we should be measuring to capture patient benefits from using clinical genetics services. None of the measures identified in this review was preference-based i.e. could establish the weight, or

importance, that individuals attach to changes in health state or well being after using a clinical genetics service. Domains captured by the measures identified in the review included health status, anxiety, depression, coping, decision-making, distress, family environment, knowledge, mood, perception of risk, perceived personal control, psychological impact, quality of life, satisfaction, meeting of expectations, self-esteem, spiritual well-being and worry.

The findings from the systematic review were used to design a Delphi survey, which is a research tool that uses an iterative multistage process to transform opinion into group consensus. In this case, the approach was used to establish where there was consensus amongst patients and genetics healthcare professionals about which outcome domains were thought to be important (Payne et al. 2007). The Delphi survey identified consensus across patients and genetics health professionals that the following nine outcome domains are valued: satisfaction with service, decision-making, knowledge of the genetic condition, accuracy of diagnosis, perceived personal control, ability to cope, perception of risk, meeting of expectations, and quality of life.

The systematic review provides an index of available validated outcome measures, and together with the outcome domains identified in the Delphi survey, may be useful to researchers designing intervention studies in clinical genetics as a guide to selecting appropriate outcome measures.

However, this programme of research also identified some aspects of patient benefit that are not captured by existing validated measures. Simultaneously with, but separate from the systematic review and the Delphi survey, qualitative research was conducted using focus groups and interviews with members of families affected by genetic conditions, and with genetics health professionals to identify patient outcomes that are valued by those stakeholders. When the findings from the qualitative research were compared with those from the systematic review, and the Delphi survey, it was clear that the qualitative research confirmed many of the findings from the Delphi survey. Significantly, however, it also emerged that there are some benefits that are highly valued by patients and families affected by genetic conditions, that are not being captured by available validated outcome measures. For example, no existing measures can capture (1) all of the potential emotional benefits, such as alleviation of guilt and of worry about the risks to children (2) the ability to make informed decisions relating, not only to health, but also to many non-health aspects of life and (3) benefits to relatives and future generations (McAllister et al. 2007a, b; 2008a, b).

Directions for Future Research

The nine outcome domains identified in the Delphi survey provide a useful starting point to develop a core set of outcome measures suitable for evaluating clinical genetics services. There is work to be done in developing international consensus about what measures to use to best capture these domains. Further research could

work towards developing preference-based measures that could establish the weight, or importance, that patients attach to changes in these domains after using a clinical genetics service.

The findings from the qualitative research have demonstrated that the outcome measures used to date capture only some of the potential patient benefits from using clinical genetics services. There is scope to develop new outcome measures to better capture those benefits that families can potentially derive from using clinical genetics services. Many of these are quite specific to the problems faced by families affected by genetic conditions, such as (1) improvements in patients' ability to communicate with at risk members of their family about the condition and associated risks (2) the alleviation of feelings of guilt about having (potentially) transmitted a condition to children (3) hope for a fulfilling or rewarding family life through acceptance of and adaptation to the condition in the family, effective use of the health and social care systems, and/or through reproductive choice. The clarification of outcome domains that are highly valued by patients also provides some focus to guide the development of new interventions, designed, perhaps, to improve family communication, hope for the future and emotional regulation. Using the methods of HSR, these new interventions could then be compared with standard care in intervention studies, to accumulate evidence to enable assessment of service quality on the basis of patient outcomes. Ultimately, over time, this approach could ensure that patient benefits are maximised.

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Direct to Consumer Testing

Helen Wallace

Key Points

This chapter considers:

- How and why commercial gene tests are being marketed outside of clinical genetic services;
- Why commercial gene test companies give widely divergent interpretations of the same DNA;
- Whether conflicting interpretations matter and how they might be harmful;
- Whether there are any steps that should be taken to protect consumers.

Keywords Genetic susceptibility · Regulation · Polygenic · Validity · Utility

Introduction

In September 2008, an article in the Sunday Times reported the results of an investigation in which three commercial genetic testing companies gave widely divergent interpretations of the journalist's DNA (Fleming 2008). The report followed a 2006 investigation by the US Government Accountability Office (GAO), which concluded that four websites marketing genetic tests over the internet were providing information that misled consumers (US GAO 2006). These investigations raise important questions about the quality of commercial genetic tests that are marketed outside publicly-funded clinical genetics services: known as direct-to-consumer (DTC) tests.

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In this chapter, DTC genetic testing is considered to include any health-related gene sequencing service offered to the general public outside specialised clinical genetic services. The focus of this chapter is on germline genetic testing, which provides information based on the "genetic make-up" of an individual. Privacy, surveillance and discrimination issues, and issues about relationships and ancestry, are omitted from the discussion, which focuses on the quality of health-related information.

How and Why Are Commercial Gene Tests Being Marketed?

Unlike clinical genetic services, which focus on the diagnosis of genetic disorders and, increasingly, the identification of relatively rare genetic mutations which predispose to familial forms of cancers or other disorders, most direct to consumer (DTC) genetic testing services identify common genetic variants by sequencing all or part of a customer's DNA. Usually these services identify a number of single nucleotide polymorphisms (SNPs) which have been associated with common disorders or traits, such as type 2 diabetes, hypertension or various cancers. The service will usually include several panels of SNPs associated with different diseases or with the metabolism of drugs, nutrients, or harmful substances (for example, identifying genetic variants associated with "antioxidant capacity" or "nicotine addition"). Some companies are now testing very large numbers of SNPs using proprietary gene chips, or even the whole genome (Hogarth et al. 2008).

The customer may access the testing service directly from the genetic service company or via a distributor (see Fig. 1), which may be another company's website; an alternative healthcare provider; a sports centre, pharmacy or other high street store; or a private clinic. The biological sample is usually provided by the customer using a sampling kit, which typically involves a mouth swab or "spit kit", or, more rarely, a blood sample. The sample is usually posted to the service company but

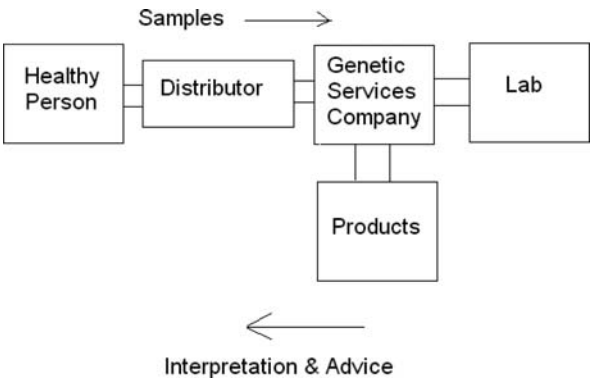

Fig. 1 Direct to consumer gene test marketing

is sometimes collected by personnel employed by the company or their distributor. Other information – such as a lifestyle questionnaire – may be collected from the customer. The sample is then sent to a laboratory for analysis, which may or may not be owned by the service company and can be located in a different country. The customer is then provided with an interpretation of the laboratory findings based on the SNPs identified.

The interpretation may be provided by the lab which identifies the SNPs, but is usually elaborated or devised by the genetic services company, perhaps using a proprietary algorithm. Some companies undertake their own genetic research but many rely on genetic association studies in the published literature. Many, but not all, test results are accompanied by lifestyle advice or advice to take medicines or supplements. These interpretations and advice may be given face-to-face, or supplied in a report and/or using online information resources, which may be updated over time.

Genetic service companies often have, or seek, licensing agreements with companies marketing products such as supplements, functional foods and skin creams, which are claimed to be "personalised" or tailored to the customer's genetic make-up. Web-based services may gain advertising revenue from such products, rather than seeking a licensing agreement. Some, but not all, genetic services companies seek customers' consent to use their DNA for medical research, which may be conducted by third parties.

The direct to consumer services considered in this chapter are aimed at the general population, rather than a clinical subset of people selected on the basis of family history or symptoms of disease. However, consumer motivations to use the service may include concern about genetic susceptibility to a family illness, or unexplained health problems (Burrill & Co. 2008). There is no current data on the uptake of such services, but numbers of customers are likely to be small, especially outside the USA. However, the vision is to expand the market to the entire population: for example, the CEO of DeCode Genetics, Kari Stefansson, predicts that, within five years, "*every reasonably educated person will have had a genetic profile*" (Fleming 2008).

At the time of writing, all DTC consumer genetic testing services are loss-making and future profitability depends on a significant expansion in the market, and/or on licensing or advertising deals for marketing associated "personalised" products or medical services such as health checks and scans. Selling or advertising such products and services, rather than the tests themselves, is the most likely source of significant future revenue. Investment is provided by venture capital – including from the food, pharmaceutical, supplements and cosmetic industries who are interested in "personalised" marketing of future or existing products – or, less frequently, from shareholders, based on the company's intellectual property (IP) and anticipated growth. Some companies own gene sequence patents; others have patented proprietary algorithms and other aspects of their service, such as the sampling kits their customers use to collect their DNA.

Marketing of DTC genetic services is conducted mainly via the internet or existing customer bases: for example, via alternative health providers and supplement distributors. Some companies recruit customers via universities or pharmacies to

take part in studies of the service: blurring the line between commercial testing and research. Many companies have obtained a high profile through media coverage, rather than through traditional advertising. To achieve media success they rely on various forms of endorsement from scientists and celebrities, and claims that they are delivering the promised fruits of the widely-publicised Human Genome Project (HGP).

Companies typically claim that customers can use the genetic information they provide to personalise lifestyle advice, optimise wellness and take control of their own health. Apart from the fact that many services bypass the medical profession, the vision is that popularised by the US leader of the HGP, in which, by 2010, a healthy 23-year-old college graduate gives a cheek-swab of DNA to his doctor and receives a battery of genetic tests to assess his genetic risk of cancers, heart disease and Alzheimer's disease, leading to a regime of prophylactic drugs, colonoscopy and the motivation to quit smoking (Collins 1999).

There are a variety of commercial drivers behind this vision, which raise important questions about whether this approach is really of benefit to health (Wallace 2008). They include attempts by the tobacco industry to convince smokers that only a genetically susceptible minority are at risk of lung cancer (Wallace 2009); and a pharmaceutical industry strategy to breakdown the role of doctors as gatekeepers to medical services and expand the drug market to more healthy people (creating the "pre-symptomatic patient") (Gilham and Rowland 2001). The food industry is also making significant investment in nutritional genetic tests, with the aim of using them to market new functional food products in the future (da Costa e Silva et al. 2007). Genetic profiling is part of a wider growth in personalised marketing, via the internet and, in future, via mobile phones, virtual shopping malls, and modern smart card versions of retailers' customer loyalty card schemes (where DNA could also act as a biometric identifier for an individual customer).

It is particularly important in this context to consider whether people are being given reliable and useful interpretations of their genetic risk and whether the expected health benefits are real and outweigh any harms.

Why do Different Companies Give Different Interpretations?

A critical appraisal of the scientific basis of commercial genomic profiles published in 2008 found significant associations with disease risk for fewer than half of the 56 genes included in commercially available genomic profiles used to assess health risks and personalise health interventions (Janssens et al. 2008). The authors also questioned how the companies studied could provide meaningful genetic risk assessments for complex diseases in the absence of information about multiple genes and gene-gene interactions, and how personalised advice on supplements and diets could be given in the absence of any reliable data on gene-diet interactions.

A number of different problems therefore arise for people seeking reliable, useful and consistent information about what their genes mean for their health.

The first problem is that companies can cherry-pick the literature, or rely on poorly-conducted studies. By 2002, 600 positive associations between common gene variants and disease had been reported but only 6 of these had been consistently replicated (Hirschorn et al. 2002). Although the quality of some studies has improved many remain poor and there remains a tendency for the risk associated with a particular variant to reduce over time. For example, of 32 candidate breast cancer susceptibility genes, all may be false, because the odds ratios from meta-analyses are reducing over time and converging to the null (Breast Cancer Association Consortium 2006; Ioannidis 2006; Pharoah et al. 2007). An overview of meta-analyses of genetic associations for heart attack or coronary artery disease, concluded that even with large-scale evidence from statistical meta-analyses, significant associations may be subject to bias (Ntzani et al. 2007).

The second problem is that only a small proportion of the estimated heritability of complex diseases has yet been explained (Maher 2008). This means that it is at best premature to attempt to give individuals genetic explanations of why common diseases run in families. For example, nine genes showing replicated associations with type 2 diabetes explain only a very small proportion of the familial aggregation of this condition (Zeggini et al. 2007) and testing for 18 SNPs does not appear to improve prediction of type 2 diabetes compared to measuring existing risk factors (Meigs et al. 2008). Similarly, common variations in the so-called "fat gene", FTO, account for only about 1% of the variance in body mass index (BMI) in the UK population. It remains unclear whether more genetic variants have yet to be discovered or whether heritability has been significantly over-estimated, as a result of the assumptions made when it is calculated (Wallace 2006). In pharmacogenetics, despite many claims that genetic testing is the key to avoiding adverse drug reactions, the extent to which a given drug response is likely to be determined by genetic factors has rarely been explored (Ozdemir et al. 2005).

The third problem is the widely-accepted failure of the common disease-common variant hypothesis (CD-CV), which states that the genetic component in the causation of common diseases is likely to arise from a relatively small number of genes. This now appears unlikely to be correct, except in special cases (Mayo 2007). This means that, even if commercial companies include only validated SNPs, the "black box" computer algorithms that they use to calculate a person's risk could give many different answers.

If multiple genetic factors are involved, a variety of different genetic models are consistent with existing data: yet the risk information provided to relatives is dependent on these models (Slatkin 2008a, b). In fact, the number of different possible models of how multiple genetic and environmental factors could interact to cause disease is infinite, and hence it may be impossible to distinguish valid and invalid models even if future studies are much larger than today (Terwilliger and Weiss 2003). The difficulties in validating predictive models of complex physical systems are well known, but are only just beginning to be explored in the context of predicting biological phenotypes from whole-genome SNP data in mice (Lee et al. 2008).

A number of commercial companies aim to refine genetic risk predictions using their own customer base, but this ignores the well-known lesson that models of

complex systems require external validation with independent data sets. Even well-calibrated models of complex systems can have no predictive value, especially if the underlying physics or biology is poorly understood (Carter et al. 2006).

Finally, even if risk predictions are reliable and accurate, this does not necessarily mean that a test is useful as a means of tailoring lifestyle advice or medication. Clinical utility depends on whether health outcomes are improved by a combination of taking the test and the proffered advice or products. For pharmocogenetic tests, results of assessments have been disappointing, with limited evidence of clinical benefits except for a few specific tests (Gardiner and Begg 2006). For lifestyle interventions, evidence is largely lacking on gene-environment or gene-diet interactions.

The issue of clinical utility is different for genetic tests than for most other types of test, because genetic risk factors cannot be removed or reduced; unlike smoking, or LDL cholesterol levels, or blood pressure. For risk factors that are amenable to intervention, it is generally reasonable to assume – at least as a first approximation – that individuals at highest risk are also those who have most to gain from an intervention. However, this is not the case for genetic risk factors. Those who are at highest genetic risk may or may not be those who have the most to gain from a particular medicine, supplement or change in lifestyle. Harm to population health will result if a genetic test is used to target lifestyle advice or medication at a high risk group which has less to gain from the intervention than the low risk one: assessing the clinical utility of the test, not just its clinical validity, is therefore essential. For this reason, any assessment of the likely impact on health of genetic tests combined with environmental or lifestyle advice requires knowledge of the magnitude (and sign) of any gene-environment interaction. No interaction means that the test performs no better than randomly selecting the same number of people from the population (Wallace 2006).

In summary, different risk predictions can result from including different genetic variants in the risk assessment panel for the same condition, or from interpreting the risk associated with these genes in different ways. If multiple genetic and environmental factors are involved, the risk prediction will depend on what factors are included and how they are combined. Evidence of utility is also lacking, and no common genetic variant yet exists which meets medical criteria for screening in the general population. High utility for genetic tests for multifactorial diseases is likely only in specific situations: for example, for some pharmacogenetic applications; in small high-risk subsets of the population; or if large gene-environment interactions are identified.

Do Conflicting Interpretations Matter?

For the reasons outlined above, there should generally be a presumption against the validity and utility of genetic susceptibility tests, because evidence for clinical validity and utility are both largely lacking and early claims have been refuted far more

often than they have been confirmed. This means that many tests have no validity, and none have demonstrated clinical utility as a screening test for the general population. The US Secretary's Advisory Committee on Genetics Health and Society (SACGHS) defines the clinical utility for decision-making as the balance between the benefits and harms of testing and ensuing follow-up evaluation, treatment or prevention (SACGHS 2008).

Failure to assess clinical validity and utility matters because it will inevitably lead to multiple, conflicting interpretations of genetic risk and associated advice and products. A wide variety of commercial interests aim to use genetic tests as the basis for personalised marketing of a wide variety of services and products: including medical scans, functional foods, medicines and supplements. Harm may be caused by:

- Wrongly identifying those at "high genetic risk" or wrongly implying that these individuals have more to gain than others by taking particular advice or medication;
- Confusing or undermining public health messages, including advice to quit smoking or eat healthily;
- "Medicalising" genetic risk: increasing costs and side-effects and exposing individuals to an unnecessary battery of tests and over-treatment;
- Creating unnecessary burdens on publicly funded health services, which may be required to provide follow-up advice or tests.

In addition, misinformation can create unnecessary anxiety or false reassurance about an individual's risk. It is clear to specialists that testing for susceptibility to common disorders is very different to having a predictive genetic test for a genetic disorder such as Huntington's Disease. However, complex disorders, such as Alzheimer's Disease, schizophrenia or cancer are no less serious than Huntington's Disease. Unless people taking tests for susceptibility to these conditions are properly informed that genetic association studies are often wrong or, at best, have very low predictive value, they may make misinformed choices and decisions. This is further complicated by the existence of tests of rare mutations which strongly predispose to familial cancers. Awareness of the existence of such tests may leave customers confused about the much lower predictive value of SNP tests.

For less-feared conditions such as obesity and other diet-related diseases, the public health consequences of widespread misleading genetic information could be very serious, even if the impact of such misinformation on individuals may appear to be relatively trivial.

Finally, many DTC gene testing companies include genetic variants of APOE in gene panels for risk of heart disease, although some of these variants have also been associated with an increased risk of Alzheimer's Disease. This raises important ethical questions about whether such tests should be used at all and, if so, what information should be given.

What Steps Should be Taken to Protect Consumers?

DTC genetic tests provide a clear example of one type of market failure that is commonly used to justify regulation – namely, lack of reliable information for consumers about the product they are buying. The market fails for two main reasons: firstly, because many companies do not even provide a list of genes or SNPs included in their services, allowing no opportunity for independent verification of their claims; secondly, even if this information is provided, checking its validity and utility is a specialist, time-consuming process, beyond the reach of many customers and even medical professionals.

This problem is compounded by the fact that there is far more false than reliable information in the published literature on gene-disease associations, and that data on clinical utility is often lacking. A background of "genohype" also creates a situation in which many people believe that the services they purchase are at the cutting edge of medicine and that the only question they need to ask themselves is "Do I want to know?", not "Can I trust the information I am given?".

Other chapters in this book discuss existing regulatory frameworks and how they might develop in the future. The most important step to protect consumers from misleading genetic information should be revision of Europe's Medical Devices Directives in line with the new Protocol to the Council of Europe's Convention on Human Rights and Biomedicine (Council of Europe 2008). This would require criteria for clinical validity and utility to be met before genetic testing services are offered. Only an independent regulatory assessment of the evidence can provide the necessary information for informed decisions.

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Competency Based Core Curriculum for Training Specialists in Clinical Genetics

Helen M. Kingston

Key Points

- Genetic services need to reflect the health care needs of particular populations and are subject to national regulation.
- Identification of the core competences required by Clinical Geneticists will form the framework for developing training programmes that allow international recognition of specialist training.
- Competency based assessment will maintain quality control by ensuring that performance meets a specified standard.

Keywords Competency based curricula · Clinical genetics competences · Specialist training in clinical genetics · Assessment of competence

Introduction

Clinical Genetics is a recognised medical specialty in most, but not all European countries. The increasing movement of the medical workforce between countries within the European Union highlights the need for consistency and equivalence in specialist curricula amongst the member countries, so that mutual recognition of specialist training can be achieved. Individual countries have their own regulatory and professional bodies, which determine specialty training and service delivery, based on curricula developed with input from medical specialists. The European Society for Human Genetics (ESHG), as the overarching specialist Society in Europe, has produced guidelines on the provision of Genetic

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Services in Europe (Ayme et al. 2003). Recommendations on the core competences required by various health professionals, including specialist Clinical Geneticists, have been proposed by and are published on the ESHG and EuroGentest websites (Skirton et al. 2008: www.eshg.org and www.eurogentest.org). Within the Union Européenne des Médecins Spécialistes (European Union of Medical Specialists; UEMS. www.uems.org.), Clinical Genetics is represented by a Joint Multidisciplinary Committee (MJC), whose remit is to harmonise training across Europe and oversee the approval of continuing specialist medical education. The MJC, in conjunction with the Education Committee of the ESHG, has produced a document outlining the aims and objectives for specialist training in Clinical Genetics (Available at www.ESHG.org).

The Specialist Role of Clincal Geneticists

Clinical Geneticists provide a specialist service to families with genetic disease due to inherited single gene disorders, chromosomal disorders, birth defects or diseases with a genetic predisposition that can affect any system of the body and any age of patient. Their expertise complements those of other non-genetic specialists who may manage the medical or surgical aspects of these diseases. Geneticists have particular expertise in managing genetic issues that extend over several generations of extended families, which encompass clinical diagnosis, genetic investigation, assessment of genetic risk, predictive, prenatal and preimplantation genetic diagnosis, as well as provision of genetic information and supportive counselling. Multidisciplinary teams within the specialty consist of medically trained clinical geneticists, non-medical genetic counsellors and clinical scientists (cytogenetic, molecular and biochemical), all of whom work closely with non-genetic specialists in providing holistic care. Geneticists also deal with issues of ethics, confidentiality and consent that are particular to genetic conditions. In a rapidly advancing field, geneticists are involved in education of the public and other health care professionals and participate in basic scientific and applied research as well as service development for patients affected by genetic disease.

Competency Based Specialty Training

The purpose of a specialist curriculum is to set out the aims and objectives of a training programme and should include content, process and outcomes, defining the knowledge, skills and behaviours to be acquired and identifying methods of learning, teaching, supervision, feedback and assessment.

Over the last decade an emphasis has been placed on the development of competency based medical curricula. However, the concept of identifying educational competences in an attempt to achieve consensus on the definition and assessment

of educational outcomes is not new. The theoretical framework devised by Bloom (1956) led to the development of three major outcome domains; namely, acquisition of knowledge and intellectual abilities, proficiency in manipulative skills and development of attitudes and values, often referred to now as "knowledge, skills and attitudes" (KSA). It follows from this that a competency based curriculum will define the outcome of the training in terms of skills and performance, rather than just the educational process itself.

Competency may be interpreted in different ways, but is basically defined as "the ability to do something successfully". A useful expansion of this definition is to consider competence as a combination of related knowledge, skills and attitudes that impacts on professional job responsibilities, correlates with job performance, can be measured by well-accepted standards and improves with training and personal development (Lucia and Lepsinger 1999). In clinical practice, acquisition of competence is based on a set of minimum criteria that need to be achieved in order to practice in a safe and effective manner, which are agreed by consensus of an expert group. Competency may be viewed as a step in the process of achieving proficiency and expertise. To this extent, competence will vary across different groups, as well as over time, during career development.

In the USA, Canada, the UK, the Netherlands and other countries, general medical curricula are now competency based. The Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Medical Specialities (ABMS) in the USA, identified 6 general competences for residents that comprise: (1) patient care, (2) medical knowledge, (3) practice-based learning and improvement, (4) interpersonal and communication skills, (5) professionalism and (6) systems-base practice (Jackson et al. 2007).

The Royal College of Physicians and Surgeons of Canada, in their CanMEDS 2005 framework (Frank 2005), also defined the key roles of a medical specialist and described sets of related competences that need to be achieved by physicians. The seven key roles they identified for physicians are: (1) Medical Expert, (2) Communicator, (3) Collaborator, (4) Manager, (5) Health Advocate, (6) Scholar and (7) Professional. This system has been adopted by several other countries, including the Netherlands, where competency based postgraduate training programmes became a legal requirement in 2006 (Scheele et al. 2008). Other countries, including the UK have devised competency based curricula according to their own national requirements (www.pmetb.org.uk and www.jrcptb.org.uk/specialty).

To achieve equivalence of training between different countries, international consensus is required on what constitutes core competences in specialist training. Regional and continental differences such as language, culture, social policy, public opinion, economics and access to care are some of the variable factors that need to be considered (Plasschaert et al. 2002). Nevertheless, it may be possible to generate internationally acceptable core competences that are able to accommodate local requirements, based on the experience reported by Barrett and Bion (2006) during the second phase of a 3 year project to develop a pan European competency based training programme for intensive care medicine. Using consensus techniques (modified Delphi and nominal group), internationally applicable competency stems were

identified and subdivided into several constituent elements, following input from stakeholders in many different countries.

The emphasis placed on the different professional roles of Clinical Geneticists varies within and between countries. Some specialists are clinically orientated and may provide continuing medical as well as genetic care, whilst others may direct laboratory services or have a predominantly academic focus. Nevertheless, the requirements to practice may be defined by a common set of roles and core competences, which represent what is required by a genetic specialist to achieve a good medical outcome. It follows that a competency based educational process should enable trainees to access individualised training, with definition of the knowledge that needs to be acquired and the tasks that need to be performed, whilst allowing flexibility in achieving the required outcomes. Within Clinical Genetics, generic roles such as professionalism, multidisciplinary team-working, research and health care management reflect those required by all medical practitioners. Roles specific to the specialty include diagnosis, assessment and genetic management of a diverse array of conditions, as well as risk assessment, understanding and interpreting laboratory genetic investigations and involvement in population screening programmes. In a rapidly developing specialty it is crucial that new technological and therapeutic advances are incorporated quickly into the expanding set of competences required of the medical specialist, an area that highlights the importance of life-long learning and continued professional development.

The challenges of achieving equivalence and recognition of specialist training in genetics across international boundaries, whilst at the same time allowing training programmes that fulfil the service requirements and statutory regulations of the individual country, are considerable. A proposed set of specialty-specific core clinical competences have been drawn up by the Eurogentest expert group (Skirton et al. 2008) that could provide an appropriate framework for establishing minimum standards for specialist clinical geneticists and inform development of individual curricula (Table 1). The document uses the definition of competence put forward by Plasschaert et al. (2002) as being the knowledge base and behavioural standards expected of an independent professional and each competence is subdivided into several learning outcomes that encompass knowledge, skills and attitudes.

Competency Based Assessment

Assessment of competence involves measuring achievement against defined standards and is based on performance data gathered from a variety of sources. There are many methods of assessment applied to general medical training that are relevant to specialist training in Clinical Genetics, but considerable variation in how they currently applied in different training programmes. A crucial aspect of assessment is the delineation of standards, as well as validation of methods, which need to be reliable and reproducible. This process is facilitated by having a common set of goals and performance indicators.

Table 1 Core clinical competences for clinical geneticists proposed by the Eurogentest expert group

1. Identify individuals and families whose disorder or condition is determined, partly or fully, by a genetic component
2. Determine the accuracy of the clinical diagnosis and, if needed, initiate additional clinical examination to make a diagnosis
3. Be familiar with the feasibility and accessibility of genetic services that could help individuals and families through genetic counselling
4. Provide an accurate specialty-focussed view on the nature of a genetic disorder
5. Determine the need for and utility of genetic tests relating to a disease or specific condition
6. Understand the meaning of genetic test results and translate those results into practical disease-specific information for both patients and other professionals
7. Help individuals and families to understand the information provided during genetic counselling
8. Facilitate understanding between individuals, families, their family doctors and specialists about genetic disorders, test results and inheritance patterns
9. Determine the risk of occurrence or recurrence of a disease or condition
10. Understand the genetic and environmental components of common disease
11. Provide genetic information that helps individuals or couples make informed reproductive decisions
12. Work within the boundaries of ethical practice

Written or oral examinations are widely applied to assess knowledge and have several formats including:

- short answer or essay questions
- multiple choice or matching questions
- structured oral examinations
- objective structures clinical examinations (OSCEs)
- objective structures performance-related examinations (OSPREs)

Many methods of assessing competence are work-place based and include:

- written case reports
- direct observation of practice
- mini clinical evaluation exercise (miniCEX) or encounter cards
- case-based discussions
- multisource feedback from colleagues and patients
- completion of log books and collation of portfolios

Most of these methods of assessment are described, with reference to key papers, on the canMEDS website (Bandiera et al. 2006). Studies have been undertaken looking at validity, reliability, feasibility and utility of different assessment methods in a number of countries including Canada, the USA and the UK (Hatala et al. 2006; Norcini and Burch 2007; Wilkinson et al. 2008) but there are still lessons to be learned.

It is likely that the competences identified for specialist training in Clinical Genetics will underpin specialist revalidation and recertification processes in many

countries, based on similar methods of assessments to those listed above. Continuing Medical Education (CME) ensures that competences achieved during training are maintained and updated throughout the specialist's practising life. National CME systems are well established in most countries and Europe has a system of cross-border and international recognition of CME through accreditation of educational meetings by the European Accreditation Council for Continuing Medical Education (EACCME) (www.uems.be)

Specific Aspects of Specialist Training

The common core curriculum for training in Clinical Genetics approved by the ESHG and UEMS is available at: www.ESHG.org. Along with the aims and objectives for a specialist curriculum (Table 2), the UEMS Joint Multidisciplinary Committee and the ESHG Education Committee (2009) highlighted the following features of specialist medical training programmes in Clinical Genetics.

Table 2 Summary of the educational aims and objectives for specialist training in clinical genetics proposed by the UEMS Multidisciplinary Joint Committee and the ESHG Education Committee (2009)

Knowledge and skills

Theoretical genetics/Basic science which should include
- Understanding cellular and molecular mechanisms that underpin human inheritance
- Understanding patterns of inheritance and methods for risk assessment
- Genetic epidemiology and biostatistics

Clinical/Medical knowledge and skills
- Pedigree construction
- Diagnosis, investigation and genetic management of individuals with both common and rare inherited/genetic diseases and their families
- Risk assessment and role in genetic testing
- Paediatric genetics including training in dysmorphology (knowledge of common dysmorphic syndromes, their aetiology and the use of dysmorphology databases) and investigation of learning disability in children
- Adult genetics to include knowledge of late onset disorders and disorders with a significant genetic component presenting in adult life (including predictive testing)
- Prenatal Genetics and knowledge about fetal development and teratogens
- Population genetics, including genetic screening programmes
- Special areas of genetics including
  - Inherited metabolic disorders
  - Neuro- and neuromuscular genetics
  - Cardiovascular genetics
  - Cancer genetics
  - Neurosensory genetics (visual and hearing conditions)
  - Pharmacogenetics
  - Other subspecialties of specific interest to the trainee
- Subspecialty training: some trainees will elect to develop expertise in a subspecialty area such as cancer genetics, dysmorphology or neurogenetics

Table 2 (continued)

Genetic counselling and communication skills
- Training in genetic counselling for all types of genetic disease and situations encountered in clinical genetic practice. This includes counselling in relation to prenatal diagnosis for late onset such as neurogenetic and cancer genetic disorders, including predictive testing. Where applicable, training in co-counselling with other professionals such as genetic counsellors
- Understanding ethical issues and importance of consent and confidentiality
- Development of good communication skills with patients, colleagues in genetic centres and other specialists and healthcare professionals, including understanding and handling of crisis reactions

Laboratory skills
- Thorough knowledge of principles of laboratory techniques used in diagnostic testing
- Interpretation of results from cytogenetic, molecular genetic and biochemical genetic analyses
- The time spent and the practical expertise gained in laboratory work may vary between countries, but should be sufficient to ensure acquisition of highly specialised knowledge

Other aspects of the training programme

Maintaining good medical practice
- Develop a commitment to lifelong learning through continuing professional development and attend relevant courses and conferences
- Participate in audit and clinical governance
- Adhere to established consent and confidentiality procedures
- Understand ethical and legal issues

IT skills
- Use of information technology including online resources and databases

Management training
- Knowledge about general healthcare policy, goals and priorities
- Understanding the organisation of genetic services
- Opportunities to participate in departmental activities related to organizational planning, financial management, and monitoring and maintaining quality standards
- Development of multidisciplinary team working and leadership skills

Teaching
- Develop teaching skills by participating in the education and training of various categories of staff
- Involvement with patient groups and patient education

Supplementary education and training
- Subspecialty training: some trainees will elect to develop expertise in a subspecialty area such as cancer genetics, dysmorphology or neurogenetics

Research
- Medical genetics has a rapidly changing knowledge base and during specialty training the clinical geneticist should be encouraged to participate in research. Some trainees will wish to take time out from the clinical training programme to undertake an intensive period of research leading to a higher academic degree. On completion of training some academic clinical geneticists will continue to lead research programmes whilst many others will collaborate with laboratory based colleagues in the genetics team

Entry Criteria

These may vary from country to country but would generally include a specified period of general medical training to include adult and/or paediatric medicine internship or residency prior to commencing specialty training in Clinical Genetics. Some countries may have a minimum period of training to be undertaken before specialisation.

Quality Assurance

The following key aspects of quality assurance are proposed:

- Competency based curricula should form the basis of a training programme.
- A written agreed curriculum for the training period should be set up as a contract between the trainee and the supervisor if not otherwise determined by national regulations.
- Trainees should maintain a Training Log including details of clinical and laboratory experience, educational activities, research and publications.
- A mechanism should be in place for continuous assessment of trainees against agreed quality standards. Some countries will have a nationally prescribed system for assessment and certification.
- Specialist examination may be compulsory in some countries.

Time Frame for Specialist Training

It is recognised that the length of training may vary between countries as may the time spent on particular aspects of training, according to the varied roles of established specialists. The following principles were proposed:

- The training period should minimum 4 years full time work; part time work would extend the training period.
- An educational training programme will be agreed for each trainee according to the specialty specific curriculum.
- During a longer training programme, up to 1 year could be in another speciality of importance for clinical/medical genetics.
- The time spent in laboratory work may vary between countries according to national curricula.
- A period of research resulting in a PhD or other higher exam may, if appropriate, replace training for a variable period of time according to national guidelines. However, in absence of national guidelines, it is not recommended that this time period is longer than 1/3 of the total training period.

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Ensuring Education and Quality in the Practice of Health Professionals (Non-medical) Working in Genetic Services

Heather Skirton and Domenico A. Coviello

Key Points

- The science of genomics is increasingly important to healthcare provision in Europe and has an increasing impact on the diagnosis, prevention and treatment of common disease.
- The number of tests being performed is changing rapidly with a concurrent increase in the number of individuals that have to make decisions about testing that may profoundly influence not only their own lives, but the lives of their family members.
- More professionals with different backgrounds will be involved in genetic services, either directly or in dealing with the impact of testing to provide psychosocial support for families.
- New professions are rapidly evolving in Europe. Genetic nurses and genetic counsellors are health professionals with specific training and expertise in the activity of genetic counselling. Genetic counsellors may have a background in nursing, midwifery, social work, psychology or biology applied to health science and work as part of the multi-professional team in clinical genetics or other specialist services.

Keywords Education and training of non-medical genetic specialists · Genetic nurses and counsellors · Core competence · Genetic tests · Psychosocial support

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The Development of Genetic Counselling Practice Within Genetic Services in Europe

Although more than a century ago physicians such as Huntington (1872) concluded that some of the conditions they studied were inherited, genetic counselling was not seen as a specific component of healthcare provision until after the Second World War. Clinical genetic services were established in both Europe and in North America in the 1940s. During the 1960s, the accuracy of cytogenetic testing of human chromosomes increased, making prenatal and postnatal diagnosis of chromosome abnormalities possible. However, huge growth in genetics services occurred during the 1980s, following significant developments in recombinant DNA technology. Until that time, genetic counselling for single gene disorders had, of necessity, largely performed by clinical geneticists, consisted of discussion of the inheritance pattern and recurrence risks because the options for families were very limited. With the expanding opportunities for families to consider a range of genetic tests, including diagnostic, predictive and prenatal, there was a corresponding need to expand services that provided the individuals with the opportunity for thorough discussion of the options available as well as support when making decisions and adjusting to the results (Cassiman 2005). These areas of service are the basis for genetic counselling practice.

Clinical genetics services are well-established in many countries. Initially most services were provided by medical doctors, mainly in paediatric clinics. However with an increasing workload and the increasing number of genetic tests available laboratory scientists also get involved in genetics services. Moreover due to the changing emphasis on the need for psychosocial support for families, professionals from other backgrounds have been recruited to work within the specialty. The function and operation of a clinical genetics service is described by Kingston in chapter "Competency Based Core Curriculum for Training Specialists in Clinical Genetics". Working alongside medical geneticists, molecular geneticists and cytogeneticists, the genetic counsellor contributes as part of the team to provide an holistic and comprehensive service to families concerned about or affected by a genetic condition (Skirton et al. 1997).

The title "genetic counsellor" relates to health professionals with *specific training and expertise* in the activity of genetic counselling. Genetic counsellors may have a background in nursing, midwifery, social work, psychology or biology applied to health science and work as part of the multi-professional team in clinical genetics or other specialist services.

The Profession of Genetic Counsellor

There is sometimes confusion about the activity described as genetic counselling and the professional role of the genetic counsellor. The definition of genetic counselling has been included in a separate chapter, but has been described as a process that includes:

> Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
>
> Education about inheritance, testing, management, prevention, resources and research.
>
> Counseling to promote informed choices and adaptation to the risk or condition. (Resta et al. 2006)

There is an area of overlap between the work of medically trained geneticists and genetic counsellors, both of whom perform the task of genetic counselling. However while medical geneticists are trained and highly skilled in diagnostic techniques, the education and practice of genetic counsellors focuses more on interventions that will affect the psychosocial health of the individual and the family. Their training reflects this need for advanced counselling skills.

There is a large body of research that has highlighted the potential negative impact of a genetic condition or risk on the psychological and social health of the individual. The impact of the condition is far reaching and does not just have an impact on affected or at risk family members. For example, Sobel and Cowan (2003) found that after a negative test result, those who had previously shared the feeling of being at risk with other relatives family members experienced feelings of disconnection with their family members and felt they no longer belonged to the family. Guilt at having passed on a condition is common in parents, particularly in female carriers of X-linked conditions (James et al. 2006). Within a family there may be attempts to maintain secrecy to avoid stigmatisation and to reduce the chance of causing worry in children (Peters et al. 2005), this can result in stress to those who are aware of the secret as they live with form of anticipatory loss that they cannot share (Rolland 1999). The data in these and many other studies underpin the need for support by skilled professionals to help clients to manage emotional effects of the genetic condition in the family (McAllister et al. 2007).

The main components of the role of genetic counsellor are therefore:

- To communicate effectively with counselees and their families. This communication includes obtaining the family medical history, providing the individual and/or family with reliable information about the condition, inheritance pattern and recurrence risks and options available to them, and facilitating discussion about the options available to them.
- To offer the counsellee and/or family appropriate psychological support, particularly at times of decision-making or adjustment (for example to a new diagnosis).
- To provide education on relevant subjects and issues to counsellees and to other health professionals.

In order to perform these tasks, the education and training of the genetic counsellor needs to be planned to ensure that they are able to interpret complex scientific information to inform their own risk assessments and to enable them to explain such information in a comprehensible way to counselees. As many of the issues around clinical genetics are highly sensitive and emotive, the genetic counsellor must also be trained to manage a counselling session, ensuring that the counselee is

able to express their emotions in a safe environment, explore the choices and make an informed decision without coercion.

The Evolving Role of the Genetic Counsellor in Europe

The role of the genetic counsellor has evolved slowly in Europe over the past three decades. In the UK, initially nurses were recruited to the genetic service to support the doctor during clinical appointments. However, this role was extended as it became clear that they could take undertake tasks to prepare the family for the genetic consultation and provide some follow up care. Pre-clinic consultations between the genetic nurse and the consultant often included taking a family history, drawing the pedigree and obtaining clinical records in preparation for the main clinical consultation with a medical geneticist. As nurses developed expertise (mainly through working closely for long periods with medical colleagues), the role developed so that some nurses were also able to discuss the genetic inheritance pattern, make genetic risk assessments and discuss options with the consultant (Skirton et al. 1997).

The health and educational systems operating in European countries differ greatly and this has had implications for the development of the genetic counselling profession. For example, in some countries a strongly medically oriented model of healthcare exists, and the medical doctor is perceived as the only type of professional capable of developing the requisite competence to provide genetic counselling to patients. This approach may be reinforced where financial reimbursement for healthcare is only available to those with a medical qualification. A related issue is the status afforded to allied health professionals by colleagues and the general public. In countries where nursing and other health professions are viewed as markedly inferior to medicine, the patient may not have confidence in the information provided by the genetic nurse or counsellor, whereas in those countries where nurses, midwives and other allied health professionals have been working autonomously for decades, public trust has already been established. In addition, in each country, there are specific legal frameworks governing the practice of health professionals. In France, for example, the practice of genetic counsellors is governed by law, whereas in other countries there is no statutory regulation of genetic counsellors at present. Statutory regulation of nursing and midwifery is universal in Europe and this creates an anomaly whereby the practice of those genetic counsellors with a nursing or midwifery qualification is subject to legal regulation while the practice of genetic counsellors who have no other professional qualification may not be. This anomalous situation needs to be addressed in each country, for example in the United Kingdom, attempts are being made to ensure that the statutory regulation of genetic counsellors is undertaken by the Health Professions Council.

In those countries where genetic nurses and genetic counsellors work alongside medical geneticists, both groups of professionals will have a range of skills

necessary to provide appropriate patient care, and there will naturally be some considerable overlap in those skills. However, as will be clear from the competences listed later in this chapter, genetic nurses and counsellors are not trained as diagnosticians. Medical geneticists are therefore always involved in cases where a diagnosis must be made or clarified. Genetic nurses and counsellors are thoroughly trained to provide psychological support to the patient, especially in those areas of adjustment to the genetic diagnosis and facilitating informed decision making. When a team approach is used, the complementary nature of these skills allows each professional to focus on areas where their own expertise will most effectively enhance the care of the patient.

In Europe, the educational preparation for those genetic counsellors who did not have a nursing qualification followed a pattern that originated in the North America. Genetic counsellors in the US had been educated through a number of Master level programs, which were approved on an individual basis as suitable training providers for genetic counsellors. The first master degree in genetic counselling was started in the UK (at Manchester University) by a graduate of one of those programs, with the first graduates completing the program in 1994. Whereas some graduates had a background in one of the health professions, others were graduates of other baccalaureate programs, for example in genetics, biology or psychology. There are now a number of other Master programs in Europe, including in France, Spain, Portugal and Romania. The Netherlands was the first country in Europe to put formal arrangements in place for educating and assessing genetic nurses and counsellors, through practical experience in a host genetic centre and attendance at national courses. However a new system involving an academic program at Master level has been introduced. Any Master's degree course to prepare genetic counsellors for practice must include a substantial practical component to enable the student to develop the requisite clinical skills, as well as addressing the student's need for material on human genetics, clinical genetics and counselling. The essential components of a Master's degree course in genetic counselling are listed in Table 1.

It has been explained that genetic nurses and genetic counsellors may come into the profession by slightly different routes but perform the same roles. For brevity, the term genetic counsellor will be used from this point to denote either a genetic nurse or a genetic counsellor.

European genetic counsellors may therefore have a background in one of the health professions, or they may have entered the profession via a Master's degree in genetic counselling. Given this diversity, there is a need to ensure that all practitioners who are working in a role are appropriately educated and prepared for practice. Ensuring quality of both education and practice is essential to protect the safety and best interest of patients and their families (Skirton et al. 1998). For these reasons, a competence based system has been developed that can be applied in each country, according to the legal, educational and health service context within that country.

Table 1 Components of a Master's degree course in genetic counseling

Underpinning knowledge	Clinical skills	Practical placements
Basic human genetics including DNA structure and replication, inheritance patterns, chromosomal structure	Advanced counselling skills, including use of skills to facilitate decision making and support psychosocial adjustment	Practical experience in suitable health care settings, such as paediatrics, obstetrics, neurology
Variations in gene and chromosomal structure and their implications for human health	Family history taking and pedigree drawing	Practical experience in suitable social or educational care settings, such as schools for children with special educational needs, industrial environments for adults with physical or mental disability
Processes involved in finding disease genes	Genetic risk assessment	Practical experience working alongside genetic counsellors and medical geneticists in clinical settings
Methods of genetic testing	Applications of genetic testing, including diagnostic, prenatal, carrier and pre-symptomatic tests	
Clinical genetics – signs and symptoms clinical disease, screening and management	Ethical and legal practice	
Probability and statistical methods related to genetic healthcare	Research skills	

Establishing a Set of Competences for Genetic Nurse and Counsellors

A set of core competences for genetic nurse and counsellors has been developed by a group of European experts in the field of genetic healthcare. The writing of the core competences was guided by previous work undertaken by professional groups in the UK and the US, in particular those prepared by the United Kingdom specialist organisation, the Association of Genetic Nurses and Counsellors. Members of a Working Group in that organisation had devised a set of competences upon which the entire professional registration system for genetic counsellors in the UK is based (Skirton et al. 2003). The scope and standards of practice for genetic nurses (Greco et al. 2006) written by members of the International Society of Nurses in Genetics provided much background material. In addition, the expert group used the

Table 2 Core competencies for genetic counsellors, proposed by the Eurogentest expert group

Competence
1. Establish relationship and clarify clients' concerns and expectations
2. Make appropriate and accurate genetic risk assessment
3a. Convey clinical and genetic information to clients, appropriate to their individual needs
3b. Explain options available to the client, including the risks, benefits and limitations
3c. Evaluate the understanding of the individual related to the topics being discussed
3d. Acknowledge the implications of individual and family experiences, beliefs, values and culture for the genetic counselling process
4. Make an assessment of clients' needs and resources and provide support, ensuring referral to other agencies as appropriate
5. Use of a range of counselling skills to facilitate clients' adjustment and decision-making
6. Document information including case notes and correspondence in an appropriate manner
7. Find and utilise relevant medical and genetic information for use in genetic counselling
8. Demonstrate ability to organise and prioritise a case load
9. Plan, organise and deliver professional and public education
10. Establish effective working relationships to function within a multi-disciplinary team and as part of the wider health and social care network
11. Contribute to the development and organisation of genetic services
12. Practice in accordance with an appropriate code of ethical conduct
13. Recognise and maintain professional boundaries and limitations of own practice
14. Demonstrate reflective skills and personal awareness for the safety of individuals and families
15. Present opportunities for clients to participate in research projects in a manner that facilitates informed choice
16. Demonstrate continuing professional development as an individual practitioner and for the development of the profession

competences developed by the US based National Coalition for Health Professional Education in Genetics (NCHPEG 2007), however these are far more general and do not relate specifically to genetic counsellors.

This work is part of the major project to develop core competences in genetics for all health professionals. The basic core competences for genetic counsellors are listed in Table 2, but a full table including suggested learning outcomes can be found at the website of the European Society for Human Genetics (ESHG) (http://www.eshg.org/) and at the web site of EUROGENTEST project (www.eurogentest.org).

Assessing Competence

At present there is no European-wide method of assessing competence and therefore ensuring the quality of the practice of genetic counsellors. In the Netherlands and the United Kingdom, a system of registration/accreditation for practitioners exists and is administered at the national level through the professional organisations. In France the practice of genetic counselling is governed by a legal framework. However, in

many countries there is neither professional organisation nor legal status for genetic counsellors.

In order to develop the core competences to a level that assures a quality service, practical training and experience are needed in addition to theoretical and academic preparation. For this reason, the current systems of registration/accreditation for genetic counsellors require candidates to provide evidence of a period in practice as well as completion of an academic qualification. In the UK, assessment of competence is carried by an elected Board who oversee the assessment of a portfolio of evidence submitted by the candidate (AGNC 2006). Evidence must be provided to support each of the competences before registration is granted. Use of a portfolio system of assessment allows the candidate to demonstrate competence in the context of his or her practice setting and may therefore be a useful tool for assessment at a European level in the future.

Future Directions

In order to create a more coherent approach to development and assessment of competence at the European level, new committees of the European Society of Human Genetics have been established, with the aims of both setting standards and ensuring recognition of the professions at European level: Accreditation Committee for Clinical/Medical Geneticists; Accreditation Committee Genetic Nurses/Counsellors; Accreditation Committee for Laboratory Geneticists.

The Accreditation Committee Genetic Nurses/Counsellors has set up a network of practitioners from 24 countries who are working collaboratively to define the required standards of professional practice for genetic counsellors and the minimum recommended standards of education. The Accreditation Committee for Laboratory Geneticists has recently started to meet, although the legal framework in Europe is quite heterogeneous. For example, in Italy the law requires all basic science professionals to get a second degree obtained following the School of Specialization in Medical Genetics (4 years full time) in order to be enrolled in a Medical Genetic Laboratory in the National Health System.

The efforts of professionals across Europe to ensure minimum standards of education and practice in genetic healthcare is essential for patient safety. The aim of the efforts is to establish equitable care for individuals and families affected by genetic disease.

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Quality Issues in Clinical Genetic Services: Ethical Aspects

Göran Hermerén

Key Points

Bullet points, reflecting the most important issues of my chapter

- Quality in genetic services presupposes clear, consistent and well-argued for ethical premises.
- Without such premises, priorities, public confidence and quality of genetic services are likely to be negatively affected.
- Choice of alternative formulations or provisions in quality assurance guidelines are based on, and intended to protect, ethical values.
- Sometimes there are tensions in our culture between these values, which give rise to ethical conflicts or problems.
- Ethical condiderations enter into several different levels of discourse, five of which are discussed in the present chapter.

Keywords Ethics · Quality · Goals · Values · Genetic services

Introduction

What can go wrong in genetic testing? Patients can be harmed, if inappropriate FISH (fluorescence in situ hybridization) probes are used, if FISH signals are interpreted incorrectly, and/or if incomplete or incorrect interpretation results in an incorrect diagnosis. But there are more dimensions to quality in the provision of genetic services, and they raise a variety of ethical issues (Chadwick 1997).

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In this chapter I will give an overview of ethical issues relevant to quality assurance of clinical genetic services, and try to demonstrate that ethics will enter into several places, not just in the formulation of the goals. The approach will be holistic and process-oriented, like the one I proposed earlier for evaluation of ethical aspects of nanomedicine (Hermerén 2007).

The main message of this chapter is that quality in genetic services presupposes clear, consistent and well argued for ethical premises. If they are missing, priorities, public confidence and quality of genetic services are likely to be negatively affected. Choice of alternative formulations or provisions in quality assurance guidelines are based on, and intended to protect, ethical values.

Ethical problems are raised by conflicts between values, rights or interests. An ethical problem presupposes that there are alternatives with non-identical consequences for the parties involved, and that these parties have different interests, values and/or rights, all of which cannot be satisfied at the same time. Hence, a decision has to be made, which will favour some at the expense of others.

As an illustration, consider the OECD (2007) guidelines, Best practice C.vii:

> Individual laboratory performance in proficiency testing schemes may be disclosed on a voluntary basis by the laboratory concerned but should not be made public by proficiency testing scheme providers unless so required by law.

Which are the alternatives? Two alternatives to the first part above include

> (A) "Individual laboratory performance in proficiency testing schemes may not be disclosed by the laboratory concerned. . ."

> (B) "Individual laboratory performance in proficiency testing schemes must be disclosed by the laboratory concerned. . ."

The choice of alternatives will have different consequences for those tested, their relatives, clinical geneticists, other health care professionals, laboratories and those financing the tests. The choice between the alternatives will favour not only different values but also values of different stakeholders; hence the choice between the alternatives is not ethically neutral.

Quality and Ethics

Uncertainty about terminology and the most appropriate quality system could negatively affect the quality of genetic services. But the more fundamental question is, of course: why is quality important? Which goals can be achieved by improving the quality of genetic services? What is the ethical basis for these goals? Which values, and whose values, are promoted in that way?

On a rights-based approach, one would look for the underlying ethical values in declarations of human rights, like those of the UN and the Council of Europe. Since these declarations have been adopted by elected representatives in a democratic procedure, they would also have democratic legitimacy in a way guidelines from professional organizations would not. Anyway, the idea is that improved quality would help to ensure that these rights are protected.

A utilitarian justification would be different. If a classical utilitarian theory of the sort advocated by Bentham (1960) is the starting point, the reason for efforts to improve the quality of genetic services should be that they would help to maximize happiness. If, however, contemporary utilitarianism of the sort proposed by Singer (1993) is the starting point, the justification should be that improved quality would help to maximise interest satisfaction of the stakeholders: more strong interests would be satisfied in that way.

A Kantian deontological approach would start with basic principles like humans should always be treated as ends in themselves, not merely as means, supplemented by principles like: if it is ethically acceptable for a certain agent in a specific situation to do something, then it should be ethically acceptable for any other agent in the same situation to do the same.

Various ethical starting points can be combined and – via different routes – lead to similar conclusions. Thus, we will not necessarily end up with conflicting recommendations depending on the chosen ethical framework. But in certain cases this cannot be excluded. For example, the utilitarian arguments for disclosing information to relatives of those tested (=index persons) about test results are strong, especially if it can make a vital difference to the health and quality of life of these relatives. But if the starting point is the right not to know, based on deontological ethics or certain provisions in declarations of human rights, the result is likely to be different.

The Strategy

Ethical considerations will enter not only in the statement of the goals but also in several other places indicated by the structure of this chapter, where five different levels will be separated:

(1) Description of the present situation (raising issues of hope and hype).
(2) Identification of problems and concerns.
(3) Analysis of goals in clinical genetics.
(4) Identification of obstacles, threats and opportunities.
(5) Comparison between different strategies of dealing with obstacles, threats and opportunities.

The general problem is how to get from where we are to where we want to be: from the present situation to the achievement of the goals, exploiting the opportunities and dealing successfully with the various obstacles. This approach to the problems of quality is different from the one in the OECD guidelines or the Council of Europe Recommendations (OECD 2007; Council of Europe 2009).

Whether the conflicts of interests (values, rights) are between different individuals or – as is more often the case – between individuals and public health concerns or the good of the community, it is useful to begin by identifying the stakeholders involved and their roles. Which particular combination of stakeholders is relevant in

each particular case requires an analysis of that situation. The roles of the stakeholders, and what they legitimately want to achieve or avoid, will depend on the purpose of the genetic investigation.

The Present Situation

The provision of genetic services in Europe varies and raises several issues (Godard et al. 2003). There is increasing understanding of the importance of the distinction between monogenic and complexly inherited diseases, also outside of the ranks of specialists in genetics, as well as of the role of epigenetics. These developments and distinctions, as well as some of those alluded to below, are dealt with in other chapters of this book.

As indicated by the OECD and other guidelines, there is increasing awareness of the need to monitor and harmonize the quality of laboratory performance, the quality of result reporting, as well as the education and training standards for laboratory personnel. But much remains to be done (Ibarreta et al. 2004).

Much recent discussion has focussed on molecular genetics and cytogenetics. The genetic background of some rare and low-penetrant disorders has been studied carefully. Outcome measures in clinical genetic services have been proposed and are discussed in other chapters of this book.

Rapid technical development by combining nanotechnologies with micro array analysis will speed up the diagnostic process and make it possible to get quick answers to many questions. Moreover, the genome can be typed efficiently, quickly and inexpensively by SNPs (single nucleotide polymorphisms).

High quality clinical genetic services are available, particularly in the developed countries, but in a global perspective the access to these services varies enormously.

Identification of Problems and Concerns

The concerns will determine both what is relevant to focus on in the description of the present situation, which particular aspects of the goals should be considered, and which obstacles and opportunities are primarily important to deal with in the situation at hand.

The topics addressed in the guidelines of the European Society for Human Genetics (ESHG), WHO, OECD, and the Council of Europe indicate areas of concerns to these organizations, including uncertainty about terminology, lack of mutual recognition of quality assurance frameworks, the need to strengthen international co-operation and increase public confidence in the governance of genetic testing.

In view of historical misuses of genetics, one overriding concern is to avoid that genetics is being used for eugenic purposes. Other concerns include equality of access and attention to what is in the best interest of those unable to give a free

and informed consent, as well as conditions for adequate counselling and support. The ESHG recommendations are also specifically concerned with the danger that promising tests of yet unproven value might be introduced too early and with the status of clinical genetics in the medical curriculum.

The relations between (i) the concerns raised by genetic testing in general and (ii) the concerns raised by the quality of clincical genetic services are not quite clear. It can be argued that no clear distinction can be maintained. But if a sharp distinction is proposed, (ii) can be considered to be included in (i), to be identical with (i), or (i) and (ii) to be related as two partly overlapping circles.

Article 5 in the Council of Europe recommendations (2009) deals explicitly with quality of genetic services. Some other articles are also relevant to quality issues, like article 16.3 ("The wish of a person not to be informed shall be respected"), but others may be considered to be more general, like article 3 (on primacy of the human being) and 4 (on non-discrimination and non-stigmatization).

Similarly, in the ESHG recommendations (2003), "quality" is mentioned explicitly in some recommendations, but other guidelines are also relevant for quality, for example recommendations (9, 10, 16, 17, 18), while still others may be considered to be more general. So I conclude that the concerns raised by the quality of genetic services are included in the more general concerns raised by genetic testing.

Which are the more specific concerns raised by the provision of clinical genetic services? This question is not easy to answer in a value-neutral way. What is a cause of concern to someone with, for instance, egalitarian values, may not be a problem to a social Darwinist. A person sensitive to the possibility of introducing eugenics via the back door (social pressure and cost-benefit considerations favouring increased frequency of prenatal testing and abortion) will see partly different problems than a person who is insensitive to such issues.

But even so, several general concerns shared by many can be identified, in addition to the ones already indicated. For example, the speed and comprehensiveness of new test methods may produce complex information that is difficult to interpret. Chance has been replaced by choice under uncertain and partly unknown conditions. This has not always made the situation easier for those tested and raises intriguing issues of justice (Buchanan et al. 2000). It may also change the doctor-patient relationship, affect our understanding of ourselves, change our views of normality and the concepts of health, disability and disease.

There is clearly a concern about data protection (European Commission 1995) and what might happen, if test results are accessed by third parties (relatives, employers, insurance companies,. . .) against the wishes of the tested individual. Will this threaten the autonomy of the index person, increase risks of stigmatization or discrimination, or undermine the respect of human dignity? Such concerns are addressed in several existing guidelines and recommendations.

Genetic testing of children gives rise to concerns, since children are unable to give a qualified informed consent. But also the difficulties of providing information to adults of what tests can show and what the test result means in an understandable and non-directive way have been studied; and the results give rise to concern. Studies show that body language, the choice of words, and the

order in which the information is presented may have decisive impact on the decision.

Under what conditions is an index person obliged to inform his/her relatives of test results that may be useful for them to know? This issue is also addressed in existing guidelines and recommendations. Even if there is no *obligation*, perhaps an educational effort is called for to encourage tested persons to disclose such information, especially if it can make a vital difference to the health and quality of life of their relatives (Chadwick et al. 1997).

Is there a right not to know? A right not to inform those tested and their relatives of test results? This has been debated both in clinical practice and research (Chadwick 1997; Knoppers et al. 2006)? What would be the basis of such rights? Which conception of autonomy? What if exercise of these rights would clash with the obligation to do good or prevent harm (Beauchamp and Childress 2000)? Then we would have to face a conflict of values.

Furthermore, there is a growing concern over the increasing number of tests sold via internet without adequate information before and after the test. The concern is due to the marketing of these products, in which the limitations of the tests are rarely made explicit (EGE 2003). For example, what about the sensitivity and specificity of the test? What do the results show? The low predictive value of test results for complexly inherited diseases increases the concern. The underlying value conflict is between freedom of enterprise and protection of consumer interests.

The availability of – and the problems raised by – clinical genetic services differ in developing and developed countries. This obvious point has important implications for several ethical issues, including those concerning social justice. There is a general concern over fair access to clinical genetic services, also in developed countries. Are they available to those who would benefit from them rather than to those who are willing and able to pay for them?

A related set of concerns has to do with the scarcity of resources – which is a common problem in all national and publicly funded health care systems. In order to treat a health problem, it first has to be diagnosed adequately and accurately; if not, the proposed treatment may be ineffective or harmful. But how far should the clinical geneticist go, how much resources should be spent on finding the cause of a problem or a disease?

The list of concerns is long, and in order to be able to say something constructive about how they should be dealt with, the goals of clinical genetics have to be specified first.

Analysis of Goals in Clinical Genetics

(a) General goals

The description of the present state of the art clarifies the situation. The identification of causes of concern points out challenges which ought to be met in one way or other. But we also need some more precise idea of in what direction we want to go, and why. In other words, the goals need to be made explicit.

On a general level the goals of clinical genetics are obviously related to the goals of medicine. This is hardly surprising, since clinical genetics is a medical speciality. But the aim of clinical genetics is often not to provide a cure but to offer information and facilitate informed and autonomous choices. "Goals" will here be used in a wide sense, including both "positive" goals, that is, what the various stakeholders want to achieve, and "negative" goals, that is, what they want to avoid.

Goals are not static. There are also goals on different levels (operational, discipline-specific and individual). The operational ones are not independent of the technical and economic development of society, whereas the basic goals of medicine remain more stable over time (Fleischhauer and Hermerén 2006).

Genetics is the branch of medicine that studies the role of hereditary factors in causing diseases, birth defects, or inherited susceptibility to health problems. This is done, for instance, by molecular genetic, microbiological, cytogenetic methods of analys or by getting information about the diseases or causes of death of the biological relatives of the persons tested.

The general aim is to facilitate autonomous choices, prevent and/or provide relief from suffering, to combat disease, to restore, maintain and improve health as well as quality of life. But already these are several goals, also because "autonomous choice", "suffering", "health" and "quality of life" can be understood in many different ways.

If the goals and underlying values are stated in fairly general terms, there will probably be a high degree of consensus concerning them. But the goals and the values can be made more precise, and their scope can be clarified. Then (i) the consensus may disappear or be undermined, and (ii) potential conflicts between the goals and values will become more conspicuous.

For example, the goal to predict onset of, or susceptibility to, a particular disease may under certain conditions clash with the goal not to cause distress and to abstain from preventive measures of doubtful value. Analogously, the goal to conduct population screening in order to learn more about the genetic nature of a disease or about genetically determined susceptibility to disease may clash with the goals not to infringe privacy and to prevent stigmatization.

(b) Specific goals

There are also more specific operational and discipline-specific goals related to the provision of clincical genetic services. To achieve these goals could be steps on the way to achieve some of the more general and basic ones, including to facilitate autonomous choices.

They include, for instance, to minimize and, if possible, eliminate false negative and false positive test results; to give careful consideration to the extent to which test results will influence the individual tested and his/her relatives and children; to protect the privacy of test results; to ensure that pre- and postexamination counselling is carried out by a medical geneticist or an equivalent specialist (Council of Europe 2009).

Further specific goals include that clinical practice respects international and national guidelines as well as hard and soft law, when applicable; that internationally

accepted standard terminology should be adopted and used consistently also with respect to quality assurance systems; and that there should be a quality assurance system and accreditation of laboratories that meet the standards of the quality assurance system (OECD 2007).

Clearly, acceptable standards will depend on the type of test. When standards are not met, the ambition must be to educate poor performers, not to punish them, so that the general level of genetic services is improved for the benefit of those tested and those who finance the genetic services.

Some of the more specific goals of clinical genetics services provision have been debated from different points of view. For instance, owing to the importance attached to patient autonomy and the right of self-determination, non-directive genetic counselling has been a generally accepted goal for a long time. But this goal has been questioned and so has the possibility to achieve it.

(c) Quality goals and ethics

Quality goals can be classified in different ways. The quality-oriented goals of clinical genetic services are clearly multidimensional. They cover, for instance, the

- quality of the test: it should meet generally accepted criteria of scientific and clinical validity,
- quality of the data and of reporting of the results of the testing from the laboratory to the clinical geneticist,
- quality of the information from the clinical geneticist to the tested person before and after the testing,
- quality of the support given to persons who have been tested,
- quality of the education of the laboratory and health care staff.

These dimensions of quality assurance raise different issues and cannot be covered by the same formula.

Each of these aspects can be clarified further. For example, the contents of the information about the purpose of the test and what it might show can be specified, as well as the significance of the test result, including possible implications for procreation choices. Moreover, it could be clarified what consent forms – if such are used – should contain, how they should be presented and discussed with those tested (or in some cases proxies), as well as how the consent is to be documented.

The processing time is another important aspect of the quality of the genetic services. If a genetic service of the same quality is provided by two laboratories, but one laboratory needs twice as long time as the other, this is obviously negative – since patients are anxiously waiting for the test result. To minimize anxity, the waiting time should be as short as possible without compromising other quality requirements.

Another aspect relevant to the quality of clinical genetic services is what client records should contain, for instance, about the reasons for the visit to the clinician, patients' descriptions of the problems experienced and or their concerns, the family history of hereditary diseases, including a family pedigree, information on past and

present pregnancies, including genetically related problems identified in newborns (OECD 2007).

Similarly, the qualifications and the education of the staff providing clinical genetic services can be clarified. This holds also for when, how and by whom the education is to be given, how often it should be repeated, and how it should be documented that health care staff have received this education.

In setting the levels of the standards of quality, like in setting standards of safety, ethical considerations play a decisive role. The interests and values of those involved can be promoted or frustrated by different quality standards concerning what is to be done to reduce risks, increase safety, protect confidentiality, facilitate cross-border flow of health data, improve sensitivity and specificity of the tests. Ultimately, the value premises have to refer to goals and values ranked in order of importance.

Standards of free and informed consent, for example, are based on ideals of respect for persons and the value of autonomy. Similarly, standards of what patient records should contain are based on the obligation to prevent harm and to do good, as well as on experience of what information is needed in order to achieve these goals.

Standards of confidentiality are analogously founded on the value attached to privacy and integrity. The more important it is to minimize the risk of discrimination and stigmatization, the better protection of test results is required. Standards of availability and access to clinical genetic services are in the same way based on ideas and ideals of fairness and justice. Like other health-care services, they should be distributed on an equitable basis according to need.

Clarity about the positive and negative goals is necessary in order to be able to evaluate strengths, weaknesses, gaps, opportunities and threats in genetic service delivery. If clarity is essential, how do we find out about the goals? There is an array of well-established methods in the social sciences which can be used for this purpose, including focus groups, interviews and surveys. Other methods include analysis of documents and actions.

In this way it is possible to get input not only from patients and their relatives but also from providers and other stakeholders about what they view as the most essential elements of quality in genetic services. How important do they consider the availability of genetic specialists to be, for example, compared to free and informed consent or establishment of procedures and policies of confidentiality?

Identification of Obstacles, Threats and Opportunities

Once the problems and concerns as well as the goals have been identified, it becomes easier to identify opportunities and obstacles. But what may be a considerable obstacle or threat for some stakeholders may be a small one for others.

“Opportunities” and “obstacles” are value-loaded terms. The expression “opportunities” has a positive ring; it suggests something good. Analogously, “obstacles” has a negative ring; it suggests something bad. We must be aware of the power of words, how they affect the way we perceive and think.

Poor economy, rigid legislation where important distinctions are missing, ignorance, hostile attitudes of the general public, inappropriate organization, poverty, lack of adequate infra-structure, poor integration of genetic services into the health care delivery system, lack of adequately trained doctors and staff represent different kinds of obstacles to quality in genetic services

So: What can be done, or should be done, given the goals and generally accepted values in society, to deal with the obstacles and exploit the opportunities in order to achieve the goals in a quicker, more cost-effective and ethically more acceptable way? Clearly, this is a complex question that needs to be divided into several ones.

An obstacle identified in most guidelines is lack of up-to-date genetic knowledge. Such knowledge is essential both to clinicians and genetic counsellors. Recurrent education provided by clinical geneticists would be one way of dealing with this obstacle. This is proposed in many guidelines, though in ESHG recommendation (16) there is a somewhat surprising shift of tense (from "is" to "has been recommended"), as if ESHG did not support this idea.

Different obstacles are to be tackled in different ways. Thus it is important to identify and distinguish between them. If the obstacle is lack of procedures to protect data from being accessed by third parties, like insurance companies, relatives or employers, certain strategies suggest themselves. If the problem is overlaps or gaps between legal regulations, something else is to be done. Then articles in media and lobbying in parliament may be needed to achieve a change of the legal situation.

Other strategies are appropriate, if the problem is that access to clinical genetic services vary in different regions, or from country to country – encouraging medical tourism. If genetic services are poorly integrated into health care delivery systems, still other actions may be called for, including organizational changes. If certain individuals, groups, employers or insurance companies have unrealistic expectations about the predictive value of genetic tests of complexly inherited diseases, educational efforts are called for.

Comparison of Different Strategies

Three general main types of strategies to deal with obstacles suggest themselves: to eliminate, reduce or bypass them. Comparison between different ways of dealing with the obstacles and opportunities will raises ethical issues, different from the ones so far discussed, first concerning the choice of criteria, then concerning substantial issues.

The criteria that suggest themselves immediately are time, cost and effectiveness. If one strategy needs more time than another, this would a relevant consideration, especially in a medical field that is rapidly developing, and where anxious patients are waiting to get the test results. Costs are also obviously relevant. Whose costs are to be counted, and how are they to be estimated? Winners and losers can be created by ignoring or diminishing certain costs. Money is not available for everything contemporary medicine is able to offer, so priority setting becomes inevitable.

But a prime consideration is whether the strategy proposed will be effective. Will the strategy to exploit opportunities and deal with obstacles take us closer to

the goals? If not, considerations of time and cost will lose significance – it would be like using a hammer just because it is cheap and easy to handle without considering whether it is effective – when a screwdriver is what is needed.

In addition to time, cost, and effectiveness, ethical acceptability is a fourth important parameter. Even if it would speed up the progress of medicine, we should not accept exposing people to very serious risks. Specific ways of dealing with the obstacles and opportunities have to be evaluated ultimately according to the extent they are compatible with important values in our culture, including human dignity, integrity, autonomy, privacy, confidentiality, solidarity, justice, and a few others.

If there is a choice between different *methods* or *strategies* to tackle opportunities and obstacles, it is essential to make clear that (a) the goals are important, (b) the strategy used is necessary to reach the goal, and that (c) there is no other less controversial or harmful strategy to deal with the opportunity or obstacle.

Concluding Remarks

Sometimes consensus is bought at a certain price. Clearly, many of the principles in existing recommendations or guidelines are vague and open-ended.

For example, OECD recommendation E.1 states that "Laboratory personnel should have appropriate professional qualifications that meet recognized standards", but what the recognized standards are left open, as are the criteria of "appropriate". Analogously, E.3 states that "Existing specialist education and training programmes relevant to molecular genetic testing that meet recognized standards should be formally adopted. . .". But also here it is left open which the recognized standards are, and the same holds for the criteria of "relevance".

Likewise, in several of the ESHG recommendations problems are pointed out and it is said that they require "careful consideration" (e.g. recommendations 15 and 16), without specifying criteria of carefulness, what such considerations should take into account, what they would allow and what they ought to forbid. Persons with very different ideas on such issues might very well agree on the general recommendation, and disagree on specific issues.

Such recommendations, valuable as they were at the time when they were written, should be regarded as starting points for further clarification. Some clarification is provided in Explanatory notes and Annotations. But more remains to be done. It is important to continue the dialogue between the various stakeholders, regulators, ethicists, geneticists and others involved, in view of societal and regulatory changes – and new scientific discoveries and test methods.

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Democratic Expert Influence Through Bioethical Advisory Committees? The Case of PGD Legislation in Sweden

Maria Hedlund

Key Points

- Bioethical government advisory committees have profound influence on political decision-making on gene technology issues, concerning not only patients with genetically related diseases, but also, potentially, the whole society.
- Decision-making on issues concerning all society should be democratically legitimate in all aspects, including the work of government advisory committees.
- Democratic legitimacy of expert advice is desirable not only for the democratic values per se, but also for the quality of political decisions.
- In the case of PGD legislation in Sweden, the national government advisory committee functioned as a bridge between political representatives, specialist civil servants, and scientific experts, but the connection with public opinion was more or less absent.
- Had the advisory committee worked more openly and allowed a multiplicity of perspectives being heard, the democratic and quality aspects in this legislation process would have been strengthened.

Keywords Democracy · Expertise · Bioethics · PGD · Sweden

Introduction

The aim of this chapter is to defend the view that democratic legitimacy of bioethical government advisory committees is desirable. Democratic legitimacy of expert advice is desirable not only for the democratic values per se, but also for the quality of political decisions, and the point of departure is a political decision-making process on gene technology in Sweden, where a bioethical government advisory

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committee plays a significant role. More specifically, I will illustrate the role of this advisory body in three instances of a legislative process that started with the regulating of reproductive issues, but gradually comprises more directly gene technology specific issues, namely pre-implantation genetic diagnosis (PGD), embryonic stem cell research, and gene therapy on gametes. I will use the three cases to comment upon expert advisory bodies from a democratic perspective. First, I will say something about democracy and bioethical advisory committees, and put the Swedish bioethical government advisory committee in context.

Bioethical Advisory Commissions and Democracy

National bioethical organisations such as bioethical government advisory committees have profound influence on political decision-making about gene technology issues. These questions of course concern patients with genetically related diseases and their relatives, but possibilities to change our hereditary disposition have importance also for people who are not directly concerned. Effects on future generations are possible, but are hard to discern. The view on what is normal and abnormal can be influenced in ways that stigmatise many groups of people not falling in the frames of what is apprehended as normal. In addition, manipulation of the human genome can be seen as an inappropriate way of "playing God". I argue that gene technology concerns all society and therefore it is important that expert bodies advising political decision-making about regulation of gene technology are democratically legitimate. Furthermore, as a democratic process is open to a multiplicity of perspectives, the quality of the decisions made is likely to increase.

The meaning of democratic legitimacy is not evident, however. Neither is the claim that government advisory committees should be democratically legitimate. Objection is raised to the view that legitimacy of those committees is dependent of their capacity to live up to certain democratic values. Exactly which these values should be is contested, but at a minimum, government advisory committees should have a capacity to contribute to public debate and include the views of ordinary people in their considerations (Dzur and Levin 2004). Criticism against this view points at the function of bioethical government advisory commissions being advisors of the political decision-makers, who must have the possibility to seek advice wherever they need (Johnson 2006). This criticism is not entirely misdirected. Ultimately, the disagreement of the democratic issue of bioethics – or other – government advisory committees is about a struggle for power (cf. Martin 2008), and bioethical committees once arose precisely to prevent democratic influence (Evans 2002). Nevertheless, I argue that democratic values like equality, inclusion, and public debate cannot be removed from certain issue areas, but must permeate all society. This is not least important in a field with such all-embracing possible consequences for society as genetics (cf. Best 2006).

Most liberal democracies have some form of expert body with the commission to give advice to the political decision-makers in bioethical issues (Dodds and

Thomson 2006). In Sweden, the Swedish Council on Medical Ethics has this kind of commission (www.smer.se). Characteristic of the Swedish Council on Medical Ethics is that it consists not only of ethical, medical, and other expertise, but also of political members, who formally take the decisions of the council. This gives the Swedish Council on Medical Ethics a connection to elected representatives missing in medical-ethical committees in many other countries. However, the Swedish construction is not the only possible way to make a bioethical government advisory commission democratically legitimate. The Danish bioethical council consists of no political representatives, but work with out-turned activities in society, like public hearings and an annual recurrent ethical forum for young people (www.etiskraad.dk). The bioethical commission of New Zealand explicitly holds that it does not need to reach consensus, but can "provide advice reflecting diverse views" (www.bioethics.org.nz), something that can be contrasted to the consensus building, that is a norm in the Swedish Council on Medical Ethics (Hedlund 2007).

Scientifically and ethically charged issues can be difficult for ordinary people to grasp. Still, political decisions about the conditions for medical and gene technological research and application can have far-reaching consequences for the citizens (cf. Bengtsson 1999). The democratic connection of bioethical expert bodies is therefore essential and the question of how this happens is far more extensive than how many parliamentary members they include. The internal way of working, the status as political advisers, i.e. the actual impact on political decisions, the connections of the advisory commissions with society and their capacity to contribute to an informed debate, are all factors that also has to do with democratic legitimacy of bioethical government advisory commissions.

The Swedish Council on Medical Ethics

The origin of the Swedish Council on Medical Ethics is a hearing on medical-ethical questions with medical experts and representatives of continuing committees and interest groups arranged by the standing committee on social questions in September 1984 to particularly illuminate existential questions raised by the medical progress. In the hearing, a recurrent view was that such questions concern all society and have to be debated by all, not only by experts. Many of the hearing participators maintained that it is not meaningful to discuss if the one or the other new medical conquest would be applied without first gaining a comprehensive view on medical ethics (Hedlund 2007).

In March 1985, the government decided to establish a "from the current routines freestanding" council with the task to analyse medical-ethical questions from an overall perspective of society and function as a "mediating body between science, public opinion, and the responsible politicians" (Ministry of Health and Social Affairs 1985-03-05). This body – the Swedish Council on Medical Ethics – has its commission as a Government-appointed committee, but without specific directives and without a time limit. The chair, seven political members and the same number

of specialists plus a secretariat constitute the main part of the council, and further experts are summoned on occasion. The Ministry of Health and Social Affairs appoints all members at renewable three-year mandates, and some members have had their mandates renewed several times. The Swedish Council on Medical Ethics, which independently initiate issues to handle and suggests subjects for official investigation, assembles once a month. To almost every meeting and especially when a new issue is on the agenda, experts are invited to provide facts and information about e.g. new medical techniques. The meetings are closed and the discussions, which are declared particularly trustful, proceed until the members of the council agree on a common opinion and therefore often extend over several meetings. When agreed on a question, the council presents its view in reports, which normally carry great weight for the standpoints of the Ministry of Social Affairs. As several of the political members also are members of the standing committee on social questions, the standpoints of the Swedish Council on Medical Ethics have considerable chance to pass through the policy-making process in the Swedish parliament (Hedlund 2007).

To illustrate the influence of the Swedish Council on Medical Ethics in the political policy-making process in Sweden, and some democratic problems connected to this influence, I will present three instances that constitute part of the legislative process on medical gene technology from the beginning of the 1980s up to 2006. These instances are pre-implantation genetic diagnosis, embryonic stem cell research, and gene therapy on gametes, chosen to illustrate different aspects of my argument for democratic legitimacy.

Pre-implantation Genetic Diagnosis (PGD)

In 1992, the Swedish Council on Medical Ethics (SCME) made a standpoint on pre-implantation genetic diagnosis, declaring that PGD could be done "as a part in clinical research" and "for the time being" be prohibited in clinical application (SCME 1992). The standpoint was partly built on a report on risks and advantages with PGD written by the Swedish Medical Research Board (MRB 1991), and the arguments not (yet) to allow clinical application dealt with feared risks with the method. Such risks were about the baby being born with damages caused by the examination, that PGD could be made on other indications than the risk of hereditary predisposition for serious illness, e.g. sex selection, and that the integrity protection of the embryo could be impaired. There was also a risk, according to the Swedish Council on Medical Ethics, that PGD could open the door for gene therapy on gametes, so that fertilised eggs with a transformed genetic code might be inserted in a woman's body (SCME 1992).

The arguments for PGD diagnosis to be permitted not only in clinical experiments, but also in clinical research, which the Swedish Council on Medical Ethics opens up for with the formulation "for the time being", dealt with the possibilities of the method of doing good, e.g. develop knowledge impossible to get otherwise and that could gain other areas as well (SCME 1992).

In the beginning of 1995, the government proposed a bill building mainly on the views of the Swedish Council on Medical Ethics and the Swedish Medical Research Board, that PGD in clinical application should be used only in connection to "diagnosis of serious, progressive, hereditary illness leading to an early death and where no cure or treatment exists". No legal regulation was proposed, but the parliament should specify "certain guidelines" to provide a basis for the general advice of the National Board on Health and Welfare (Government bill 1994/1995:142). In the spring of 1995, the standing committee on social questions, and the parliament confirmed these guidelines for PGD (Standing committee report 1994/1995:SoU18; Parliamentary records 1994/1995:102, 18§).

However, it appears a bit unclear that clinical application of PGD was now permitted, and that this was done with reference to the standpoints of the Swedish Research Council and the Swedish Council on Medical Ethics (Government bill 1994/1995:142, pp. 28–29). Neither the Swedish Research Council, nor the Swedish Council on Medical Ethics, would permit clinical application of PGD when they made their standpoints in 1991 and 1992. Yet this is exactly what the guidelines admit, let alone with strict restrictions. An explanation why is that the government and consequently the parliament based their decisions on misleading information (Munthe 1999). Medical experts on the National Board of Health and Medicine approve of clinical application generally. In this case, the experts were the very same individuals that wanted to apply the technique and had figured as experts in the Medical Research Board and the Swedish Council on Medical Ethics. In 1992, they claimed that PGD was an internationally established routine. However, this contradicts what "leading international experts" said in 1995 about PGD not being in clinical use, i.e., not an established routine (Munthe 1999:55, pp. 70–71). The point is that the politicians and the Swedish Council on National Medical Ethics did not know that, but trusted the information given by the national experts without checking its credibility. This information then became the basis for the decision to approve the guidelines.

Embryonic Stem Cell Research

In May 2001 the Swedish minister of Education and Science announced that the Swedish Research Council (SRC) was about to propose guidelines about embryonic stem cell research to the regional committees of research ethics. The content of the proposal, published in December 2001, was that using of stem cells from spare embryos is acceptable; that creation of embryos for the purpose of research only is not acceptable; and that creation of embryos by cell nuclear transfer can be ethically defensible, but cannot be allowed under current legal circumstances (SRC 2001). However, when the Swedish Research Council published this proposal, it no longer found guidelines to the regional ethics committees be sufficient. Rapid research progress and, in the marks of this, great expectations on what embryonic stem cell research might bring about, gave rise to extensive ethical concerns,

e.g. the question of where the eggs would come from. According to the council board, these factors made it urgent that embryonic stem cell research become subject for legislation. Therefore, the Swedish Research Council made a request to the Swedish government to legislate on embryonic stem cell research (Hedlund 2007, pp. 164–165).

Meanwhile the members of the Swedish Council on Medical Ethics were also considering embryonic stem cell research. Their line of argument was about the conflict between the possibility of gaining new knowledge and demands of respect for the human embryo. Referring to the principle of goodness and the principle of not making harm, the council concluded that it would be ethically irresponsible not to do research on embryonic stem cells and thereby say no to new knowledge that would be of great importance for seriously ill people. Their judgement, which they presented in a report published in January 2002, was slightly different from that of the Swedish Research Council insofar as they did not recommend a prohibition against creation of embryos for research purposes or against creation of embryos by cell nuclear transfer (SCME 2002-01).

Shortly thereafter, Ministry of Health and Social Affairs gave supplementary directives to the Government-appointed committee on Genetic Integrity, already working with other gene technology related issues. The message of these supplementary directives, that were to be handled with priority, was that embryonic stem cell research and related issues as somatic cell nuclear transfer and donation of eggs would be allowed in Swedish legislation, and the purport of the directive was that the committee should elaborate on the legal construction (Government directive 2002:58). In December 2002, the Committee on Genetic Integrity presented the report *Legal regulation of stem cell research* and suggested that embryonic stem cell research and the related issues should be regulated by changes of existing legislation of in vitro fertilisation, IVF (Government inquiry report 2002:119). This was also the content of the Government bill (2003/04:148). Different bodies, to which a proposed measure was submitted for consideration, claimed that the permitting of embryonic stem cell research as such ought to be subject of a parliamentary decision. The government responded to these claims by referring to the statement of the Swedish National Council on Medical Ethics that it would imply a big ethical responsibility to refrain from new knowledge with potential to help seriously ill people. The government did not, however, comment on the state of things, that the very permission of embryonic stem cell research should be a question for the legislative body, and the parliament voted for the Government bill unchanged (Standing committee report 2004/2005:SoU7; Parliament records 2004/2005:68).

Gene Therapy

Gene therapy on gametes brings to the fore the possibility that genetic changes descend to next generation, something that might give rise to great worry. In the first Swedish legislation connected to gene technology, the Act of Measures in Research

or Treatment Purposes with Fertilised Eggs from Human Beings, gene therapy on gametes was prohibited although the technique did not yet exist. The government emphasised that legislation about activities not yet existing normally does not take place, but that the particular importance of this very question motivated not only an exception from normal legislation procedure, but also a double prohibition against gene therapy on gametes to assure the prohibition would be correctly interpreted. The legal construction was a prohibition to insert to a woman's uterus a fertilised egg that has been an object of experiment, and the prohibition was supplemented by a ban against experiments on fertilised eggs with the purpose of developing methods to bring about gene therapy on gametes. The reason for this supplementary rule was to prevent that a kind of activity not in use at the time, in a future would lead to "human improvement experiments" (Government bill 1990/1991:52, p. 30).

In praxis, the formulations in the Act gave rise to uncertainty of the scope of the prohibition, and in 2002, the Government-appointed Committee of Genetic Integrity made a suggestion of an "editorial adjustment" in the 1991 Act. The purpose of this adjustment was to make clear that gene therapy on gametes was explicitly forbidden, and that this prohibition would not be interpreted as an obstacle to somatic cell nuclear transfer (Government inquiry report 2002:119, p. 94).

Two years later, in 2004, the same committee reconsidered gene therapy on gametes. The reason for this reconsideration was that "in research contexts" in connection with PGD, the question has been raised whether mitochondrial diseases could be prevented if the cytoplasm of the egg cell is exchanged, that is, a kind of gene therapy on a gamete. The method means that the hereditary disposition is changed and that a genetic change descend, which accordingly would be the purpose of the operation. The committee of Genetic Integrity based its new conclusion on consultation with the Swedish Council on Medical Ethics, and proposed that research with the purpose of developing methods to bring about hereditary effects be permitted. Still it would be prohibited virtually to bring about such effects, but the legal construction suggested by the committee was an implant prohibition "for the time being" (Government inquiry report 2004:20, pp. 319–322), a formulation that opens up for future application of such exchange of cytoplasm.

Earlier in the legislative process, the unforeseeable consequences for future generations were regarded so large a risk that gene therapy on gametes was prohibited even before the technique existed (cf. above). Now the committee, with reference to the Swedish Council on Medical Ethics, considered research progress invalidated this judgement, and proposed that the prohibition against research aiming at method development should be loosen up (Government inquiry report 2004:20, pp. 320–321; SCME 2004-09-13, p. 6). This content of the committee proposal was also the content of the Government bill. However, the prohibition that the committee wanted to keep, namely the prohibition against actually bringing about hereditary effects, the government wanted to lift out from the Act. Instead, the issue of bringing about hereditary effects by gene therapy on gametes was to be reviewed by the regional ethical boards. This meant one further opening to future application.

Democratic Perspective

As the Swedish legislation process on medical gene technology illustrates, experts apparently influenced the political regulation. New medical technologies were permitted as the medical expertise judged them being safe, or argued that utility exceeds potential risks. Ethical aspects of the use of different gene technologies motivated the need of regulation. Remarkably, technical possibility eventually became ethical acceptable. The case of gene therapy on gametes clearly demonstrates this. When medical researchers saw potential areas of use for the method, the prohibition was removed from the law. Instead, research ethics committees, in which a majority of the members are researchers, will judge individual research projects from case to case. Consequently, the responsibility to decide when this is ethically acceptable was handed over from the legislator to medical and other scientific experts.

It is also evident that the view on ethics governing this process is one of research ethics, omitting a more comprehensive view. In the embryonic stem cell debate, ethical apprehensions about embryo research dominated, but, as many actors in the process stressed, there are also other ethical aspects with embryonic stem cell research, like the question of egg donation and the use of new knowledge. The difference between research ethics and ethics that are more comprehensive appears clearly in the research ethics reviews accomplished by the regional committees of research ethics, as they balance risk and utility for the individual subject of an experiment, but do not consider possible consequences for society. Several actors raised this problematic in their comments on the stem cell research law proposal circulated for consideration, but was not responded upon by the government more than indirectly, namely by referring to the commission of the Swedish Council of Medical Ethics (Hedlund 2007, pp. 182–187).

From a democratic perspective, factors worth scrutinizing in these respects are consequences of small expert assemblies, the consensus seeking culture, and the deliberations behind closed doors. The political process preceding the parliamentary guidelines on PGD demonstrates that small expert assemblies might be a democratic problem. No one controlled the statements from medical experts that PGD was established routine abroad, and one can question if it is suitable that an advising body of the government uncritically trust representatives of the very business that is under scrutiny, especially if the outcome of the considerations might gain the self-interest of these actors. It is a democratic problem if such considerations take part in such informal and maybe trustful contexts that nobody reflects upon to control their information. It might also be a quality problem, if potential criticism remains unheard.

One characteristics of the legislation process of medical gene technology in Sweden is the over-arching consensus in which the decisions seem to have been taken. Views diverging from those of the government gained little hearing, and real argumentation about different standpoints is hard to find. This is especially true when it comes to the main actor in this process, the Swedish Council on Medical Ethics, for which consensus is an explicit aim. The medical ethical nuanced questions that the council handles are twisted and turned from many possible angels, and

discussions about the same question can proceed for a long time. When the council eventually reaches a standpoint, every member knows why a certain view is settled. However, this knowledge is reserved for the members of the council. A distinctive feature with the council discussions is namely that the members "do not talk about what they talk about" outside of the council (Hedlund 2007:193–194). The discussions in the Swedish Council on Medical Ethics accordingly are marked by confidence in that all said is kept in the group; the only thing being public is the final consensual standpoint. The democratic and quality aspects of the consensus seeking culture resemble the ones of small expert assemblies insofar as divergent perspectives are scarcely produced, and as minority views run the risk of being silenced. This has implications for democratic legitimacy as well as for the quality of the decisions taken.

Conclusion

Early in the Swedish legislative process on medical gene technology, the Swedish Council on Medical Ethics was established, and throughout this process, its influence has been profound. The political representative members give the council a kind of democratic legitimacy that is missing in many of their counterparts in other countries. However, political representation is not the only way to make an advisory board democratic. Democracy is also a matter of public debate and a multiplicity of voices to have a say and being heard. The public function of the Swedish Council on Medical Ethics is to be a mediating body between science, the responsible politicians, and the public opinion. The Swedish Council on Medical Ethics certainly builds such a bridge between political representatives, specialist civil servants, and scientific experts, but the connection with public opinion is more or less absent.

Nevertheless, if the outward contacts are limited, the internal work of the council is more open. Different views are being balanced and the standpoint that eventually unites the council is well motivated. The working process resembles a kind of deliberation. The ceiling is high and all opinions have a say. All members are equivalent in the discussions and it does not matter who says what; the arguments count. The Swedish Council on Medical Ethics could thereby be characterised as a body of deliberating elites. The outward closeness is by the members emphasised as necessary for this trustful working climate. For the council to get democratic legitimacy beyond the political representation, however, it should open up for the surrounding society. An extensive discussion about different ways to democratise advising expert bodies has recently begun (see e.g. Andersson et al. 2006; Dodds and Thomson 2006; Braun 2005; Dzur and Levin 2004; Weed 2004; Friele 2003; Irwin 2001), and more research is needed about how organisations advising governments could be more democratic – if they should be democratic at all. This is not an evident statement, which is demonstrated by the debate on national bioethics organisations referred to in the introduction. However, I argue that government advisory organisations should be democratic, and this short overview of the influence of one such organisation hopefully demonstrates this need.

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Quality Issues in Clinical Genetic Services; Regulatory Issues and International Conventions

Dolores Ibarreta and Stuart Hogarth

Key Points

- Genetic testing is an activity which transcends national borders. Rare disease genetics has long involved an international exchange of human samples and related data and this globalisation is increasing in areas such as cancer diagnostics and consumer genetics. This international trade takes place in an environment where regulatory and oversight procedures vary significantly between jurisdictions.
- The last decade has witnessed an international discussion about both technical issues relating to the quality of genetic testing and broader ethical and social issues such as genetic discrimination. International Organisations such as the Council of Europe, the Organisation for Economic Cooperation and Development and the World Health Organisation have acted as policy fora and standard setting bodies.
- Key policy documents are the Council of Europe's (1997) Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology (also called The Convention on Human Rights and Biomedicine) and its 2008 Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes and the OECD's (2007) Best Practice Guidelines for Quality Assurance in Molecular Genetic Testing.
- Whilst these documents enshrine broadly accepted international standards it remains to be seen how they will be implemented and enforced at level of individual nation-states.

Keywords Quality assurance · Accreditation · Licensing · Council of Europe · Organisation for Economic Cooperation and Development · World Health Organisation

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The Human Genome Project was international in scope encompassing researchers from the US, UK, France, Germany, Japan and China. More recent genomic research has confirmed this trend for global collaboration: the HapMap project was funded by the Japanese, Canadian, Chinese and US governments. In this atmosphere of cross-border collaboration, it is perhaps unsurprising that the formal launch of the Human Genome Project, was accompanied by an international discussion of the policy issues arising from the application of new genetic discoveries in clinical practice. This discussion encompassed both ethical and social issues such as genetic discrimination and technical issues relating to the quality of genetic testing.

Molecular diagnosis of genetic diseases has rapidly moved from the laboratory into medical use and the quality issues have become more pressing. Genetic testing is offered internationally, through both public and private sector services, and there is evidence that human samples and related data are being exchanged across borders in an environment where regulatory and oversight procedures vary significantly between jurisdictions. This expanded use and "internationalisation" of genetic testing raises novel issues and is challenging the current regulatory frameworks governing genetic services. This globalising trend is reinforced as genetic testing moves beyond the world of rare disease genetics. Partnering with clinics across the world, companies running their own reference laboratories are creating an international market for predictive tests for common diseases and gene-expression tests in oncology. Consumer genetics companies are creating an international market for susceptibility tests by selling direct to the public over the internet. These services are provided under widely varying conditions, diverse and heterogeneous quality schemes, differing national regulations and often in the absence of reference measurement systems.

International discussion of these issues was initially stimulated in two key fora. The first one, and perhaps more important, was the workshop held in February 2000 by the Organisation for Economic Co-operation and Development (OECD): Genetic Testing: Policy Issues for the New Millennium, where it was agreed that urgent steps should be taken to develop international, compatible best practice policies for genetic test validation, including QA and accreditation and to explore ways to improve genetic training for professionals and counselling and information supplied to the public. The meeting report recommended a comparative analysis of emerging patterns in the organisation of genetic services and quality assurance systems across OECD countries to facilitate an understanding of the factors influencing the availability of tests and services and the policies to be developed to meet the expected increase in demand.

At around the same time, a Temporary Committee of the European Parliament focused on the implications of human genetics and other advanced medical technologies was established. The final report of this Committee, though never adopted, recognised that there was an increasing trend for samples for genetic tests to cross international boundaries and that this highlighted the need for an international approach to harmonising Quality Assurance. To this end, it was recommended that:

- international data should be collected on the current state of genetic testing services and Quality Assurance schemes;
- areas for potential co-operation that would lead to developing international standards should be identified, such as proficiency testing and interpretative guidelines;
- international collaboration for the testing of rare conditions should be encouraged and facilitated.

Other international bodies such as the Council of Europe and the United Nations have discussed genetic testing in a global context and some of the agreements reached highlight the issues of quality of these tests, though not as a main concern. A list of the international agreements adopted so far is provided below.

1. Council of Europe

The first clear international call for quality in genetic testing came from the Council of Europe. The Council of Europe, founded in 1949, seeks to develop throughout Europe common and democratic principles based on the European Convention on Human Rights and other reference texts on the protection of individuals. Its main goal is to achieve unity among its members and, with 47 members, it has a significant pan-European dimension. Its goals, include the protection of human rights, pluralist democracy and the rule of law; promoting awareness and encouraging the development of Europe's cultural identity and diversity; finding common solutions to the challenges facing European society; and the consolidation of democratic stability in Europe by backing political, legislative and constitutional reform.

In 1992 the Council of Europe, Committee of Ministers, published Recommendation No. R (92) 3 on Genetic Testing and Screening for Health Care Purposes (February 10, 1992). The document calls for a "Rule for Good Practices in Genetic Testing and Screening" highlighting the need for proper education of health professionals, the importance of ensuring that qualified physicians are responsible for testing, and participation of the laboratories in external quality assurance schemes.

In 1997 in Oviedo, the Council of Europe adopted the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology (also called The Convention on Human Rights and Biomedicine). The aim of the Convention as defined in its Article One, is to protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. While the Convention covers genetic testing, it makes no reference to issues relating to quality. To address this, and a number of other gaps, the Council of Europe prepared an Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes. This additional protocol, adopted in May 2008, sets down principles relating to the quality of genetic services, prior information and consent, and genetic counselling. It lays down general rules on the conduct of genetic tests,

calling for measures to ensure that genetic services are of appropriate quality: a quality assurance programme implemented in each laboratory; that laboratories are subject to regular monitoring; that tests meet generally accepted criteria of scientific validity and clinical validity; and that the persons providing genetic services have appropriate qualifications to enable them to perform their role in accordance with professional obligations and standards. The protocol also deals with direct-to-consumer genetic tests, a market which seems to be growing rapidly. It specifies the conditions in which tests may be carried out on persons not able to consent. Also covered are the protection of private life and the right to information collected through genetic testing. Finally, the Protocol touches on genetic screening.

The Protocol was opened for signature in November 2008. Once signed, the protocol is legally binding in international law. A second additional protocol is envisaged that would cover genetic tests used for non-medical purposes, particularly in the fields of employment and insurance.

2. UNESCO

Another body which has played a role in the development of international standards for genetic testing is UNESCO, the United Nations Educational, Scientific and Cultural Organization which seeks to promote knowledge sharing and capacity building among its 193 members.

In 1997, the UNESCO adopted the 'Universal Declaration on the Human Genome and Human Rights'. Like the Council of Europe convention published in the same year, this document contains no direct reference to quality issues, but it does state that any "Research, treatment or diagnosis affecting an individual's genome shall be undertaken only after rigorous and prior assessment of the potential risks and benefits pertaining thereto and in accordance with any other requirement of national law" (Article 5). After the completion of the Human Genome Project in 2003, UNESCO also adopted an International Declaration on Human Genetic Data,. It aimed to ensure the respect of human dignity and protection of human rights and fundamental freedoms in the collection, processing, use and storage of human genetic data, human proteomic data and of the biological samples from which they are derived. Article 15 addresses quality issues, calling for the necessary measures to ensure the accuracy, reliability, quality and security of the genetic data and the processing of biological samples. It also requests "rigour, caution, honesty and integrity in the processing and interpretation of human genetic data, human proteomic data or biological samples, in view of their ethical, legal and social implications".

The UNESCO Declarations have moral, but not legal, force. Nevertheless, they play an important role by setting out good practice and guiding principles which can inform the development of legislation and policies on these issues.

3. WHO

The World Health Organization (WHO) has been the directing and coordinating authority for health within the United Nations system since 1948. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

In May 2003, the WHO Executive Board expressed the need for WHO to take a more systematic approach in the field of genomics. This expression calls on a previous 2002 report from the WHO Advisory Committee on Health Research, "Genomics and world health". This report does not mention directly the quality assurance of the tests but it does stress the importance of the quality of training of professionals and of the quality of genetic counselling.

4. OECD

The most important international achievement in terms of quality of genetic testing at international level is perhaps the work on quality assurance carried under the auspices of the Organisation for Economic Co-operation and Development (OECD). The Organisation provides a setting where governments compare policy experiences, seek answers to common problems, identify good practice and coordinate domestic and international policies. Though there are 30 full members, OECD also shares expertise and exchanges views with more than 100 other countries and economies. Discussions at OECD can evolve into negotiations where OECD countries agree on common rules for international co-operation, and they may also result in guidelines, which although having no legal authority, help to establish the basis for a unified international approach.

The OECD's work on quality assurance began in 2003 with a survey of genetics laboratories across 18 OECD member countries (Austria, Belgium, Canada, the Czech Republic, Finland, France, Germany, Ireland, Italy, Japan, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, the United Kingdom and the United States). The results were published by the OECD in October 2007. The survey confirmed the steady growth of molecular genetic testing and its widespread availability, revealing a significant international trade in the field. Sixty four per cent of the molecular genetic testing laboratories reported that they either received or exported specimens across their national border.

However, the survey also identified some shortcomings in the quality assurance of these services. There were significant variations in the regulatory frameworks, and oversight procedures had not penetrated diagnostic molecular genetic testing laboratories across all OECD countries. Considerable differences existed in the use of licensing, certification, and accreditation procedures posing a number of challenges for molecular genetic testing, particularly with respect to the standards under which clinical tests are performed and results are reported, and the training and qualifications required by laboratory personnel. The survey revealed what seemed to be a lack of understanding amongst the international community on the mutual acceptability of quality assurance systems. The combination of an international traffic in genetic testing and a lack of agreed harmonised quality assurance mechanisms highlighted the need for efforts to develop international consensus.

An international group of experts convened by the OECD worked over several years to produce a set of Best Practice Guidelines for Quality Assurance in Molecular Genetic Testing. The OECD guidelines were adopted by its Council in May 2007 and are a political commitment on the part of member countries, focusing on quality assurance in molecular genetics including direct-to-consumer genetic

tests. The guidelines include minimum standards for laboratories to follow for quality assurance so that patients can be reassured of the services provided, even from abroad. Adherence to these guidelines is voluntary since there is no international regulatory body to ensure compliance, but OECD states have committed to upholding them within their national borders. There are no conflicts between the OECD guidelines and the above-mentioned protocol concerning Genetic Testing for Health Purposes recently adopted by the Council of Europe.

The guidelines propose that informed consent to test should be the norm; pre- and post-test counselling should be available; advertising and technical claims should be accurate; information regarding the clinical and analytical validity of tests should be made available; laboratories should be accredited to international standards and take part in proficiency testing in a public manner; reporting should be done in patient and family centres; personal genetic information is to be protected, and personnel performing tests should be properly qualified and trained.

Overall, these guidelines offer principles and best practices for quality assurance directed at policy makers, directors of molecular genetic testing laboratories and those involved in the regulation and provision of molecular genetic testing. The guidelines, as explained in their preface, seek to assist both OECD and non-OECD governments in the development and introduction of appropriate quality assurance procedures to:

- ensure minimum international requirements for quality assurance systems and molecular genetic testing laboratory practices;
- facilitate mutual recognition of national or regional quality assurance frameworks;
- strengthen international co-operation and facilitate the cross border flow of samples for clinical purposes;
- increase public confidence in the governance of Molecular Genetic Testing.

Conclusions

The work we have outlined above provides a robust, consensus-based platform for the development of initiatives to ensure the quality of genetic testing. Future challenges lie in the implementation of these standards at national level and their refinement and application to emerging sectors and markets. New initiatives at international level are emerging to harmonise regulatory approaches to the consumer market, building on the existing framework we have outlined here. The OECD guidelines, though not legally binding, do represent a commitment for those Members that adopt and ratify them setting good basis for international harmonization. They will also serve in emerging economies like China and India which are only now developing clinical genetics services and who have started to put resources into the development of national policies for the translation of genetic knowledge into their health care systems. This trend reinforces the growing need for international quality standards for the provision of genetic testing, including the

necessary infrastructure, tools, resources, guidelines and procedures leading to the establishment of quality genetic services and competence in genetic testing.

The key question on how these international efforts are going to be implemented is still open. While the work of the OECD and the EC has established international consensus on standards and best practices for ensuring the quality of genetic services, there remains much work to do to implement the standards in member countries.

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IPR Issues and High Quality Genetic Testing

Geertrui Van Overwalle

Key Points

– Patents for genes and genetic tests
– Patent thickets and refusal to license
– Facilitating access to patents
– Research exemption, licensing, patent pools, clearing houses
– Compulsory licenses
– BRCA saga

Keywords Patents · Genes, genetic tests and tools · Breast and ovarian cancer testing · Genes BRCA1 and BRCA2 · Refusal to license · Blocking effect · Solutions

Abbreviations

EPC	European Patent Convention 1973 (available at http://www.epo.org)
EPO	European Patent Office
EPO OD	Opposition Division of the EPO
EPO TBoA	Technical Board of Appeal of the EPO
EPO EBoA	Enlarged Board of Appeal of the EPO
ESHG	European Society of Human Genetics
EU Biotechnology Directive	Directive 98/44/EC of 6 July 1998 of the European Parliament and of the Council on the legal protection of biotechnological inventions, *Official Journal L* 213, 30/07/1998 p. 0013 (available at http://eur-lex.europa.eu)

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MPLA	MultiPlex Ligation-dependent Amplification method
PCR	Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
TRIPs	WTO Agreement on Trade Related Aspects of Intellectual Property Rights, 1995
WHO	World Health Organization

Introduction

Over the last years, the patenting of genetic tests sparked significant interest worldwide. Newspapers commented on patent cases and, quite often, portrayed patents as a negative story (Caulfield et al. 2006, 2007). The commotion surrounding the current patent framework for genetic testing is hardly surprising. Although patents on human genes and diagnostics are not novel, patents on genes for diagnostics are indeed a rather special combination. And although licensing has become daily routine in genetics to gain access to patented technology, the emergence of patent clusters and the restrictive licensing behaviour of some patent proprietors has been experienced as quite disturbing.

In an attempt to provide a better understanding of the contentious patent issues at stake in genetic testing, the present contribution first surveys the current legal framework for patenting genetic tests, thus sketching the patent regime from a patent *holder's* perspective. The paper then examines strategies to gain freedom to operate in the genetic field, thus zooming in on the patent landscape from a patent *user's* perspective.

Generally speaking, genetic testing relates to identifying changes in chromosomes, genes, or proteins to find changes that are associated with inherited disorders (http://www.ghr.nlm.nih.gov/handbook/testing/genetictesting). More narrowly, *medical* genetic testing aims at probing genetic material for disease associated geno- or karyotypes (medical applications of cytogenetics, DNA & biochemical tests) (Sequeiros 2008). The present contribution focuses, even more specifically, on medical genetic *DNA/RNA* testing, and reviews patent and licensing issues related to genes, and diagnostic methods and tools from an international and European perspective, illustrated with a concrete, real life example, namely the well known BRCA-case.

Patenting of Genetic Testing

Genes

Based on the principle of non-discrimination with regard to technology, it is agreed on the international level, that biological material should be regarded as patentable subject matter (article 27 (1) TRIPs). It is further accepted that human genes can be subject of patent protection if they meet the patentability criteria such as novelty,

inventive step and industrial applicability (article 27 (1) TRIPs). However, states may take a decision to deny patents on their territory for inventions claiming human genes based on ethical grounds in case the commercial exploitation of such patents runs counter to *ordre public* or morality (article 27 (3) (b) TRIPs) (Van Overwalle, 2008). Till now, few countries have used the option to carve out human genes from their patent laws (Van Overwalle 2008).

On the European scene, patent law did not contain an explicit rule concerning the admissibility of patents on human beings or human body material for a long time (cf. article 52 EPC). As a matter of routine, the European Patent Office (EPO) granted EUROPEAN PATENTS for DNA sequences and genes without a great stir, provided they met the conditions of novelty, inventive step and industrial applicability. This lenient policy was first formally challenged when a patent was granted for "a DNA fragment encoding human H2-preprorelaxin" (see claim 1 of European patent EP 112.149). In its decision, the EPO concluded that an invention concerning a human gene was not an exception to patentability because it would not be universally regarded as outrageous: "[. . .] it did not amount to patenting life because DNA as such was not life but one of the many chemical entities participating in biological processes; no offence to human dignity had occurred as the woman who donated tissue was asked for her consent and her self-determination was not affected by the exploitation of the claimed molecules" (EPO OD, 1995, *Howard Florey Institute*).

In the meantime another player, the European Parliament, entered the debate and enacted the EU Biotechnology Directive in an effort to harmonize upcoming patent practices and legislation in the biotech field. The Directive takes the view that neither the human body at the various stages of its formation and development, nor the simple discovery of one of its elements including the sequence or partial sequence of a gene, can constitute a patentable invention. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element (article 5 EU Biotechnology Directive) (see Box 1).

Box 1 Article 5 EU Biotechnology Directive

1. The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.
2. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element
3. The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application

After the EU Biotechnology Directive was passed by the European Parliament, the EPO amended their Regulations and added a rule confirming the patentability of isolated human genes (Rule 29 EPC). The question then arose to what extent this new rule was in conformity with the exclusion of inventions the exploitation of which would be contrary to *ordre public* or morality (article 53 (a) EPC) (See Box 2). Based on earlier case law (EPO EBoA G1/98, 1999, *Novartis AG*), the EPO adopted the view that the new rule "only gave a more detailed interpretation of the meaning of article 53 EPC as intended from its inception". It thus followed from the text of the rule itself that genes were not to be considered as an exception from patentability on grounds of *ordre public* or morality (EPO TBoA T272/95, 2002, *Howard Florey Institute*).

Box 2 Article 53 European patent convention (EPC)

European patents shall not be granted in respect of:

(a) Inventions the commercial exploitation of which would be contrary to "ordre public" or morality; such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States;
(b) Plant or animal varieties or essentially biological processes for the production of plants or animals; this provision shall not apply to microbiological processes or the products thereof;
(c) Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

The patentability of human genes was also fiercely debated in the EU member states, when discussing the availability of NATIONAL PATENTS for human body material. Since the Directive did not leave any manoeuvring room to cut out human genes from patent law as non patentable subject matter, the major discussion revolved around the exact *scope* of gene patents. Should a patent for a DNA sequence encompass all possible future applications, or should such a patent be restricted to the specific use described in the patent application? In other words, should DNA patents follow the regime of the classical, wide, absolute protection (*absoluter Stoffschutz*), or should a restricted, purpose-bound protection (*zweckgebundener* or *funktionsgebundener Schutz*) apply?

In France and Germany a restricted scope for DNA patents has been adopted (Van Overwalle 2006). However, most EU countries have not introduced any special rules for DNA patents and have thus opted for the conventional, broad scope.

The debates in the EPO, the EU Parliament and the national parliaments indicate that human gene patents were not readily accepted in Europe. Reopening the discussion might prove to be difficult, however, as the necessary political consensus to put the issue back on the agenda of the European Parliament seems to be absent at the moment.

Diagnostic Methods

On the international level it is generally agreed that national patent legislatures can exclude diagnostic, therapeutic and surgical methods for the treatment of humans or animals from patentability (article 27 (3) (a) TRIPs). The option to exclude such methods is based on public health considerations: medical and veterinary practitioners should be free to take the action they consider adequate to diagnose illnesses. In other words, those who carry out diagnostic methods as part of a medical treatment of humans or animals should not be inhibited by patents. It was agreed that this exclusion shall not apply to products, in particular substances or compositions, for use in any of these methods.

Long before the TRIPs agreement came into being, the EPO already decided to exclude diagnostic methods from patent protection when "practiced *on* the human or animal body" (Our italics) (Currently article 53 (c) EPC) (see Box 2). The exclusionary provision in the EPC is constructed more narrowly than its TRIPs counterpart, implying that the *only* methods excluded from patent protection are diagnostic methods practiced *on* the human body. Unfortunately, the EPO legislator did not define the term "diagnostic method", so it was left to the courts to delineate the exact scope of the exclusion. The EPO jurisdictions initially clarified that only diagnostic methods claiming *all* steps involved in reaching a medical diagnosis (viz. examination, recording any significant deviation from the normal value, attributing that deviation to a particular clinical picture) were excluded from patentability and thus not patentable. In other words only diagnostic methods whose result immediately makes it possible to decide on a particular course of medical treatment are excluded. Methods *not* containing *all* the steps involved in making a medical diagnosis do not fall under the exception and are considered patentable. In other words methods providing interim results (even if the results can be utilised in making a diagnosis) are not excluded from patentability and are patentable (EPO TBoA T385/86, 1987, *Bruker*).

A classical example of an invention which would not be excluded from patent protection under this approach is a method relating to the *in vitro* determination of medical laboratory parameters (concentrations of molecules or cells in a body liquid e.g. urine). The sample (the urine) is mixed with the reagents in a reaction vessel, and the detectable change is evaluated by the instrument which belongs to the system. None of the method steps is carried out on the body. Only if direct interaction with the body made a real difference whether the object of the invention was achieved and if the entirety of the diagnostic method had to be practised on the body would the exclusion apply.

EPO case law later departed from this interpretation and held that the expression "diagnostic methods practised on the human body" should not be considered to relate only to methods containing *all* the *steps* involved in reaching a medical diagnosis, but to *all methods* practised on the human body which related to diagnosis or were of value for the purpose of diagnosis (EPO TBoA T964/99, 2001, *Cygnus*). All that was needed to justify an exclusion was that the claimed method comprised *one* step which served diagnostic purposes or related to diagnosis and was to be regarded as an essential activity pertaining to diagnosis and practised on the living human body. This U-turn in the EPO position was motivated by the fact that early case law amounted to setting a different standard for diagnostic methods compared to methods of surgery or therapy, the latter being excluded from patent protection if they comprised only *one* single step of a surgical or therapeutic nature. It was further held that the criterion "practised on the body" was in any case satisfied if direct contact with the body was involved. It remained unclear whether some other kind of interaction with the living body might equally suffice to satisfy this criterion, for example a non-invasive method using radiation that could be performed for measurement and analysis purposes and that could form the basis for a diagnosis.

A classical example of an invention which would be excluded from patent protection under this approach is a method, which in essence is carried out by a machine, but which includes steps which (at least theoretically) can be performed by a physician on the body of a patient.

The ongoing debate on the scope of the exclusion of diagnostic methods recently came to a halt with an authoritative EPO ruling (EPO EBoA G1/04, 2005, *Diagnostic methods*). The decision first clearly confirms that practicing a diagnostic method requires *several* method steps due to the inherent and inescapable multi-step nature of such a method, contrary to surgical or therapeutic methods which can be achieved by a single step. It is accepted that the method steps to be carried out when making a diagnosis as part of the medical treatment of humans include: (i) the collection of data (examination phase), (ii) the comparison of found data with standard values (comparison phase), (iii) the finding of any significant deviation (ie a symptom), and (iv) the attribution of the deviation to a particular clinical picture (the deductive medical decision phase).

The ruling further holds that only methods including *all* steps are excluded from patent protection: only methods pertaining to the diagnosis for curative purposes as a purely intellectual exercise representing the deductive medical decision phase (the diagnosis for curative purposes stricto sensu), *as well as* to the preceding steps which were constitutive for making the diagnosis (examination, data gathering and comparison), *and* the specific interactions with the human body which occurred when carrying out those of the said preceding steps which were of a technical nature. A method for obtaining intermediate findings of diagnostic relevance does not fall under the exclusionary provision and is patentable (EPO EBoA G1/04, 2005, *Diagnostic methods*).

It is justified to require that all method steps of a technical nature of a diagnostic method should satisfy the criterion "practised on the human or animal body". In other words, the performance of each and every one of these steps should imply

an interaction with the human or animal body, necessitating the presence of the latter. If, on the other hand, some or all of the method steps of a technical nature are carried out by a device without implying any interaction with the human body (e.g. by using a specific software program), these steps may not be considered to satisfy the criterion "practiced on the human or animal body". By the same token, this criterion is not complied with either in respect of method steps carried out *in vitro* in a laboratory, such as method steps carried out *in vitro* by diagnostic devices known as DNA microarrays (EPO EBoA G1/04, 2005, *Diagnostic methods*).

In short, current EPO case law suggests that diagnostic methods carried out *in vitro* are considered unpatentable, whereas diagnostic methods not carried out on the human or animal body, but practiced *in vitro* are considered patentable (Thomas 2007, 2003).

Carrying Out Genetic Testing

Where a gene is patented, patent holders have the right to stop others from making or using the patented gene. Where a patent for a diagnostic method is granted, patent owners have the right to refrain others from using the diagnostic method (article 28 TRIPs). Various strategies can be designed to limit the right of the patent holder and to facilitate access to patented technology for users, in case diagnostic labs.

Research Exception

A first way that comes to mind to enable the free use of patented genes and methods is the research or experimental use exemption. Prevailing patent acts in many EU member states suggest that the rights that are conferred by a patent shall not extend to acts done for experimental purposes relating to the subject-matter of the patented invention. Unfortunately, the wording of this exception differs from country to country, resulting in a legal patchwork of provisions having a different and uncertain scope. Furthermore, the exemption is directed to "research" and it remains unclear to what extent said exemption can shield diagnostic testing. On the one hand, it can be argued that diagnostic testing falls within the research exemption, because patient blood or tissue sampling is often necessary to do research. On the other hand, it can be claimed that diagnostic testing can not fall within the exemption because once a diagnostic test is established, the act of diagnosis could be defined as and/or confined to the act of providing the referring medical doctor with an opinion as to whether or not the patient carries a deleterious mutation. Recent EPO case law seems to opt for this last viewpoint (EPO EBoA G1/04, 2005, *Diagnostic methods*).

Licensing

As it is most unlikely that genetic testing will fall under the research exemption, securing a license from the patent holder is a second option to gain access to patented genetic testing technology. Roughly speaking, three licensing approaches

can be distinguished in the diagnostic field (Matthijs 2007). In the first or so-called "open" model, put to practice with the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene, free access is granted to gene sequences for diagnostic testing using commonly available technologies for mutation analysis, but royalties are collected on gene based commercial test kits. In the second or so-called "monopoly" model, witnessed in the BRCA gene case, an exclusive licensing policy is applied with relatively high prices (see below). In the third model, operationalised with the Hereditary Haemochromatosis (HH) gene, the company offers to license laboratories to carry out testing, but at a cost that makes the company's own, commercial test kit more economically attractive owing to their requirement of up-front payments and a per-test fee.

Apart from a few a-typical license agreements, license arrangements offer wide possibilities to tailor the needs and uses of both patent holders and diagnostic laboratories.

Compulsory Licensing

In the event a patent holder refuses to grant (reasonable) licenses, a compulsory license might bring relief to gain access to patented technology. Based on a wide set of international agreements (articles 8 (1) and 30 TRIPs, Doha Ministerial Declaration of 14 November 2007, Declaration on the TRIPS agreement and public health of 14 November 2007), various EU member states introduced a compulsory license specially tailored to the needs in the field of health care. Most prominent in this regard are the newly introduced license schemes of Belgium and France (Van Overwalle 2006). Such compulsory license schemes allow others than the patent holder to exploit an invention protected by a patent for (a) a medication, a medical appliance, a medical appliance or product for diagnosis, a derived or combinable therapeutic product, (b) the process or product necessary for the manufacture of one or more products indicated under (a) and (c) a diagnostic method applied outside of the human or animal body.

Collaborative Licensing

When access to genes and methods necessary to carry out a genetic test is not limited by the restrictive license behaviour of a the license holder, access may be hampered by the existence multiple patents held by different patent owners. When such patent clusters are present, arrangements bundling a set of patents can help to gain access (Van Overwalle et al. 2006; Van Overwalle, 2009). One such model enabling access to a bunch of patents with a single license is a patent pool. A patent pool is an agreement between two or more patent owners to license one or more of their patents to one another, and to license them as a package to third parties who are willing to pay the royalties that are associated with the license (Verbeure 2006a; Verbeure, 2009). A key example of a genetic pool, supported by the WHO, is the SARS corona virus pool (Simon 2007; Correa, 2009). However, the SARS pool is no longer actively being pursued, because with no further outbreaks of SARS, the economic driver

for the formation of such a pool has been removed (Personal communication James Simon, 21 January 2009).

Another model to simplify access to a cluster of patents is a clearing house. A clearing house operates as an intermediary platform between technology/patent holders and technology seekers. It can perform various tasks, ranging from providing information on available technologies, assisting technology owners and/or buyers in initiating negotiations for a license, setting allocation formula for patents, cashing in licence fees from users on behalf of the patent holder (van Zimmeren et al. 2006; Van Zimmeren, 2009). Classical examples of such clearing houses include national copyright societies for playing music on air (e.g. SABAM in Belgium). An example in the genetic field is PIPRA (Public Intellectual Property Resource for Agriculture) aiming to facilitate access to new agricultural technologies for developing countries (http://www.pipra.org).

These new collaborative licensing models have gained wide attention. Meaningful in this regard is the attitude of the European Society of Human Genetics (ESHG) supporting the practical exploration of alternative models for licensing like patent pools and clearing houses (ESHG 2008). The ESHG even suggested the establishment of a European wide patent clearing house for genetic and biological inventions. In other words, a clearing house for European research institutes in genetics which might "facilitate the concentration of gene patent talent and accelerate protection of IP" (ESHG 2008).

A Real Life Example: The BRCA Saga

To bring some more shade and depth to the prevailing legislative framework, we turn to a real life example, more in particular the patenting and licensing of breast and ovarian cancer testing.

The Patenting of Breast and Ovarian Cancer Testing

In the course of 2001 a series of European patents dealing with diagnostic testing for early onset breast and ovarian cancer based on the genes BRCA1 and BRCA2 were granted to the US company Myriad Genetics. In line with the governing EPO rules on human gene patents, all three patents relating to the BRCA *genes* were granted (EP0705902, EP0705903, EP0785216) (see Box 3 and Box 4). Following current EPO legislation and case law on diagnostic methods, the one patent relating to a *method* for diagnosing breast and ovarian cancer was equally accepted (EP0699754) (see Box 3 and Box 5), as well as various diagnostic *techniques* and *tools*. One of the most frequently used techniques to test for BRCA is PCR. The original Mullis patent expired a few years ago, but other patents still protect various aspects of the method (see Box 6). An alternative technique which can be put to work to test for breast and ovarian cancer is Multiplex ligation-dependent amplification method (MLPA), which has been protected by various patents in the US (patents are pending

in Europe) (see Box 7). Yet another way to test breast and ovarian cancer is to use Lightcycler 480 High Resolution Melting Master. Most related patents are owned by Roche Molecular Systems Inc. (see Box 8).

Box 3 BRCA1 and BRCA2 patents (Europe)

Patents relating to BRCA1
- EP0699754 "Method for diagnosing a predisposition for breast and ovarian cancer" granted on 10/01/2001
- EP0705902 entitled "Nucleic acid probes comprising a fragment of the 17q-linked breast and ovarian cancer susceptibility gene", granted on 28/11/2001
- EP0705903 entitled "Mutations in the 17q-linked breast and ovarian cancer susceptibility gene", granted on 23/05/2001

Patent relating to BRCA2
- EP0785216 entitled "Chromosome 13-linked breast cancer susceptibility gene BRCA2", granted on 08/01/2003

Box 4 Major BRCA1 *gene* claim (Europe)

"1. An isolated nucleic acid which comprises a coding sequence for the BRCA1 polypeptide defined by the amino acid sequence set forth in SEQ. ID. NO:2, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ. ID. NO:2" (Claim 1 from EP705902B1, as published on 28/11/2001)

Box 5 Major BRCA1 *method* claim (Europe)

"1. A method for diagnosing a predisposition for breast and ovarian cancer in human subject which comprises determining in a tissue sample of said subject whether there is a germline alteration in the sequence of the BRCA1 gene coding for a BRCA1 polypeptide having the amino acid sequence set forth in SEQ. ID. NO:2 or a sequence with at least 95% identity to that sequence, said alteration being indicative of a predisposition to said cancer" (Claim 1 from EP699754B1, as published on 10/01/2001)

Box 6 Major patents related to PCR (Europe)

- EP0201184, entitled "Process for amplifying nucleic acid sequences" entails the process for exponentially amplifying at least one specific double-stranded nucleic acid sequence
- EP0236069, entitled "Apparatus and method for performing automated amplification of nucleic acid sequences and assays using heating and cooling steps" deals with an apparatus for automated temperature cycling and a method of using this
- EP0258017 entitled "Purified thermostable enzyme and process for amplifying, detecting, and/or cloning nucleic acid sequences using said enzyme" covers this thermostable enzyme having DNA polymerase activity and a method of using this enzyme.
- EP0395736 entitled "Purified thermostable enzyme" comprises a DNA sequence encoding a thermostable DNA polymerase.

Box 7 Major patents related to MPLA (Europe)

- EP1130113-A1 (US6955901-B2), entitled "Multiplex ligatable probe amplification" is owned by De Luwe Hoek Octrooien (NL)
- EP1472369 (US6960436-B2), entitled "Quantitative methylation detection in DNA samples" covers a method for the cytosine methylation detection in a DNA sample and is owned by Epigenomics AG (DE)

Box 8 Major patents related to Lightcycler (Europe)

- EP512334, entitled "Methods for detecting a target nucleic acid in a sample", assigned to Hoffmann la Roche
- EP872562, entitled "Instrument for monitoring nucleic acid amplification reactions", assigned to PE Corp NY US
- EP906449, entitled "System and method for carrying out and monitoring polymerase chain reactions", assigned to Utah University US
- EP912760, entitled "System and methods for monitoring for dna amplification by fluorescence", assigned to Utah University US
- EP1033411, entitled "Fluorescent donor-acceptor pair", assigned to Utah University US
- EP581953, entitled "Process for determining -i(in vitro) amplified nucleic acids", assigned to Evotec Biosystems, DE

The grant by the EPO of the series of patents covering the breast cancer *gene*, its mutations, as well as *diagnostic* and therapeutic applications based on the gene's sequence, evoked strong reactions and led to the questioning of the nature, legitimacy and scope of gene patents and diagnostic methods instrumental to public health (Matthijs and Halley 2002; Verbeure 2006b). The award by the EPO of patents on additional *tools* and *techniques* necessary to carry out genetic testing hardly met any (public) resistance. Significant in this regard is the position of the ESHG admitting that they see "no harm in the patenting of novel technical tools for genetic testing (e.g. PCR or chip technologies), as they can promote investments and still allow for invention around" (ESHG 2008).

The Licensing of Breast and Ovarian Cancer Testing

After Myriad Genetics obtained several European (and US patents) for breast cancer *genes* and the related *diagnostic screening method*, it licensed the breast cancer test exclusively to a limited number of commercial genetic laboratories within specific geographical regions (Walpole et al. 2003). These laboratories were apparently allowed to carry out testing of only a limited set of BRCA1 and BRCA2 mutations, while the complete sequence analysis was still carried out only by Myriad. In turn, the licensing policies applied for the complementary *diagnostic technology* seemed rather loose. These days, the PCR, MPLA and Lightcycler patents all require licenses, but mostly on a non-exclusive basis and at reasonable royalty rates.

The highly restrictive licensing policy from Myriad gave rise to a strong and worldwide reaction (Baldwin 2007; Bird 2007; Herrlinger 2005; Matthijs and Halley 2002; NRC 2005). In order to address these concerns, OECD member countries agreed to Guidelines for the Licensing of Genetic Inventions used in health care (OECD 2006). The Guidelines set out principles and best practices for those in business, research and health systems who enter into license agreements for genetic inventions used for the purpose of human health care. They are targeted at those involved with innovation and the provision of services in health, and particularly at those involved in the licensing of such inventions. Overall, the Guidelines seek to foster the objectives of stimulating genetic research and innovation while maintaining appropriate access to health products and services. In the same spirit, the ESHG developed Recommendations underlining that rights holders should license genetic inventions for health applications, including diagnostic testing, on terms and conditions that seek to ensure the widest public access to, and variety of products and services (ESHG 2008). The ESHG held that foundational genetic inventions – as well as methods for diagnosis – should be licensed so as to be broadly accessible, at a fair and reasonable price.

Concluding Remarks

The genetic community is very sensitive to possible unfair use of the patent system in the field of genetic inventions, witness the strong reactions against the grant to Myriad Genetics of patents dealing with diagnostic testing for early onset breast and

ovarian cancer based on the genes BRCA1 and BRCA2. The impasses identified and the criticism voiced is not always directed to the *existence* of the patent *system* as such, but rather to some excesses in the *exercise* of patent *rights* and the unrestrained behaviour of individual patent owners, in an effort to maximize profit.

It is hoped that the new compulsory license for public health will address undesirable effects and unreasonable behaviour from patent holders in an adequate manner, thanks to its preventive and dissuading effect towards patent holders applying (extremely) restrictive licensing policies. It is also to be expected that new models of collaborative licensing may contribute to facilitating access to genetic testing when clusters of patents are rendering access to genetic testing technology too complex and uncertain Huys et al., 2009.

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Lexicon

EUROPEAN PATENT. On the basis of a single application and examination procedure one can protect an invention in up to 36 European countries, all contracting states which have ratified the European Patent Convention of 1973 (EPC). The term "European patent", however, is misleading from three points of view. It is not a single patent that is valid for the whole of Europe: the application and granting procedures are uniform, after which the patent is broken up into a "bundle" of national patents which are further subject to national legislation and, more particularly, to national regulations with regard to nullification and impairment. Nor is a "European patent" a patent granted by the European Union (EU): European patents have nothing to do with the EU apart from the fact that all EU Member States have also signed the EPC. Furthermore, it is on the basis of the EPC that the European Patent Office (EPO) was brought into being, for dealing with European patent applications. It bears repeating that the EPO is not an EU institution, either.

NATIONAL PATENT. In Europe it is also possible to obtain patent protection by separate application to each of the national patent offices within Europe.

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Quality Issues in the Evaluation and Regulation of Genetic Testing Services: A Public Health Approach

Caroline F. Wright and Ron L. Zimmern

Key Points

- The evaluation of genetic testing services is essential for ensuring quality, and determining whether genetic tests offer a health benefit to the population. However, this is complex process, because any given test may be used in different contexts and for different purposes.
- It is therefore useful to distinguish between: an assay, the measurement of a genetic sequence; a test, the use of an assay in a particular context; and a service, which embraces performing, processing, and interpreting the test, in addition to informing and supporting the patient.
- This distinction has important practical implications for both evaluation and regulation of medical testing services.
- Quality standards may be set for all three aspects of genetic testing, relating to the testing process itself, the possible outcome(s) and structure of the service, then monitored and improved using a formal audit cycle.
- Different regulatory models may be appropriate for the three aspects of genetic testing services, including statutory legislation, professional self-governance and voluntary guidance.

Keywords Public health genomics · Genetic testing · Quality

Introduction

Public health has been defined as *"the art and science of promoting health and preventing disease through the organised efforts of society"* (Acheson 1988). It is concerned with assessing needs and trends in the health and disease of populations,

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as distinct from individuals. Although historically public health has focussed on the social and environmental causes of disease, the initiation and subsequent completion of the human genome project has lead to an increasing trend towards genetic testing throughout health care, which in turn prompted the establishment of the sub-discipline of public health genetics. This has been formally defined as the "*effective translation of genome-based knowledge and technology for the benefit of population health*" (Stewart et al. 2007), and brings together the science of genetics and molecular biology with epidemiology, social science and public health. The ultimate aim is to use genetic information as a means of improving health.

The public health perspective is one that questions whether scientific advances, new technologies, legislation and policies add or detract from improvements in human health. To this end, the public health genetics approach includes four key activities: informing public policy; education and training; communication and stakeholder engagement; and developing and evaluating health services. It is in this last pursuit that quality issues in the evaluation and regulation of genetic testing services are most pertinent.

Assays, Tests and Services

The evaluation of diagnostic tests is central to ensuring quality in genetic testing services. However, this is complex process, because a test may have multiple different purposes, including making or excluding a diagnosis, evaluating prognosis, assessing risk, monitoring health, and guiding treatment. The performance of a particular test can vary hugely between different contexts, and a test that is effective for one purpose or in one population, may not be in another. Therefore, the involvement of health care professionals throughout the testing process is critical to correct interpretation of the results. How, then, can the overall quality of a *genetic testing service* be evaluated?

For the purpose of both evaluation and regulation, it is useful to distinguish between three elements that comprise a genetic testing service, which are all conveniently represented in the name itself: assays, tests and services. The most fundamental part of a genetic testing service is the *assay,* the scientific measurement of the genetic sequence or product of interest, without which the rest of the service would be redundant. The performance of an assay for a particular gene is relatively straightforward (though labour intensive) to evaluate, through determining the accuracy and precision with which the assay correctly measures or identifies the genetic sequence of interest. Where possible, this can be determined through comparison with a gold standard. Clear and precise performance standards can be set for a particular assay, and laboratory quality assurance systems used to ensure they are met and maintained (OECD 2007).

A layer of complexity is added when an assay is transformed into a *test* (Zimmern and Kroese 2007), which can be defined as the application of a particular assay:

- for a particular disease;
- in a particular population;
- for a particular purpose.

The evaluation of a test is therefore much more cumbersome and involved than just assessing the technical performance of the assay, and includes specifying the disease of interest, the exact population that will be tested, and the purpose of the test within a care pathway.

The ACCE model, developed by the US Centers for Disease Control and Prevention (Haddow and Palomaki 2004) provides a framework for evaluating genetic tests, comprising:

- *Analytical validity* of the assay, i.e. the accuracy with which it measures the genetic sequence of interest;
- *Clinical validity* of the test, i.e. the ability of the test to distinguish between those who have (or will have) a disease from those who are (and will remain) healthy. This includes not only evidence of a proven association between the genetic sequence and the disease of interest, but also evidence of the clinical performance of the test (its sensitivity, specificity, predictive values, etc.);
- *Clinical utility* of the test, i.e. the overall risks and benefits associated with introduction into routine practice;
- *Ethical, legal and social implications (ELSI)* of the test.

The standards for individual tests will therefore be primarily those that must be set for the parameters specified in the ACCE framework, particularly those that relate to the analytical and clinical validity of the test. Standards of clinical validity will differ according to clinical context, and vary according to how the test is to be used and for what purpose. The value of a test in any given clinical scenario is related not only to its technical performance, but also to the pre-test probability that an individual (or population) has the disease of interest. Therefore, a thorough assessment of the clinical validity must include the sensitivity, specificity and predictive values of the use of a test for a particular purpose in the target population to be tested, which is generally associated with a specific clinical pathway.

Whilst this process may seem conceptually straightforward (albeit time consuming and expensive) in the case of tests for inherited single gene disorders, where the causal mutation and pre-test probability of having a disease is well established, it is much more complicated for predictive genetic susceptibility testing, where the disease-associated variants are incompletely penetrant. In such cases, a particular genetic sequence may suggest a predisposition to future disease, rather than being an indicator of current disease. The incremental improvement provided by a particular test in the assessment of an individual's risk of developing a disease (within a particular timeframe) may be small. Therefore, the context in which the test is used and the incremental benefit of using, versus not using, a specific test for achieving a particular purpose, or reaching a decision relating to the health care of a patient, is paramount to assessing the overall quality of care.

The final aspect of quality in genetic testing services is the *service* itself, including both laboratory and associated clinical services, and the broad overarching context in which a particular test is offered. Any clinical test should sit within an integrated care pathway, from the point at which a patient is offered a test, through sample handling and processing, to interpreting and communicating results, and finally recommending and providing for appropriate actions. Ensuring quality at each point along the pathway depends upon assessing the relevant professionals and services. Whether a service provides and meets the professionally assessed needs of its clients – its professional quality – can be judged by assessing both the outcomes and the professional abilities of those providing the service (Øvretveit 1992).

However, the number and level of integration of different services varies widely between different specialties, between commercial testing kits and in-house laboratory developed tests (LDTs), and between state and private test providers. A typical genetic test service might include GPs, clinical geneticists, genetic counsellors, specialist nurses, molecular and cytogenetic genetic laboratories, commercial laboratories and private test providers. Therefore, whilst an audit cycle can be applied to each of these services independently, a wider quality management cycle is needed to ensure quality of care throughout the process, and regulation is required to ensure that standards are being set, met and maintained.

Quality and Standards

The Institute of Medicine defines the quality of care as *"the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge"*. Quality is necessarily a multidimensional concept that encompasses both the science and technology of health care, and its application in practice. The quality of a health service intervention has also been conceptualised as the extent to which the intervention meets the standards which have been set for it. The establishment of standards is therefore a key feature in quality assessment.

One of the most comprehensive frameworks for evaluating quality is that of Donabedian, who conceptualised three dimensions of quality of care (Donabedian 2003):

- *Structure*: the context and conditions under which care is provided;
- *Process*: the activities of medical practice;
- *Outcome*: the impact of care on health status.

In this chapter we concentrate on genetic testing services in their entirety, but we should not forget that this includes both the standards that we might set for individual tests as well as standards for the provision of the entire service. In this context, s*tructure* might refer to the testing service (both clinical and laboratory) and the resources and entities that are required to perform the tests, *process* to the

activities involved in performing the test and interpreting the result, and *outcome* to the effect of the test result on the patient (or population). Since there are multiple possible components within each of these areas, this framework provides a broad, joined-up approach to assessing overall quality.

Furthermore, Donabedian specified seven elements within the framework that should be considered when evaluating quality, and an eighth dimension was proposed by the RAND corporation. With respect to testing, these can be broadly categorised into those relating to the *purpose* of the test and those relating to the *delivery* of the test (Burke and Zimmern 2007):

Test purpose:

(1) *Legitimacy* – the conformity of a test to social preferences expressed in ethical principles, values, laws and regulations;
(2) *Efficacy* – the ability of the test (and any associated services) to bring about its intended purpose when used in the most favourable circumstances;
(3) *Effectiveness* – the extent to which attainable objectives are in fact attained under routine condition;
(4) *Appropriateness* – the balance between the expected benefit and expected negative consequences of a test;

Test delivery:

(5) *Acceptability* – the conformity of a test to the wishes, desires and expectations of patients and their families;
(6) *Efficiency* (economic) – the ability of the test to lower costs without diminishing benefits;
(7) *Optimality* (economic) – the balance of improvements in health against the costs of that improvement;
(8) *Equity* – the extent to which a test meets the principle of just and fair distribution of health care, and its benefits, among members of the population.

However, simply measuring these indicators does not in and of itself ensure quality; rather, quality assurance relates to the actions taken not only to establish, but also to protect, promote and improve the quality of health care. This leads directly to the audit cycle (see Fig. 1), a systematic process for monitoring and improving performance. According to the Royal Society of Pathologists, "*each audit cycle involves defining standards, collecting data to measure current practice against those standards, and implementing any necessary changes to improve practice; undertaking a re-audit, after changes have been made, aims to show the impact of changes and completes the audit cycle*". Monitoring performance therefore requires that someone not only determines and prioritises what to monitor, but also selects a practical approach (including formulating criteria and standards), decides when and how to make assessments, and constructs an appropriate monitoring system. In addition, improving performance requires that a positive behavioural change can and is be brought about in light of the audit findings.

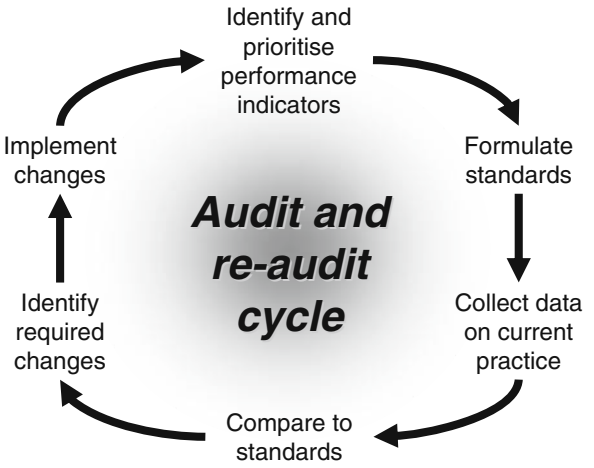

Fig. 1 The audit cycle in health care quality

Importantly, none of the dimensions of quality can be assessed in the absence of standards, against which performance can be measured. Useful standards must be understandable, measureable and achievable; they may include minimum standards (the lowest acceptable standard of performance), ideal standards (the standard of care it should be possible to give under ideal conditions) and optimum standards (standard of care most likely to be achieved under normal conditions of practice). Numerous different standards are needed to encompass the structures (service logistics), processes (test or intervention) and outcome (health benefit) of a particular health care activity.

Recognising the dichotomy between *tests* (including the assay) and *services*, and the importance of evaluating both separately as well as part of an "end-to-end" process, is critical to the assessment of quality in genetics testing services. To the extent that a test is (or should be) carried out for a particular reason, rather than as an end in itself, outcome standards must relate closely to that end; in a health care setting, this must relate to some aspect of health benefit. Assessing the quality provided by a particular genetic testing service must therefore explicitly include not just an evaluation of the scientific and clinical performance of the test itself, but also the effect of the test on patient care and on health outcomes. This process is crucial in determining whether, and when, it is appropriate to offer a particular test.

Regulation

A wide choice of regulatory vehicles is available to policy-makers, which vary in their appropriateness for regulating each component of a genetic testing service (Burke and Zimmern 2004). The options range from voluntary codes of practice and informal guidelines, to professional self-regulatory mechanisms and legal statutory

obligations. Compliance with any specific regulatory mechanism may be achieved through the use of incentives, such as receiving or withholding a professional mark that indicates a certain standard of quality, or through formal legislative means.

Legally enforceable regulation can be enacted either through the application of the existing common law, a legislative mechanism such as primary legislation (statute), or secondary legislation including regulations issued by a delegated authority. However, achieving compliance may be extremely challenging, particular with respect to tests offered between countries over the internet. Therefore, voluntary codes of practice have been suggested as a practical solution. Although codes of practice and formal guidelines do not have legal enforceability and can vary tremendously between jurisdictions, they are useful in the ongoing process of consensus-building, particularly at the international level (for example see OECD 2007). Moreover, the scope can be wide enough to address the entirety of a genetic testing service, through integration and recommendation of more narrowly focused, and potentially more formal, mechanisms at different stages in the process.

The division of genetic testing services into three separate components – assays, tests and services – has significant practical implications for the application of different regulatory mechanisms (see Fig. 2). Whilst is may be possible to legislate the *measurement* capability of an assay, it is almost impossible to legislate the *interpretation* of a test, as this is heavily dependent upon the context in which it is offered and action(s) taken as a result of testing. Moreover, whilst the safety of a test is clearly well within the remit of legislation, defining the risks associated with a test remains controversial – should it be limited to direct harms resulting from the test itself, or include consequential indirect harms resulting from the interpretation of that test?

Hence, statutory regulation is just one element in the oversight of genetic testing services, together with professional self-governance and good practice guidelines. Current in vitro diagnostics legislation, together with laboratory quality assurance systems, are used to regulate the analytical validity of the assay and ensure that the measurement is correct. Ongoing scientific research combined, with advertising

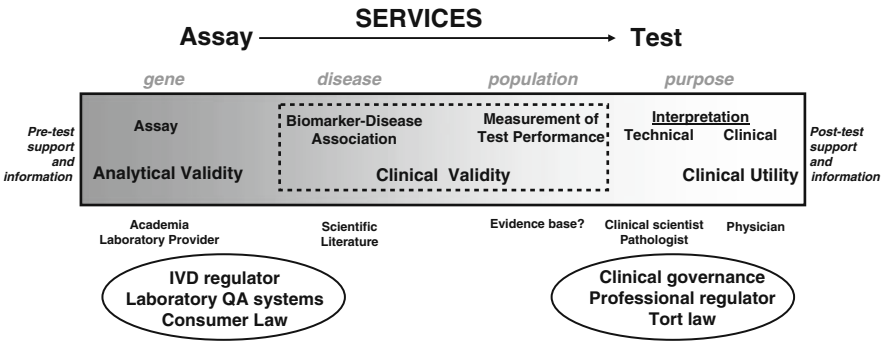

Fig. 2 Levels of evaluation and regulation of assays, tests and services

standards and consumer protection acts, to some extent ensure that there is evidence of an association between the gene and disease of interest. However, despite the availability of guidance on replicating and validating genetic findings (Chanock et al. 2007), the level of evidence associated with a specific test is frequently insufficient to prove that an association is real.

Additionally, the service aspects of the testing process, such as the level and quality of pre- and post-test information and support, and the interpretation of the test result, are regulated through professional self-governance. Standards of professional practice are generally defined and enforced by authorised professional bodies in the national context, for both laboratory and clinical health care professionals. Formal bodies, such as the General Medical Council in the UK, regulate and ensure good medical practice, and can withdraw a physician's licence to practice medicine if necessary. (It should be noted that in the absence of relevant professionals, as is the case for some direct-to-consumer genetic tests, correct interpretation of the test is uncertain, and in the absence of a valid gene-disease association, any attempt to do so it both inappropriate and impossible.) Similarly, ongoing laboratory accreditation schemes provide recognition, through a suitably qualified accrediting body, that a laboratory is meeting certain set standards and criteria.

The clinical aspects of test evaluation – specifically evidence of test performance (clinical validity) and proof of clinical utility – are currently not adequately encompassed by either formal legislation or through non-statutory means, leaving a gap in the regulation of genetic test evaluation. Moreover, in the absence of clinical evidence for test performance, it is difficult to set the standards required to assess and achieve the desired quality of care, and impossible to assess whether the test is valuable in clinical practice. There is increasing recognition of this gap, and a number of experts have proposed that establishing an evidence base for medical laboratory tests may help to address this problem (Furness et al. 2008). Whilst some genetic tests do have sufficient clinical evidence, many do not, and as tests become more complex and increasingly based around multiplexed assays, mechanisms will be needed to ensure that such evidence is generated, assessed and made available to those who need it.

Conclusion

A public health approach to quality issues in genetic testing services is one that questions whether the development and application of new genetic tests ultimately results in an improvement in human health. In order to determine whether this has been achieved, standards must be agreed relating to the structure of the service, the testing process itself, and the outcome(s) of the test, and a formal audit cycle established to evaluate and improve quality. For the purpose of evaluating a genetic testing service, it is useful to distinguish between an assay (i.e. measurement of a genetic sequence), a test (i.e. the use of an assay in a particular context) and a service (i.e. performing, processing, and interpreting the test, in addition to informing

and supporting the patient). Quality standards may be set for all three aspects of genetic testing. This distinction also has practical implications for regulating testing services, through a mixture of statutory legislation, professional self-governance and voluntary guidance at appropriate stages in the testing pathway.

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Quality Management Systems and Accreditation

Els. Dequeker

Key Points

- International and national standards
- Accreditation and certification
- Accreditation process and accreditation bodies
- Quality management in genetic laboratories
- Quality control, quality assessment, quality assurance and quality improvement

Keywords Quality management system · Accreditation

Introduction

In the last two decades, the field of medical genetics has witnessed a remarkable rate of progress both in the understanding of the association between genetic variants and human disease, and in the technical ability to perform genetic analysis. As a consequence, there is a huge growth in the demand from patients and from medical health professionals for clinical genetic testing.

There is an understandable assumption from users that the results of genetic tests are reliable, whereas studies of performance in external quality assessment (EQA) schemes repeatedly show that errors occur at a measurable rate, at all stages of the testing process (for example Dequeker et al. 2000; Seneca et al. 2008; Touitou et al. 2009). To respond to the need to improve the quality of clinical genetic testing, providers are encouraged to implement a comprehensive quality management system and to fulfil the requirements for internationally-recognized standards for laboratory accreditation (Ibarreta et al. 2004).

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International and National Standards

In the context of quality management, be it specifically in clinical genetic testing, other medical laboratories or in wider fields, quality is judged by reference to specifications described in recognized documents, which themselves define a standard or a norm.

The word "standard" has two distinct meanings in a scientific context. On the one hand, it indicates a "normative document" implying, creating or prescribing a norm or standard; well-known examples are the international standards developed by bodies such as the International Organization for Standardization (ISO; see Fig. 1). Alternatively "standard" can refer to a "measurement standard", traceable to the international measurement system and used in calibration, measurement and/or monitoring in the laboratory; examples include reference weights or materials. Important common features of these definitions are the *exemplarity* and the *authoritativeness* of standards, which provide "an accepted or approved example of something against which others are judged".

During the typical laboratory accreditation process, the laboratory is assessed against a "standard document" that contains a number of specifications equivalent to the clauses in a normative document. Other accreditation systems used documents which describe guidelines, principles or criteria as the basis for assessment (Burnett 2002).

The world's largest developer of standards is the International Organization for standardization (ISO), which is a nongovernmental network of the national standards institutes of 146 countries. In Europe, another nongovernmental organization, the European Committee for Standardization (CEN), comprises 30 national standardization institutes. Since the Vienna Agreement was signed in 1991, these two international standard organizations work closely together, by mutual agreement with the national standardization institutes. This agreement endorses, amongst many other engagements, an exchange of technical information between CEN and ISO, the adoption in Europe of existing ISO standards without text changes, and the

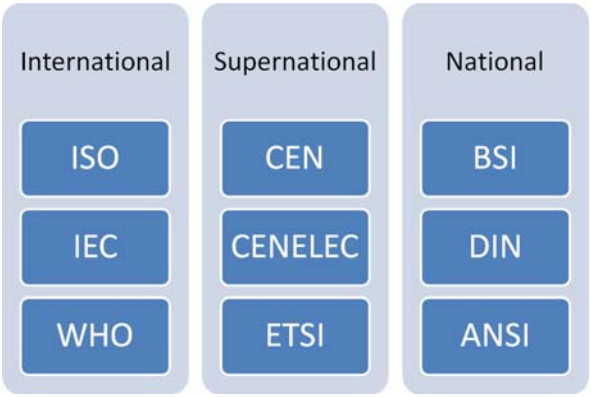

Fig. 1 Overview of normalization institutes

parallel approval of newly developed documents within both organizations. All of the approved CEN standard should be adopted in each member state of the European Union within six months after approval, and should replace all (related) national standards.

Each standard is assigned a unique identification number, often followed by the year of approval or revision. In front of the unique number, the acronym of (sometimes multiple) standardization institutes can be found that adopted the standard. For example, "BS CEN ISO xx xxx: 200y" is a standard adopted by the British Standard institute and also approved by CEN and ISO. The acronym "IEC" (for International Electro-technical Commission) is included when the standard results from the work of ISO/IEC JTC1 (joint technical committee). Depending on the status of the standard, an additional code can be included in the standard identification format (e.g., "CD" for Committee Draft, "DIS" for Draft International Standard, "FDIS" for Final Draft International Standard).

The major standards relevant to quality management in clinical genetic laboratories are summarized in Table 1. The ISO 9001, first published in 1987, is the oldest and most generic standard. ISO defines "quality management" as the comprehensive set of measures that is taken by an organization to (1) meet customers quality needs, (2) meet applicable regulatory requirements, and (3) continually improve performance. The quality system "requirements" in ISO 9001 are universal, i.e. they can be applied to any organization (private business enterprises, public non-profit organizations, government departments), independent of the organization size,

Table 1 Standards relevant to Quality Management in clinical genetics laboratories

Standard	Title	Example applications in medical genetics
ISO 9001	Quality Management systems – requirements	Certification of compliance for genetic counselling services or clinical consultations.
ISO/IEC 17025	General requirements for the competence of testing and calibration laboratories	Accreditation of testing laboratories. ISO 15189 is generally more appropriate for medical testing laboratories.
ISO 15189	Medical Laboratories – Particular requirements for quality and competence	Accreditation of testing laboratories. Pre- and post-analytical procedures, including patient contact, information and sampling can be included.
CCKL[a] praktijkrichtlijn	Praktijkrichtlijn voor een kwaliteitssyteem voor laboratoria in de gezondheidszorg	Dutch guideline base don the ISO 15189 standard and applies to medical laboratories
CPA[b] standard	Standards for the medical laboratories	CPA standard is the national guideline for accreditation of medical laboratories in the United Kingdom

[a] CCKL: Coordinatie Commissie ter bevordering van de Kwaliteitsbeheersing op het gebied van Laboratoriumonderzoek in de gezondheidzorg in The Netherlands
[b] CPA: Clincal Pathology Accreditation, UK

and irrespective of the nature of the product manufactured, service delivered, or the analytical test performed. Hence, ISO 9001 can be adapted by an architect office specialized in designing new houses as well as by a clinical genetic testing laboratory. Briefly summarized, ISO 9001 concerns *the way how* activities in an organization are performed, but does not assesses the actual results of these activities (at least not directly). While ISO 9001 describes the overall requirements for any quality system, it does not dictate details on specific criteria that should be fulfilled, which leaves plenty of room for flexibility when implementing in particular organizations from different business sectors and varying national cultures. This is a typical characteristic for all ISO standards.

In 1999, ISO published a quality standard specific for testing and calibration laboratories (ISO 17025), followed in 2003 by a standard specific for medical laboratories (ISO 15189). The ISO 15189 standard specifies particular requirements for medical laboratories to be fulfilled in order to ensure quality and competence. This standard covers all different aspects of medical laboratory activities, including provision of advice to customers of the laboratory service, the collection of patient samples, the interpretation of test results, acceptable turn around times, the lab's role in the education and training of health care staff. This standard, in addition, also specifies requirements for the pre-analytical phase as well as for a demonstration of the clinical relevance of a particular test. At present, the majority of the accredited medical laboratories in Europe already adopted this standard or are in the process to do so. In the near future, another new ISO standard (ISO 17043) will become available and will set requirements for the conformity assessment of external quality assessment schemes.

Aside from the international standards for quality management, some organizations in Europe developed over the years their own well-know standards. Examples include the CCKL Code of practice (The Netherlands) and CPA (UK) standards. At present, both have been adapted to cover (almost) all of the required elements of ISO 15189. In the US, the Clinical Laboratory Standard Institute (CLSI) published policies, processes and procedures around laboratory quality management systems, including detailed guidelines and recommendations for technologies in clinical genetic testing services. Of note, accreditation conform ISO 15189 is very rare in US laboratories. Rather, the US laboratories follow the local requirements of the Clinical Laboratories Improvement Act (CLIA) and the check list of the College of American Pathologist (CAP) for certification. Finally, the Organization for Economic Cooperation and Development (OECD 2007) recently published guidelines for Quality Assurance in Molecular Genetic Testing which are equally applicable to cytogenetics and biochemical genetics.

Accreditation and Certification

A regular confusion concerns the difference between accreditation and certification. *Certification* is a procedure by which a third party gives written assurance that a product, process or service conforms to specific requirements. These specifications

are written by the laboratory or the manufacturer itself that applies for the certificate. Furthermore, any certified third party (private company, government, etc.) that is fully independent from the certification requester can make the assessments necessary for the certification procedure. Consequently, a certification does not guarantee a comparable quality between two different businesses or services. The ISO 9001 standard is the best known certification standard. Certification of an organization's quality management system against this standard will confirm the compliance to this standard, but does not assess the specific technical competence of a laboratory. This means that ISO 9001 certification of a laboratory does not assure accurate, reliable, or state-of-the-art analytical testing.

Accreditation is the procedure by which an authoritive body formally recognizes that a laboratory is competent to carry out specific tasks. This goes way beyond certification, because (i) an accreditation certificate cannot be delivered by any third party, and (ii) it is a quality system that comprises certain technical and analytical requirements. Typical standards for laboratory accreditation are ISO 17025 and ISO 15189 (see Table 1 and above). Accreditation obliges laboratories to meet a predefined set of standards on laboratory management, facilities, staff qualifications and training, performance, and regular participation to external quality assessments. Accreditation of a laboratory can range between very specific (e.g., certifying the competence to carry out a single specific test) to very broad (e.g., covering all the analytical testing performed in a laboratory).

The two examples listed in Table 2 illustrate the differences between certification and accreditation in a context of clinical genetic testing services.

For many years, accreditation was predominantly seen as a voluntary activity. Today, however, accreditation for clinical genetic testing laboratories has been widely embraced by governments and policy makers in a growing number of countries (OECD 2007). Accreditation will become mandatory in the near future in a number of countries, such as Belgium and France. The demand for accreditation certificates given to laboratories by a recognized (international) accreditation body will help to ensure compliance with upfront set requirements from government and regulators, and may also serve as a safeguard for the public.

Table 2 Example to illustrate the difference between accreditation and certification

Example	Certification	Accreditation
Fragile X syndrome	Simple PCR-based technique to detect normal alleles of the *FMR1* gene. Diagnosis can be excluded in males.	Comprehensive protocol based on PCR and/or Southern blotting to detect and size normal alleles, premutations and full mutations. Diagnosis and carrier status can be confirmed or excluded
Karyotyping	QF-PCR or interphase FISH can identify common aneuploidies.	Comprehensive protocol of karyotyping complemented with QF-PCR, FISH and/or microarray analysis can identify the great majority of numerical and structural anomalies.

Of note, some countries implemented a so-called *licensing* system for health care facilities. This is distinct from accreditation and certification, and is usually mandatory and government-imposed (e.g., "*agrément"* in France). Licensing does not necessarily require any evaluation of quality management or technical competence.

Accreditation Process and Accreditation Bodies

Assessment of the competence of a laboratory that applied for accreditation is based on inspection of the applicant's documentation that describes the quality system (e.g., organizational structure, working and administrative procedures and methods, the competence of the personnel, etc.). Importantly, the assessment also includes verification of how the laboratory work is actually performed in practice.

The assessment is performed against the requirements set out in the international standard ISO 17025 or ISO 15189, which is used for evaluating laboratories throughout the world. This standard specifically addresses factors relevant to a laboratories' ability to reliably produce accurate data for a specific analytical test.

Accreditation can be granted one or multiple tests performed using one or more testing methodologies (molecular genetics, cytogenetics, biochemical genetics,..). Applications for accreditation must be addressed to the national accreditation body that has been assigned by the national government. Applications must include the field(s) of application and the working methods (procedures) for which accreditation is sought. Upon receipt of the dossier, the necessary documents (such as the quality manual) are reviewed by the accreditation body to estimate the amount of work required for the assessment and to appoint an assessment team. Next, an assessment including practical work, documentation, as well as administrative procedures, is performed at site. The assessment of the practical work and the documentation of earlier work drives at evaluating whether the procedures that have been described in the quality manual are being applied and whether the normative documents are being correctly interpreted and applied in the day-to-day work. The assessment of the laboratories can be complemented by comparative testing, calibrations or inspections. The findings of the assessment are documented in a report that describes all the noncompliances with the standard that were observed during the on site assessment. When this report indicates that all the requirements of the standard are fulfilled, the board of the national accreditation body will decide to grant accreditation to a laboratory.

To ensure continued technical expertise and compliance to the standard, accredited facilities are regularly re-examined. These laboratories may also be required to regularly participate in external quality assessment schemes (EQA) or interlaboratory comparisons as an ongoing demonstration of their competence. This is an important link between accreditation and EQA: the laboratories that do not participate or frequently perform poorly in EQA, or do not undertake actions to identify

the source of mistakes and take measures to avoid them in the future, may risk losing their accredited status.

Many countries around the world have assigned an organization responsible for the accreditation of their nation's laboratories, and which is international recognized by mutual recognition arrangements (MRAs). International agreements are crucial in enabling test data to be accepted between these countries. In effect, each partner in such an MRA recognizes the other partner's accredited laboratories as if they themselves had undertaken the accreditation of the other partner's laboratories. More than 40 laboratory accreditation bodies have signed a multi-lateral recognition agreement, called the International Laboratory Accreditation Cooperation (ILAC) arrangements, which greatly enhanced the acceptance of data across the national borders of the signatory countries. Especially in the testing field of clinical genetics, this aspect is very important given that trans-border flow of samples is rather high in comparison to many other areas of analytical testing of clinical samples (McGovern et al. 2007)

Quality Management in Genetic Laboratories

Each genetic laboratory has the duty to the clinicians, the patient and his family, to provide a high quality service. This genetic service comprises all steps in between the initial sample collection and the final communication of the results to the patient based on the final lab report. ISO defines quality as "*the degree to which a set of inherent characteristics fulfils requirements*". This definition is almost tightly packed to those not familiar with "the world of standards", but it might become better to life when exemplified by means of a clinical genetic testing situation: a breast cancer patient with a family history has a "requirement" for a carrier test. The "inherent characteristics" that need to be fulfilled in order to provide a quality service mean that the most appropriate analytical testing is to be done on the best suited specimen, in an accurate and timely manner, and properly interpreted.

The technical competence of a laboratory depends on a number of factors including:

- the qualifications, training and experience of the staff,
- the right equipment – appropriately calibrated and maintained,
- adequate quality assurance and quality procedures,
- appropriate sampling practices,
- testing procedures,
- accurate recording and reporting of data,
- appropriate testing environment

In addition to the above essentials, four important elements should be in place in the practical organization of a testing laboratory to ensure high-quality laboratory

results: quality control (QC), quality assessment (QA), quality assurance (QAu) and quality improvement (QIm).

Quality Control (QC), also named "internal quality control" stands for a program that is outlined in the organization for each type of test, and which includes tools for detecting errors, monitoring examination procedures, and verification of the intended quality of the results. During the analytical testing procedures, appropriate control samples should be regularly included. These might be suitable control materials (e.g., well-validated patient samples) and/or alternative controls that react to the test system in a manner as close to patient samples or patient population as possible. These control materials must help to determine the quality of samples and to monitor the test variation. Furthermore, all reagents, materials and equipment critical to the quality of the test results need to be checked for performance and suitability for intended use, before use for testing patient samples.

Although genetics laboratories are often in close contact with each other, they operate in isolation and rarely compare or benchmark their data with others. Thereto, external **Quality Assessment** (EQA) or proficiency testing provides an opportunity to undertake such comparisons and to have an independent appraisal of the laboratory's data compared to reference values/performance criteria, or to the performance of similar laboratories. The results from participation to EQA either provides confidence to the laboratory director that the laboratory's performance is satisfactory, or otherwise alerts that investigation of potential problems within laboratory is required. During recent years, several organizations initiated EQA schemes, of different scales and for different genetic disorders. Schemes are organized either by international groups such as the European Molecular Quality Network (EMQN), Cystic Fibrosis Network, Cytogenetics External Quality Assessment scheme (CEQA), European Research Network for evaluation and improvement of screening, Diagnosis and treatment of Inherited Disorders of Metabolism (ERNDIM), or by national groups such as the UK National External Quality assessment (UKNEQAS). In the United States, the College of American Pathologist (CAP) and Centers for Disease Control and Prevention (CDC) are the most recognized. At present, laboratories from other continents most often join the European or US initiatives. The most remarkable difference between the schemes organized in US and European is the inclusion of the report in the assessment: the European schemes include the evaluation of the reports and interpretation of the result, whereas the US schemes are limited to the assessment of the correct analytical result.

The ongoing process and systematic actions undertaken *"to assure that a test is measuring what it is intended to measure"* is recognized under the term **Quality Assurance** (QAu). **Quality Indicators** (QI), which are measurements of the performance of a selected process, are helpful tools to follow up the QAu. As an example, the number of unacceptable samples received compared to the total number of samples received can be used as a QI for the measurement of the success of the sample collection process. Quality Indicators can be identified for pre-examination, examination and post-examination processes, as well as for non-examination procedures. Suggestions of QI that can be used in clinical genetic testing services are:

number of tests offered, number of new tests in production, number of analyses performed, number of referred analyses, repeat rates, failure rates, percent of positive test results, the turn around time, outcome of EQA and IQC. Examples of QI for the whole organization are: the response rate to complaints, user satisfaction survey, critical non conformities, document review, internal and external audit outcome, number of completed versus open corrective action, and staff absence.

Quality Improvement is the fourth element to ensure the quality of laboratory results. This implies the formal approach to regularly assess the performance coupled to systematic efforts to improve it. The continual process leads to an improved effectiveness of the activities in a laboratory. Quality improvement can be realized by analytical test improvements, process improvement, and people-based improvement. Examples of programs are Six sigma, plan-do-check-act, and total quality management. Quality Improvement involves both prospective and retrospective reviews. In order to achieve improvement, it is important first to measure the current status before figuring out ways for improvement. This process specifically attempts to avoid attributing blame, and to create systems that prevent errors from happening.

Whilst a laboratory can demonstrate that they have all of the above attributes, even if this is assessed by an independent third party, having these attributes in place does not provides sufficient confidence that a laboratory also provides a technically competent service. Therefore, the key to ensure that all clinical genetic testing services implement the different elements required in a quality management system (as described above) is to mandate laboratory accreditation by internationally recognized accreditation bodies (www.ilac.org; www.ea.org) conform ISO 15189. This international standard specifies the requirements for both quality and technical/scientific competence in medical laboratories (Table 3).

Table 3 Contents of ISO 15189: 2007 Medical Laboratories – Particular requirements for quality and competence

4 Management requirement	5 Technical requirements
4.1 Organization and management	5.1 Personnel
4.2 Quality management system	5.2 Accommodation and environmental conditions
4.3 Document control	5.3 Laboratory equipment
4.4 Review of contracts	5.4 Pre-examination procedures
4.5 Examination by referral laboratories	5.5 Examination procedures
4.6 External services and supplies	5.6 Assuring quality of examination procedures
4.7 Advisory services	5.7 Post-examination procedures
4.8 Resolution of complaints	5.8 Reporting of results
4.9 Identification and control of nonconformities	
4.10 Corrective action	
4.11 Preventive action	
4.12 Continual improvement	
4.13 Quality and technical records	
4.14 Internal audits	
4.15 Management review	

Conclusion

For clinical genetic testing services who seek to work in a professional manner, it is essential to get their competence recognized. This can be achieved through implementation of a quality management system, participation to external quality assessment scheme, and accreditation conform ISO 15189.

Accreditation is, and will become even more important in the future, because it officially recognizes technical and scientific competence, facilitates exchanges of services, provides a valuable management tool, and enhances confidence that the needs and requirements of all users (clinicians, patients and families) are met.

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External Quality Assessment in Molecular Genetic Testing

Rob Elles and Outi Kämäräinen

Key Points

- Approaches to organising EQA schemes
- Assessment of laboratory performance
- Feedback and learning lessons from EQA
- Future of EQA in molecular genetics

Keywords Genetic testing · Quality assurance · External quality assessment · Laboratory proficiency testing

Definitions and Terminology in External Quality Assessment

Where a number of genetic laboratories carry out the same clinical tests, how do they and their users know that the results are comparable?

One way that a medical laboratory can measure the accuracy and validity of its output is to compare its quantitative or qualitative analytical results with those of a second laboratory. Informal arrangements of this type between one or more peer group laboratories are called ring trials. Where a number of laboratories participate in the scheme the results may be assessed against the consensus result which forms a comparator. This sample exchange system may evolve more formally and be established around the distribution by an organising centre of a single test material to participating laboratories. Each laboratory can compare its output against

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the result of a single reference centre which establishes a benchmark measurement. It is this latter approach that is known as External Quality Assessment (EQA) or in some countries Laboratory Proficiency Testing (LPT). The term LPT conveys the idea of a more formal assessment of the performance of a laboratory against an accepted norm or minimum acceptable level of competence with a judgement being made on the "proficiency" of the laboratory. In some countries this judgement of acceptable performance if made may be removed from the LPT agency and placed in the hands of an official body. Generally EQA is regarded as an educational opportunity and may be linked to Continued Professional Development of individual scientists or doctors (for example in the fields of Histopathology and Haematology).

In summary External Quality Assessment (EQA) and Laboratory Proficiency Testing (LPT) are terms used interchangeably and describe an external system for inter-laboratory comparison of test results.

Approaches to Organising EQA Services for Clinical Molecular Genetic Testing

Many Molecular Genetic Testing laboratories are part of or have a close working relationship to one or more Clinical Genetic and counselling services. In this situation the concept has emerged of the laboratory acting as more than a genotyping factory. The Laboratory may appropriately interpret the genotype in the context of the clinical indication for the test, the prior risk of an adverse outcome and the phenotype of the index patient. The output of the Laboratory can be thought of as a modified genetic risk to inform the counselling process. The Laboratory's interpretative role is particularly important where referrals are accepted from physicians who are not familiar with genetic testing. This concept of the genetic test and the extended role of the Laboratory has been adopted by EQA providers. In addition to assessing the accuracy of genotyping they may also consider the interpretation of the genotype including quantitative risks. The assessment by the EQA provider allows an extended range of test methods (although the assessors may comment on whether a test system is appropriate to a clinical scenario). Equally the EQA provider does not restrict the format of the data returned by the Laboratory but requests and accepts its normal report format. This allows an assessment of the report from the point of view of the accuracy with which the Laboratory transcribes demographic information, how well it carries a message to the recipient and whether it is suitable as a permanent part of the medical record. In some settings and some countries laboratories are assigned a more technical role. For these cases EQA providers may permit an assessment on the basis of genotyping accuracy only. The aim of the EQA agency is always to assess normal routines and not to force a practice on the Laboratory adopted only for the purpose of participating in an EQA exercise.

Disease Service Specific EQA and Technical EQA

Most molecular genetic EQA schemes provide patient derived biological materials together with clinical details and aim to replicate as closely as possible a normal clinical referral to the Laboratory. The schemes are designed to challenge laboratory screens and tests for a particular genetic condition and or gene/target combination. Molecular Genetic EQA schemes have addressed most of the common indications for a genetic test referral. However a challenge particular to EQA providers is the large number of disease or gene/target specific services offered. As an example in the UK alone over 400 tests are available from a network of 26 laboratories (www.ukgtn.org.uk). In 2008 the national EQA provider UKNEQAS offered schemes for 10 of these indications comprising about 74% of the single gene testing activity of the network (www.ukneqas-molgen.org.uk). The diversity problem has led to a complementary approach which offers an EQA challenge to generic pre-analytical or analytical techniques. As examples the EQUAL network tested the ability of laboratories to quantify genomic DNA and PCR products and EMQN and DGKL provide schemes to test the ability of laboratories to accurately call sequence and detect variants (Ahmed-Nejad et al. 2006; Orlando et al. 2007, Patton et al. 2006). These schemes are open to all laboratories using these generic and core techniques independently of the genes examined and disease services they offer.

Sourcing EQA Materials – Manufacture and Validation - EQA and Reference Materials

Ideally an External Quality Assessment scheme should challenge the whole pre-analytical, analytical and post analytical process. The material supplied should be as close as possible to the format of a routine clinical referral and the biological material most frequently received. In practice the difficulty of repeatedly sourcing and/or storing sufficient quantities of biological material (usually blood) to test genotypes for conditions that are always defined as rare means that. DNA is the most common secondary e.g. processed analyte for molecular genetic tests and laboratories. One justification for this is that processed DNA is often received from external molecular genetics referral laboratories as the material accompanying a test request. For EQA purposes DNA is usually processed from blood or more commonly from an immortalised lymphoblastoid cell line carrying a defined mutation. It is good practice for cell lines to be sourced from an established Cell Bank that adopts procedures compliant with a quality management system to ensure the integrity of the materials. Agreement should be sought between the Cell Bank and the EQA provider to re-distribute DNA to participating laboratories. Cell lines derived specifically for EQA purposes should have appropriate consent and must be anonymised prior to being considered for use as an EQA material. Cell lines should only be selected as challenges for the genotype(s) for which they were derived and characterised. For

example a cell line carrying a Fragile-X disease mutation must only be used for a Fragile-X EQA scheme. Laboratories must agree as a condition of participation that their analysis is strictly restricted to the clinical question indicated in the EQA challenge.

In order to manufacture material suitable for EQA, a validation process for the selected material must be completed and documented before the samples are distributed to participants. Validation usually consists of independent genotype tests carried out by at least two reference laboratories preferably (where more than one technique is commonly used) using alternative methods. To comply with accreditation requirements for EQA providers the reference laboratories should be operating a quality management system and preferably be accredited (ISO Guide 43). The validation should be fully documented and traceable to the standard operating procedures and records kept within reference laboratories and of course the independently derived results must be concordant.

An alternative source of an EQA material is a reference material formally certified by an accredited institution or standardisation body. Examples are the reference materials produced by the US National Institute for Standards in Technology, the UK National Institute for Biological Standards and Controls and the European Union Institute for Reference Materials and Measurements (http://www.nist.gov/, http://www.nibsc.ac.uk/, http://irmm.jrc.ec.europa.eu/html/homepage.htm).

In principle as higher order control materials they are suitable as challenges (for the sequence variant or genetic measurement certified) without further validation. However very few reference materials appropriate for distribution as EQA materials for molecular genetic testing are currently available.

The reverse situation does not hold. Materials sourced for an EQA scheme are not certified for use as routine or occasional run controls by the participating laboratories in clinical tests. The distribution of EQA samples to laboratories is a specific exemption under the European Union In Vitro Diagnostic Device Directive but to include them as controls for a clinical test constitutes using them as a component of an IVDD and is not permitted (IVDD Directive 98/79/EC). To avoid the practice of using EQA challenges as controls, the provider may require, as part of the terms and conditions of EQA participation, that materials will not be used as internal quality controls.

Selection of Cases

The EQA scheme organiser selects validated materials to be distributed and matches a clinical scenario appropriate to the genotype of the material. EQA is primarily educational and not an opportunity for scheme organisers to “catch out” participants through a difficult analytical challenge. Over a series of EQA cycles organisers are guided to choose material/scenario combinations that reflect the normal range of cases referred to a diagnostic laboratory. These may include, as appropriate, cases for mutation finding, carrier detection, predictive testing and prenatal diagnosis.

Difficult EQA challenges or those rarely seen should be chosen exceptionally and should be justifiable for example by some evidence that detection of a particular rarely seen variant is problematic. In addition many molecular genetic screens, for example mutation scans in large multi-exon genes, remain both expensive and laborious analyses. EQA providers may recognise this situation by inviting laboratories to restrict their analysis to a limited number of exons in a large gene or a particular sub set of tests for example a PCR test rather than a Southern blot analysis.

For many disorders the majority of samples analysed by a clinical laboratory do not carry a mutation and this experience should be reflected by the choice of cases and materials for EQA by including "normal" samples to the challenges. The information given in the EQA referral should be adequate and may include details of previous testing, any relevant family history, the ages of patients or relatives and other laboratory results. The cases should be sufficiently documented to allow the laboratory to select its approach and analytical methods and answer the clinical question associated with the challenge.

Assessment of EQA Performance; Genotype, Interpretation and Reporting

The primary measure of performance resulting from molecular genetics EQA is the ability of the participating laboratory to detect and correctly call the qualitative genotype (presence or absence of a variant) or achieve a quantitative measure (for example an array of triplet repeats) within defined and appropriate limits.

In addition ISO standards encourage EQA schemes to include an interpretative element. In genetics this is divided into two parts; clinical interpretation of the genotype (it's biological and clinical effort) and the accuracy and clarity of the clinical report e.g. a judgement on the utility of the report as a document conveying complex information to the recipient and forming a permanent part of the medical record (ISO guide 43).

In addition EQA assessors may require a number of more subtle performance requirements for the participant to achieve a full score (Table 1). For both genotype and interpretative assessment the panel will usually decide in advance a schema for assigning a quantitative score. A system used by a number of EQA schemes is a presumptive score of 2.0 with marks or fractions of marks deducted for failure to indicate key points in the schema.

Assessors will refer to guidelines and the body of experience or "case law" in drawing up assessment criteria. The criteria are drafted before the scheme reports are marked but may be adjusted in the light of an overall impression of the reports from laboratories. Assessors may consider that some elements of a report are essential and will deduct marks if they are not present; for example they may expect that the clinical interpretation includes an extended description of the genotype in words for example "mutation detected" or "mutation not detected." Other points may warrant a comment rather than deduction of marks. In addition a description is required

Table 1 EQA assessment criteria

Qualitative genotype assessment	Scoring criteria
Basic measure	• As appropriate variant detected/not detected.
Nomenclature	• Variant correctly positioned • Correct nomenclature or permissible alternative nomenclatures used • Referral to correct reference sequence
Biological effect	• Correct biological effect indicated *e.g.* frameshift, splice site variant • Pathological/non pathological/variant of unknown significance
Basic measure	• Genotype within pathological or non pathological range or intermediate range • Appropriate reference quoted
Extended measure	• Measurement within or outside arbitrary permissible limits

of the likely implication of the detected genotype for the patient in establishing, excluding (or clearly expressing the limits of exclusion) of a diagnosis, a predicted effect and the implications for blood relatives. Assessors may expect that choices for the patient are mentioned; examples include further tests, a programme of health surveillance or the option of prenatal diagnosis. It is expected that reports give a clear "take home" message to the recipient. Where the implications of a test result are significant for example establishing a diagnosis of a heritable disease in a patient a report may offer clear advice to the referring clinician. For example the report may recommend a referral of the patient for genetic counselling. Although strong advice may be offered to the clinician to avoid failure to act on critical implications of the test it is vital that reports should not be in any way be interpretable as being directive to the patient.

In assessing the EQA returns, assessors do not usually penalise the same error twice. If an incorrect genotype is indicated the interpretation of the incorrect genotype is not marked. If a systematic error appears across more than one EQA challenge or case (for example a sample exchange) this is penalised once.

EQA schemes may also comment on reporting layout style and clarity referring to practice guidelines on clinical reporting. Assessment of the reporting style is usually restricted to comments although inaccurate transcription of essential data such as patient identifiers where this compromises the integrity of the report may lead to a deduction of marks.

EQA and Poor Performance

The primary function of EQA is education through peer group review amongst professionals. Nonetheless EQA providers have a duty to do all they can to protect the public from sub standard and potentially dangerous clinical practice. Many

EQA providers therefore set minimum performance criteria. Laboratories may make errors in EQA schemes that push them into the "poor performance" category (usually significant genotype errors or clinically dangerous failures of interpretation). These laboratories will be asked to put in place measures to correct the deficit detected and may be offered assistance or technical advice as well as encouraged or required to participate in an additional round of EQA.

In some countries EQA scheme providers are required to report poor laboratory performance to an official or professional regulatory body which in turn may monitor the laboratory performance. Where EQA performance does not improve the official body may take additional measures to protect the public. EQA providers have reported that some laboratory directors have decided to withdraw from providing individual services where their laboratory has performed poorly in EQA.

Learning Lessons from EQA

Participation in EQA is a valuable opportunity for laboratories to compare their performance against that of their peers and against agreed standards of practice which helps to complement and validate the internal quality control measures they have in place (Dequeker et al. 2001). To be compliant with the quality management systems indicated by accreditation standards laboratories should review their performance immediately after they receive their EQA report and put in place measures to correct serious deficiencies and also consider comments from assessors (ISO standard 15189). Overall EQA performance especially where laboratories are involved in a number of schemes should be a part of the annual management review of the Quality Management System. A review of EQA records is also part of the external audit performed to achieve or maintain accreditation.

EQA and Post Market Surveillance

EQA is also a valuable way to assess the performance of in vitro diagnostic devices (kits) in routine use and laboratory designed assays where the design is shared amongst a number of test centres. Manufacturers should be alerted by the EQA provider where an IVDD performs poorly in a number of laboratories in an EQA challenge. The EQA provider should also issue an alert to relevant national and multinational authorities responsible for the surveillance of IVDDs for example the US Federal Drug Administration and UK Medicines and Healthcare Devices Regulatory Agency. In 2004 the EMQN EQA scheme for familial breast cancer demonstrated the failure of a primer set in common use in a national laboratory consortium. The genomic DNA deletion mutation in the EQA material issued as a challenge included the target site for one of the primers in the set. This resulted in a failure to amplify the mutation allele and subsequently to a false negative screening result in the consortium. The laboratories responded by re-designing the assay which correctly detected the deletion genotype when the same material (unknown to the group concerned) was set as a challenge in the following round of EQA.

EQA and Good Practice

There is a strong relationship between EQA and the formulation of best practice guidelines. Data gathered from EQA showing an unacceptable variation in performance and practices, for example in genotype nomenclature, can help set the agenda of a best practice meeting. Practitioners can aim to resolve differences, formulate a standard or adopt an existing standard. In turn guidelines help both EQA assessors to mark EQA returns and inform laboratories in setting their internal practice and performing well in EQA.

Inter-laboratory Comparison When EQA is not Available

Participation in EQA is a requirement of a Quality Management System and obligatory in some licensing regimes (New York State USA). However in genetics it is not practicable to organise a formal EQA for every rare disease service and every gene target. Alternatives include participating in technical EQA. In addition pairs or small groups of laboratories may organise an inter-laboratory exchange or ring trial. In the UK a register is being developed to help laboratories find partners and provide an impartial mediation of the results (www.ukneqas-molgen.org.uk). Amongst internal arrangements are the re-referral of samples through a third party to check for concordance in serial tests or internal blind re-assay as part of an internal quality assessment.

Anonymity and Disclosure in EQA

EQA scheme participants identities are usually only known to the scheme organiser and are otherwise identified to expert assessors by a numerical code. Laboratories are often asked to remove identifiers from their returns. This anonymity gives laboratories confidence that their performance will not be made public and that their return will be dealt with fairly by expert assessors. Anonymity encourages them to take part in EQA. However laboratories are asked to make the fact of their *participation* in EQA public as a mark of their commitment to quality assurance (OECD guidelines for quality assurance in molecular genetic testing, http://www.oecd.org/dataoecd/43/6/38839788.pdf, and the EuroGentest Quality Assurance database, http://www.eurogentest.org/). In addition accreditation assessors will audit EQA performance records as part of their examination of the quality management system.

The Future of Molecular Genetics EQA

As it has developed EQA is largely focussed on the clinical outcome of the diagnostic process and the ability of the laboratory to answer the clinical question posed by

the referrer *e.g.* what is the significance of the patient's symptoms or what is their risk of carrying, expressing or passing on an inherited condition? As technologies develop this should remain the focus of EQA. However our ability to analyse genotypes in parallel will make the technical assessment more complex and require us to assess the ability of the laboratory to analyse in parallel many genes and perhaps hundreds or even thousands of genotypes associated with biological pathways and networks. This in turn may lead EQA in the direction of assessing a laboratory's ability to use external bioinformatic tools. In silico EQA materials could be validated and used to challenge the bioinformatics tools and tests available on the web. These EQA materials could be genetic sequence and copy number variants that had been clearly linked to a phenotype and previously and thoroughly characterised by standard in vitro methods.

Competence of EQA Providers

EQA providers should develop and operate a quality management system to address the needs and feedback of their users and should have this system examined by a recognised accreditation agency. Although EQA providers often exist within an accredited testing laboratory operating to ISO 17025 or ISO 15189 the more specific and relevant standard is ISO guide 43. This recommendation is based upon the requirements contained in the ILAC (International Laboratory Accreditation Cooperation) guidelines for the Requirements for the Competence of Providers of Proficiency Testing (ILAC-G13:2000) and on ISO Guide 43-1. This ISO Guide gives recommendations for the development and operation of proficiency testing schemes and provides a basis for recognition of equivalence of Proficiency Testing schemes organised from different countries.

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Quality Issues in Molecular Genetic Testing

Clemens R. Mueller and Robert G. Elles

Key Points

- Two recent international documents on the regulation of genetic testing services are reviewed with respect to their impact on quality assurance in molecular genetic diagnostics, i.e. the Additional Protocol concerning Genetic Testing for Health Purposes (Council of Europe, ETS No. 203), as an addendum to the "Convention on Human Rights and Biomedicine" (ETS No. 164) released by the Council of Europe (CE) and the OECD Guidelines for Quality Assurance in Molecular Genetic Testing.
- Whilst the CE have reiterated and specified the fundamental human rights as laid out in the Convention on Human Rights and Biomedicine in view of their application to genetic testing, the OECD have compiled an internationally agreed set of criteria for practical quality assurance in a molecular genetic testing laboratory.
- Both documents address the principal actors involved: the governments and regulatory bodies in charge of oversight and control and the genetic services and laboratories themselves. Regulators are encouraged to review and develop the existing national legislation and to implement the instruments for quality assurance monitoring. Laboratories are urged to establish a quality management system and to enter a cycle of continuous improvement.
- Together, the documents provide a framework for action on quality issues of genetic testing by governmental regulators and the genetic diagnostics community.

Keywords Quality · Molecular · Testing · International · Regulation

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Quality issues in molecular genetic testing have been the focus of many public statements, regulatory documents and professional guidelines. In the public and the media, there is a widespread view that molecular genetic tests require a tighter quality control since they are considered to be essentially different from other sorts of medical laboratory tests in that they can identify constitutional and unchangeable characteristics of an individual, have a predictive power for clinically healthy people and – as heritable traits – have an impact on other members of the family. Although quite a few other medical tests share many of these features (for example HIV tests), it is the combination of these characteristics that have raised anxiety towards genetic tests in sections of the public. The concerns are mainly addressing two aspects: the reliability of genetic test results and their presumed power to bring forward unrequested information about an individual's genetic make-up and future life. In a clinical context, the latter aspect should not be of concern since a medical indication usually leads to a targeted analysis of a single gene or a few genes known to be involved in the patient's clinical condition. Genetic information resulting from such analyses is only pertinent to the clinical request and in general does not allow drawing wider conclusions. A "whole genome analysis" of an individual – though technically possible – is not medically indicated and is still of scientific interest only.

In the public and in the professional view, accuracy and reliability of test results is an important indicator of the "quality" of a genetic service. Measures to achieve, maintain and monitor quality standards are subject to legal and professional regulations worldwide. Several countries in Europe have launched legal and sub-legal regulations to address quality standards in genetic testing and many professional bodies have issued guidelines on good laboratory practice and other aspects. However, quite a few countries are lacking any regulation on molecular genetic diagnostics to the present day.

In keeping with its remit, the Organisation for Economic Co-operation and Development recommended Guidelines for Quality Assurance in Molecular Genetic Testing in 2007 as the result of a consultation process amongst scientists, laboratory directors and regulatory experts from its member states (OECD Guidelines 2007). This has set an internationally agreed standard for a bundle of measures to be applied for the implementation of a quality service in molecular genetics. The OECD guidelines consider five areas relevant for quality: A: General Principles, B: Quality assurance systems, C: Proficiency testing, D: Result reporting and E: Education and training. Within each chapter, the guidelines formulate a set of Principles as recommendations mainly addressed to regulatory bodies and a set of Best Practices as operational guidance for the genetic laboratories.

In 2008, the Council of Europe released an Additional Protocol concerning Genetic Testing for Health Purposes (Council of Europe, ETS No. 203, 2008) as an addendum to the "Convention on Human Rights and Biomedicine" (ETS No. 164). The protocol addresses in seven specific chapters the issues of

- Non-discrimination and non-stigmatisation (chapter II),
- Quality of genetic services, clinical utility of tests and medical supervision (chapter III),

- Information, genetic counselling and consent, in particular of minors and persons unable to consent (chapters IV and V),
- Tests for the benefit of family members (chapter VI),
- Private life and right to information (chapter VII), and
- Genetic screening programmes for health purposes (chapter VIII)

In line with the rationale of the "Convention on Human Rights and Biomedicine", the Additional Protocol focuses on fundamental human rights in order to ". . . protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the tests to which this Protocol applies. . ." (Chapter I – Article 1 – Object and purpose). It puts particular emphasis on the protection of the rights of persons unable to consent. Genetic tests performed on embryos and fetuses are specifically excluded from the scope of the Protocol (Chapter I – Article 2 – Scope 2b).

Although and in contrast to the OECD Guidelines, the EC Additional Protocol does not provide guidance on best practices the documents are compatible. Where they cover the same areas they strengthen each other by conveying similar messages. For example both international bodies emphasise that genetic testing should be offered in the context of health services and medical supervision and that the fundamental purpose of a genetic test is to improve the health and well being of an individual. The documents insist that professional standards should be respected, that the education of professionals involved in testing be adequate and that the performance of genetic testing laboratories be monitored. Both documents call for genetic test services and other interested parties to ensure that tests meet accepted criteria for scientific and clinical validity and clinical utility and that this data be made publically available. The documents call for appropriate pre-test information to be made available to the patient and that counselling should be available in a form appropriate to the potential implications and outcomes of the test for the individual.

Predating these international recommendations, several European countries, e.g. Austria, Switzerland and the UK, have enacted detailed national regulations. Where such national legislation does not exist yet, the CE Additional Protocol together with the more specific OECD guidelines provide a useful framework for regulators and laboratories aiming at high quality molecular genetic services. The latter will be discussed below in more detail.

A. General Principles

First of all, the General Principles of the OECD guideline underline the necessity of molecular genetic testing to be practiced within the regulatory framework of legal, ethical and professional standards of each country. This covers the regulations for operation of a laboratory, the handling and storage of patient samples, confidentiality of personal and genetic data and the requirement of informed patient consent.

A second Principle recommends that genetic testing be part of the health care system. This important Principle subjects genetic testing for medical conditions to the codes of practice of the medical profession. In this context, it is noteworthy that human genetics has not yet been recognised as a medical specialty by the EU and by some of its member states. The Guidelines further stress that pre- and post-test genetic counselling should be available and be proportionate to the complexity of the genetic test and its potential for harm. The Principles recognise the need for international collaboration in genetic diagnostics since no single country can offer the whole spectrum of genetic tests. Any promotional claims made by laboratories should accurately describe the characteristics and limitations of the tests offered.

The Best Practices call upon the national governments and regulatory bodies to critically review the effectiveness of their existing instrumentation to manage a quality assurance framework. This recommendation acknowledges that the principal instruments of quality management systems are already available (e.g. through the ISO accreditation norms) but may require adaptation and interpretation for genetic laboratories. The second Best Practice urges laboratories to make available information on the analytical and clinical validity of the tests they offer. This underlines the responsibility of laboratories to document that their test results are analytically accurate and fit for the intended clinical purpose. This, in turn, strongly discourages tests of doubtful or unproven clinical utility. A third Best Practice draws attention to the need for good communication between the laboratory and referring clinicians to facilitate counselling and clinical decision-making.

These General Principles are further detailed in the following four chapters.

B. Quality Assurance Systems in Molecular Genetic Testing

Chapter B advocates in seven Principles laboratory accreditation as the best framework for quality assurance. Accreditation is defined as a procedure by which an authoritative body gives formal recognition that a body (a laboratory) is competent to carry out a specific task (a genetic test). ISO/EN norms 15189 and 17025 have been developed for the assessment of competence of testing laboratories and are applicable to molecular genetic labs. Via the Mutual Recognition Agreement (MRA) promoted by the International Laboratory Accreditation Cooperation (ILAC) they have been internationally accepted and form the basis for reciprocal recognition of national accreditation certificates. Countries which have not signed up to the MRA should strive to establish an equivalent formalised recognition system for laboratory competence. In view of the significant trans-border flow of genetic samples and the need for inter-national cooperation in testing for rare genetic disorders, OECD considers the mutual recognition of quality assurance systems a key element of patient safety and economic equity. Governments and regulators are encouraged to identify and address impediments to accreditation and establish mechanisms to monitor the laboratories' compliance with their regulations.

The chapter then further details the central elements of the accreditation norms such as the need to establish analytical and clinical validity of all tests, the

importance of internal quality control measures, the development and regular use of reference materials and the use of internationally agreed nomenclature.

A separate chapter deals with proficiency testing (external quality assessment).

C. Proficiency Testing: Monitoring the Quality of Laboratory Performance

In keeping with the requirements of the ISO norms, the Guidelines underline the need for external monitoring systems of laboratory performance. Proficiency testing (PT), also called External Quality Assessment (EQA), is a system to measure the output performance of an individual laboratory against that of other laboratories. Typically, well characterised (validated) biological samples are sent out and a specific genetic test is requested. Labs are asked to report the results in their standard format and the reports are marked by an expert panel of assessors for accuracy of genotyping and interpretation.

The Principles of chapter C encourage regulatory bodies to establish PT systems for monitoring laboratory performance and to facilitate access to such systems. Measures to address persistent poor performers should be set in place. The providers of PT systems should document their competence by accreditation of their service to internationally recognised standards (ISO/IEC Guide 43 1996).

Operational guidance is given to the PT providers and the participating laboratories in seven Best Practices. PT providers should establish poor performance criteria in collaboration with professional bodies. In general, poor performance is considered an incorrect genotyping result or interpretation which bears the potential for harm to the patient. In order to mirror diagnostic routine procedures as closely as possible, PT schemes should be designed to cover all phases of the analytical process, including result reporting and they should be flexible in order to accommodate for the evolution of analytical methods. Laboratories should regularly participate in all PT schemes relevant for their testing menu and are encouraged to make their participation publicly known. It is recognised that PT schemes for very rare disorders may not be viable. Alternative methods for EQA include inter-laboratory sample exchange and/or participation in PT schemes for generic analytical techniques, e.g. DNA sequencing.

D. Quality of Result Reporting

Medical genetics, and even more so molecular genetics, is a relatively young area of medicine still rapidly evolving. Thus, the genetic education of most practising health professionals predates the results of the human genome project and its ensuing activities. Therefore, it is considered essential that all analytical results from genetic testing are adequately interpreted and communicated to the referring clinician in a comprehensible way. The Guidelines deal with this requirement in chapter D. The

Principles recognise that the genetic test is only one step in the process of finding a patient's diagnosis. Reports should, therefore, be given in writing, include an appropriate evidence-based interpretation of the genotype and be addressed to the referring health professional. Laboratories issuing reports directly to patients should ensure that professional help is available to them in order to understand the implications of the test result and the options for subsequent clinical decisions. The need for effective data protection and confidentiality measures is also emphasised.

Best Practices outline with great detail the items to be included in a genetic report. The recommendations are based on the following considerations: The genotype of an individual is one of their constitutional biological features and does not change with time. Therefore, a specific genetic test is usually performed only once in a lifetime. Consequently, genetic reports tend to have a long shelf life and be distributed to other health professionals and family members. This requires a genetic report to be comprehensible by itself. The specifications for reports as outlined in chapter D are in line with the requirements of ISO standards (ISO15189:2007) and the recommendations by professional bodies (e.g. Swiss Society of Medical Genetics 2003).

E. Education and Training Standards for Laboratory Personnel

The Guidelines recognise that the competence of all academic and technical personnel working in a molecular genetic laboratory is a result of education, professional qualification, and continuous development of skills and experience. It is, however, realised that specific training programmes in clinical molecular genetics are not available in all countries. Therefore, the minimum requirements for competent personnel are outlined in chapter E.

Regulators are encouraged to formally recognise existing education and training programmes if they meet international standards and to develop such programmes where they do not exist. Recognition of medical genetics as a medical specialty should become the norm thus facilitating the practice standards of individual personnel and the mutual recognition of medical and scientific qualifications issued by other countries. The Best Practices call for the establishment of measures to assure the competence in clinical molecular genetics which are comparable to other areas of laboratory medicine. Formal education and training programmes in genetics should be recognised as essential elements of professional competence. The professional qualification of laboratory directors should be equivalent to MD or PhD level including a formal training in molecular genetics and – where available – a certification in clinical laboratory molecular genetics. All other laboratory personnel should also have a documented competence in performing, interpreting and/or reporting molecular genetic tests. Programmes for continuous education and training should be implemented and be available to all laboratory personnel.

Summary

Within a short period of time, the Council of Europe and the OECD issued guidelines on Genetic Testing for Health Purposes. Whilst the CE have reiterated and specified the fundamental human rights as laid out in the Convention on Human Rights and Biomedicine in view of their application to genetic testing, the OECD have compiled an internationally agreed set of criteria for practical quality assurance in a molecular genetic testing laboratory. In essence, the OECD Guidelines draw on the same ethical framework underpinning the Council of Europe Protocol and form an interpretation of the ISO/EN norm 15189:2007 from the viewpoint of molecular genetics. Both documents address the principal actors involved: the governments and regulatory bodies in charge of oversight and control and the genetic services and laboratories themselves. Regulators are encouraged to review and develop the existing national legislation and to implement the instruments for quality assurance monitoring. Laboratories are urged to establish a quality management system and to enter a cycle of continuous improvement. Rather than issuing a new set of quality criteria, OECD has emphasised and strengthened the usefulness and applicability of the existing ISO instrumentation and has given interpretative help where required.

Although OECD Guidelines are not legally binding for the member states it can already been observed that countries are following these recommendations, e.g. in the recent gene diagnostics act in Germany and in considering a code of practice for direct to consumer testing in the UK. Compliance or willingness to implement the guidelines is considered to be a measure of economic and social maturity and is one of the instruments being used to judge the readiness of the new candidate countries applying to join the OECD.

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Quality in Cytogenetics

Ros Hastings and Rod Howell

Key Points

- Cytogenetics includes whole-genome analysis by means of chromosomal karyotyping and high resolution molecular techniques such as FISH, microarray, MLPA, QF-PCR, RT-PCR and RQ-PCR. The effective laboratory quality control system will determine the circumstances when it is appropriate to apply those different methodologies.
- A systematic approach to the validation of the techniques will ensure that reliable, repeatable tests are undertaken.
- Knowledge of the limitations of any results in relation to the technique and tissue being examined will minimise failure and misdiagnosis.
- Accurate analysis and interpretation are critical quality parameters requiring extensive knowledge of the aetiology of cytogenetic abnormalities and risk factors. Training of staff in interpretation of the results and a comprehensive means of reporting normal and abnormal results underpins the service to the patient.
- The cytogenetics laboratory providing a dependable and accurate diagnostic service will have in place a structured quality management system with reliable internal quality control and regular external audits such as EQA and accreditation.

Keywords Cytogenetics · Internal quality control · External quality control · Quality management system

Abbreviations

FISH	Fluorescent in situ hybridization
MLPA	Multiple ligation-dependent probe amplification

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QF-PCR	Quantitative fluorescent PCR
RT-PCR	Reverse transcriptase PCR
RQ-PCR	Real-time PCR

Introduction

In any diagnostic laboratory, it is essential that robust procedures are in place to minimise errors and failures, and to reassure the patient and the clinician making the referral that the laboratory is working to acceptable international standards (OECD 2005). Many laboratory tests are undertaken only once and correct accurate results are vital; in addition, it is important to minimise repeat sampling in order to avoid the hazards and stress of unnecessary invasive sampling procedures for the patient, and to provide timely results.

With respect to cytogenetics, the results of tests may have relevance in making important lifetime decisions both for the individual being tested and for their families. Not all patients have a clinical phenotype or symptoms; hence the accuracy of the tests and the results are essential whether cytogenetic analysis is used as a stand alone diagnostic test or as an adjunct to another form of analysis such as FISH, MLPA, microarrays, QF-PCR, or other molecular techniques. As cytogenetics involves an analysis of the whole genome, staff must be competent to interpret multiple genetic abnormalities of different aetiologies with different clinical case scenarios.

Two important aspects of ensuring the provision of an accurate, timely and high quality diagnostic laboratory service are, firstly, internal quality control (IQC) which ensures that technical and analytical laboratory procedures are reliable and accurate; and secondly, examination by independent bodies which confirms that the laboratory procedures are robust and also provides means by which a laboratory can benchmark its standards. Such independent bodies include, those providing external quality assessment (EQA/proficiency testing), and those involved with laboratory accreditation. where the competency of a laboratory and its adherence to accepted guidelines and standards is examined.

Internal Quality Control

General Record Keeping

In order to locate essential information at any time, every laboratory must develop a systematic form of record keeping and filing. As well as keeping paperwork in order, telephone messages should be logged, and computer files including records and email correspondence backed up regularly and organised logically so that they are readily accessible. Confidentiality must be maintained so that patient records may only be reviewed by appropriate staff: this means password protection of computer files, and lock and key for paperwork.

Document Control

All laboratory procedures should be undertaken with reference to a standard operating procedure. The documents describing those procedures must be controlled in such a way that unauthorised changes cannot be made and staff have access only to the most up to date version, which should carry clear identifiers to distinguish it from obsolete versions, and include the identity of the author. A minimum number of copies of each document should be available as is reasonably practicable, and laboratory staff should not be permitted to make their own copies of any controlled document.

Sample Log In

All incoming samples must be logged in to the laboratory record keeping system as soon as possible after receipt. The laboratory record should provide every sample with a unique accession number and give details of the sample type, condition, date of sampling, clinician responsible for requesting the test, and patient identification. A sample should only be accepted for analysis if it is clearly labelled with unambiguous patient identification (this usually includes name, date of birth, hospital number or an identification number from the originating clinic) on the accompanied request form or letter that conforms with the patient information on the sample. Local rules on the minimum requirements for acceptance may vary, but it is important that clinicians providing the samples are kept informed of the rules and are encouraged to abide by them.

Technical Processes

Metaphase cytogenetic analysis may be applied to a wide variety of specimen types, for example cultured cells of blood, bone marrow, amniotic fluid, chorion, and various body tissues that yield fibroblastic or epithelial cells. Interphase analysis can be applied to almost any type of nucleus retrieved by conventional suspension harvesting, and also from paraffin-embedded tissue sections, disaggregated cells from paraffin blocks, blood smears, buccal smears, and touch-preparations of cells from lymph nodes or solid tumour. Regardless of tissue or method, the preparation of samples should follow protocols adopted to optimise success rates, mitotic indices, chromosome morphology or DNA quality. Those protocols should be adhered to closely in order to maximise reliability and minimise variation.

Internal quality control for any individual sample includes comprehensive documentation of the processes through which that sample passes. Examples include recording batches of all reagents used in culturing, harvesting and staining, logging times of culture set-up, media changes, and harvesting, and recording which incubator was used. In the event of a real or suspected error, or a failure, accurate record keeping will permit a complete vertical audit trail of exactly what has happened to a sample from receipt to the final report.

Reagents should be labelled with expiry dates, and records kept of equipment monitoring and servicing. All reagents, whether purchased from a commercial supplier, manufactured within the laboratory, or acquired by other means must be subject to validation before routine application in the laboratory, including the reagent itself and the procedures using the reagent. Validation can be achieved by comparing new and old batches side by side and ensuring equivalence of results, or for FISH probes by checking the probe hybridizes to the correct location on metaphase preparations. When analyzing MLPA and PCR results it is essential that non-informative markers are not included when validating the technique for diagnostic use. Technical quality, for example banding resolution or clarity of FISH probe hybridization or copy number variations (CNVs) in normal control material, should be monitored continuously to assess any adverse technical trends and to ensure the sensitivity and specificity did not change.

Regular monitoring of incubator, oven, refrigerator and freezer temperatures should be undertaken, with written records kept. Equipment should be regularly serviced to ensure that the success of technical procedures is not compromised by failures of (for example) centrifuges, incubators and sterile cabinets.

A systematic approach to technical preparation is essential, including careful checking of processes, and adherence to simple rules. Examples of possible technical errors include:-

- Cross-contamination of slide preparations by splashing suspension on the wrong slides, avoided by ensuring that slides are always kept covered as far as possible, and permitting only one sample to be handled in the preparation area at any time;
- Cross-contamination of cultures may occur by using the same pipette in setting up or harvesting different cultures, again simply avoided by handling only one sample at a time, and keeping vessels capped at all times;
- Incorrect labelling of samples or slides can be avoided by ensuring that information is directly transcribed and witnessed, and by handling only a single sample at any time. Robust and detailed standard operating procedures and thorough training of staff in good laboratory practice will minimize these errors, any of which could result in a wrong result being issued. Emphasis should always be placed on minimizing time in culture (prenatal diagnosis); synchronisation to enhance chromosome length and banding resolution (constitutional cytogenetics); choosing culture regimes to maximise the detection of abnormal clones in oncological samples; appropriate sample preparation methods to maximize the quality of the interphase cells for FISH; and effective DNA extraction and analysis techniques (Rooney and Czepulkowski 1992; Hastings, 2010).

Choice and Availability of Tests

Documented procedures should be available providing information on appropriate tests to be allocated to any sample logged in to the laboratory, taking into account the type of sample, the reason for referral and any previous laboratory results

relating to the patient or the family. Staff must be trained and qualified to make informed decisions on the optimum strategy for every sample. Common examples include those referrals that require extended screening for mosaicism, or FISH tests for specific recurrent oncology rearrangements or constitutional microdeletions. Systems should be in place to ensure that samples are appropriately prioritised so that, for instance, blood from newborn babies, prenatal samples with ultrasound abnormalities, and diagnostic leukaemic samples are reported within acceptable time limits.

A laboratory providing a high quality service should offer a comprehensive range of the most widely applied routine chromosome staining methods, that is, G-banding, Q-banding, C-banding, silver staining, replication banding, DA/DAPI banding, and also FISH for recurrent rearrangements, microdeletions, centromeres and telomeres.

As well as dealing with a wide range of methods for mitotic chromosome preparations, the laboratory must be competent to analyse interphase nuclei or DNA for specific applications. FISH, QF-PCR or MLPA for rapid aneuploidy screening should be part of the prenatal diagnosis laboratory repertoire. There are also instances where conventional chromosome analysis is unreliable for detection of an abnormality, for example, tissue limited mosaicism (as in Pallister Killian syndrome), or difficulty in retrieving mitotic activity (as in the case of mature B-cell lymphoproliferative disorders or direct chorionic villus preparations). In these situations, interphase FISH, PCR, or MLPA can be useful tools for detecting chromosomal abnormalities. These techniques often also have the advantage of providing a rapid analysis of specific chromosome rearrangements or numerical abnormalities, in prenatal tissue or in haematological malignancies.

The laboratory should have policies for referral of samples elsewhere in cases requiring specialised expertise or facilities which it cannot provide, for example. chromosome breakage syndromes, microarrays, unique FISH probes, or specialist molecular methods.

New molecular techniques such as microarrays, able to detect abnormalities at a higher resolution than conventional cytogenetics, may in time become the first choice of test, with karyotype or FISH analysis having a more specialised application. Any laboratory providing a high quality service should be keeping abreast of technological developments and be ready to embrace such change.

Analysis

For every sample analysed, a record should be kept of the quality of the preparation, so that comparisons can be made between batches of reagents, or between similar tests undertaken over extended time periods. In this way, any adverse trends can be monitored, and problems recognised and rectified.

For certain tests, for example interphase FISH or mosaicism screening, confidence limits for deciding whether a result is normal or abnormal may need to

be established and clearly documented within the laboratory standard operating procedures.

Forms for keeping a record of analysis should be designed for each individual technique (e.g. chromosome analysis, interphase FISH, molecular cytogenetics) and suitable for clearly recording essential case details, probe identification if applicable, microscope or microarray platform used, results observed, an estimate of quality, (in particular drawing attention to substandard preparations) and signatures of the first analyst and the checking analyst. For each case, all observations should be recorded, and all records of analysis and other test results should be filed together. The system of record keeping and filing should make it possible to relocate any cell or DNA sample for re-evaluation.

For any individual case, the amount of analysis and the preparation quality should comply with national or international guidelines (American College of Medical Genetics 1999; Association for Clinical Cytogenetics 2007; Hastings et al. 2006; Hastings et al. 2007) given the understanding that guidelines often state the minimum requirement. A laboratory providing a high quality of service will frequently achieve more than is set out in guidelines. It should be understood that the requirements for every case have to be assessed individually, and that there may be circumstances in which the level of analysis may need to be greater than the minimum, for example screening for clones or mosaics when the proportion of abnormal cells is expected to be low.

All analysis should be checked by a second member of staff, and one of the two analysts should be fully trained and experienced in the type of analysis undertaken. If results are discrepant, a third competent analyst should be consulted. The completed analysis form, signed by the analyst and checker, should note where the results or analysis are sub-optimal or do not conform to best practice guidelines. In prenatal diagnosis, the presence of maternal contamination (MCC) should be noted and clearly recorded, as it may negate the rapid aneuploidy screening results.

At the microscope, whether for interphase or metaphase analysis, a methodical scan of non-overlapping rows should be undertaken, so the entire target area of the slide is covered. It is important not to analyse the same cells more than once, and advantageous to maximise the number of cells of adequate quality on a single slide. For metaphase analysis broken or overlapping cells should be avoided as far as possible, and for most circumstances mitotic spreads with the best chromosome morphology and banding resolution should be chosen. However, in certain haemato-oncology samples, clonal metaphases representative of the disease may be of poorer quality and a range of cells of varying quality should be examined to minimise the possibility of missing a significant chromosome abnormality. When screening interphase FISH preparations, nuclei in contact with others, or in which signals are obscured by debris or excessive cytoplasm, or with a broken nuclear membrane are generally not suitable for inclusion in the analysis. The analyst must be aware that in special circumstances it is necessary to select interphase nuclei with a particular morphology, the most frequent example being selective scoring of mature neutrophils for BCR/ABL in chronic myeloid leukaemia: these nuclei can look like small clusters of overlapping nuclei (Reinhold et al. 2003).

A full karyotype analysis includes pairing every chromosome, with each band of every chromosome pair being clear of crossovers at least once during the course of the analysis in metaphases of adequate quality. Loss or gain of a single band on any chromosome at the appropriate level of resolution should not escape detection. Suspected rearrangements at the limit of resolution should be confirmed by alternative methodologies (e.g. MLPA, microarrays, molecular analysis, densitometry or FISH) (Association for Clinical Cytogenetics 2007; Mascarello et al. 2002). Any discrepancies between the expected laboratory findings, and the clinical referral or an unexplained difference between the current and a previous test, may need to be followed up by further analysis or alternative methods (for example molecular analysis or microarray analysis) to ascertain the "real" result and exclude the possibility of laboratory error.

For microarray analysis, it is essential that the quality of the DNA, fluorescent dye incorporation, internal cut offs for calling an abnormality, conform with the internal standards before analysis. Many databases are available online where the suspected abnormality can be excluded from being a polymorphic CNV.

The International System for Human Cytogenetic Nomenclature (ISCN 2009) has been developed to convey the precise nature of a result whether it is determined from metaphase, FISH and/or microarray analysis. Although the system may seem confusing to non-cytogeneticists, correct nomenclature designations are important in order to avoid ambiguity when describing a cytogenetic abnormality.

Interpretation of Results

An understanding of the range of different genetic mechanisms and aetiologies that represent abnormal, variant, and normal results, is essential and the patient history, including previous clinical and genetic information, must be taken into consideration when reaching conclusions regarding the significance of the results of laboratory tests.

There are many examples of interpretive pitfalls encountered in cytogenetics. The skilled cytogeneticist will recognise these problems and use knowledge, published resources, and laboratory operating procedures to reach a dependable conclusion. A few examples include

- The ability to distinguish between normal polymorphic variation and an abnormality;
- Knowing when and how to follow up abnormal findings with supplementary methods for confirmation;
- Knowledge of genetic syndromes, for example those having tissue specific abnormalities such as Pallister Killian syndrome;
- The ability to distinguish normal background level of breakage and the recurrent chromosome 7 & 14 rearrangements seen in lymphocyte culture;

- Recognising common age related X chromosome gain or loss as opposed to true sex chromosome mosaicism in adult females;
- Dealing with sex chromosome mosaicism in prenatal samples, including knowing when it is not legitimate to predict a phenotypic outcome based on that of postnatally ascertained patients, and recognising maternal cell contamination;
- Awareness of breakpoint heterogeneity in oncology rearrangements;
- Underestimating the level of residual disease in chronic myeloid leukaemia by not analysing neutrophils in follow up FISH BCR/ABL studies (Reinhold et al. 2003);
- Taking into account the tumour load of a sample e.g. a low level clone in a sample with a small tumour load is significant but may not be if the tumour load is high (depending on clinical indication);
- Misinterpreting the genetic abnormality or the aetiology of the cytogenetic abnormality.

Incorrect interpretation of the results may be an especial problem in oncological cytogenetics and microarrays, and in these rapidly changing fields, awareness of current developments is essential.

Communication of the Result

While success rates will be dependent on sample quality and individual laboratory policy on processing sub-standard samples, success rate and report times should conform to Professional Guidelines (American College of Medical Genetics 1999; Association for Clinical Cytogenetics 2007; Hastings et al. 2006, 2007). Results of any failed tests should be expedited to ensure that repeat sampling can be undertaken as soon as possible.

The cytogenetic report should be clear and unambiguous with the karyotype/genomic copy number described in text as well as ISCN nomenclature. An interpretation of the findings should be given, the report clearly indicating the diagnostic and/or prognostic significance of the results, including their relevance to the reason for referral, the patient's age and other clinical factors as appropriate. The limitations of the analysis should be documented, in particular if further tests may be required. The report should also clearly indicate the robustness of the result (e.g. number of abnormal and normal cells, number of informative markers for abnormal QF-PCR results), the tissue which was analysed and whether the results were obtained from metaphases, interphase nuclei, or DNA (or a combination of these). For FISH or MLPA, probe sets or kits used to perform the analysis must also be identified including the name of the manufacturer. The report must indicate any specific limitations of the assay.

Longitudinal studies of patients, as frequently undertaken in the oncology cytogenetics laboratory, should be compared with their previous genetic test findings, and the report should make clear recommendations concerning future testing of such patients (Association for Clinical Cytogenetics 2007; Hastings et al. 2006, 2007).

Information and Resources

In order to provide a high quality service, it is essential that staff are appropriately trained, and that they have access to resources that permit them to keep up to date with developments in the field and allow them to consult literature that ensures accurate interpretation of laboratory findings. Reference books, for example, ISCN (2009), Gardner and Sutherland (2003), and Schinzel (2001) should be provided, and a selection of recognised high quality peer-reviewed journals available. Internet access for all professional laboratory staff is vital, with OMIM, PubMed, Decipher, HC Forum and the UCSC Genome Bioinformatics websites being particularly useful references.

Graduate staff should be encouraged to undertake higher specialist training, and funds should be set aside to enable them to attend educational meetings and conferences. An excellent way to identify the needs of staff is through a system of regular performance review or appraisal. Overall, in order that employees are content and productive in the laboratory, it is important that they are provided with a pleasant environment to work in, including comfortable seating, high quality ergonomic microscopes, adequate heating, cooling and lighting, minimum disruption by noise and overcrowding, and access to rest facilities.

External Quality Assessment

External Quality Assessment (EQA) is covered in detail in Chapter "External Quality Assessment in Molecular Genetic Testing". It is the usual means by which technical, analytical and interpretative performances are measured and benchmarked. The process in cytogenetics either involves the distribution of samples or images to laboratories for analysis and reporting (prospective EQA) or the submission of a selection of diagnostic cases to the Scheme (retrospective EQA) (Hastings et al. 2008; Howell and Hastings et al. 2006). For the cytogenetics laboratory seeking to provide a high quality service, participation in EQA should be continuous for all aspects of the diagnostic service. Assessment is recognised by international standards (ISO 15189 2003) and accreditation bodies as a tangible measure of the quality of a laboratory's performance (OECD 2005) and is an essential requirement if a laboratory is to become accredited.

Laboratory Accreditation

In the accreditation process, covered in Chapter "Quality Management Systems and Accrediation", the laboratory is examined by independent experts who follow international standards in their inspection of the premises, facilities, information systems, training, health and safety, standard operating procedures, quality management systems, including internal quality control and participation in EQA. All cytogenetics laboratories should seek to achieve accreditation, as it provides confirmation that the laboratory is capable of providing a robust service.

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Fluorescence In Situ Hybridization (FISH) – Quality Issues in Molecular Cytogenetics

Thomas Liehr

Key Points

Major quality issues of molecular cytogenetics are:

- Manpower: Well-trained personal, knowing chromosomes on GTG-band level and pitfalls of FISH-techniques are a must.
- Equipment: All laboratory equipment has to be available in double, to guarantee continuous work in case of damage of one machine.
- Microscope: The maximum time of operation of fluorescence microscope lamps and filters have to be observed.
- Probes and samples: Protocols with clear instructions for handling/ work-up of DNA-probes and tissue samples must be adapted by each user to the specific requirements.
- Evaluation and reporting: While evaluation can be done by technical staff, the final approval of the result and the reporting has to be done by a correspondingly qualified PhD and/or MD.

Keywords FISH · Molecular cytogenetics · Interphase · Diagnostics · Quality control

Introduction

Molecular cytogenetics is one of the youngest disciplines of cytogenetics. It was introduced in routine cytogenetics diagnostics by the first successful fluorescence in situ hybridization (FISH) experiment on human chromosomes in 1986 (Pinkel et al.

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1986). Since then numerous and in parts very colorful FISH probe-sets, variations in protocols, procedures and applications were introduced (overview in Liehr 2009a). Even though nowadays widely applied in diagnostic procedures there are no uniform, obligatory/ binding or comprehensive guidelines on FISH published, yet. At present there is one attempt to introduce quality issues in cytogenetic diagnostics in general by EuroGenetest (http://www.eurogentest.org).

Here some thoughts on important points to be taken into account to perform high quality molecular cytogenetic diagnostics and research. For general rules of good laboratory practice we refer to the E.C.A. Cytogenetic Guidelines and Quality Assurance (http://www.eurogentest.org/web/info/public/unit1/guidelines/cytogenetics/index.xhtml).

Special Quality Issues for Molecular Cytogenetics

Staff and Laboratory

When doing FISH for diagnostics it is obvious that the basic prerequisite is to have available well trained personal. I.e. the head of the laboratory and the technical staff need to have knowledge of cytogenetic and molecular cytogenetic basic techniques, including the ability to clearly identify the 24 different human chromosomes on a 300–550 band level. One can do FISH without that knowledge, e.g. by counting signals in interphase. However, without knowledge of things like e.g. heteromorphisms, signal-splitting or normal structure of human chromosomes one can easily misinterpret obtained results.

Concerning the laboratory equipment, every apparatus must be present in double as a minimum requirement for a high quality molecular cytogenetic facility. This holds true not only for refrigerators, which are critical for probe- and sample-storage, and for fluorescence microscopes, which are crucial for evaluation; also apparently not so important things like centrifuges, pipettes and water-baths can, if defect and no substitute is on hand, hamper or block a running diagnostic system.

Microscope

Very critical and often underestimated for a quality assessment of a diagnostic laboratory is the fluorescence microscope. The FISH-procedure itself can be perfect and the results brilliant, nonetheless these are not available in the corresponding laboratory due to avoidable problems with the (mercury) lamp and the appropriate fluorochrome-specific filters. I.e. the lamp was already in usage for >200 h and/or the filters are damaged and no longer intact. According to microscope and filter type a DAPI-filter must be replaced after 2,000–3,000 h, others after 3,000 or more. Also it is important that the microscope is correctly calibrated to lead to optimal results

(Liehr 2009b). According to own experience signals not visible on a microscope with older lamp and/or filters can be even intense on another one with new lamp and/or filters.

When using more than two fluorochromes plus one counterstain in our time it is standard to work with image acquisition and processing hard- and software. To the best of our knowledge at present there is no certificated FISH-evaluation program for diagnostics. Thus, each user has to be familiar with possibilities and limitations of the available program.

FISH-probes

Nowadays many companies provide probes suitable for FISH. These can be purchased labeled or unlabeled – however, normally they are accompanied by a disclaimer stating that the probe is not suited for diagnostics. There are only a few exceptions from that, like the FDA-approved tests from Abbott/Vysis (http://www.abbottmolecular.com/) and FISH-probes from Kreatech (http://www.kreatech.com/). Also in some laboratories, like ours, home made probes are in use. Fluorochrome labeled probes have to be aliquoted and stored at –20°C and should be protected against light – also during the FISH-procedure.

In any case it is necessary to perform quality tests of each probe and each batch and to confirm its identity. At least one FISH-experiment on a control sample per each new probe and batch introduced has to be done. This step is especially essential if the corresponding probe shall be used in interphase FISH, and thus, there is no chance to control its identity on metaphase chromosomes on the sample. The number and way of quality tests has to be adapted according to the probe, amount of the available probe and the sample to be applied on. In general, some accreditation guidelines suggest to test new batches in at least 10 independent tests; this is not feasible if one probe-vial provides only 10 or 15 tests, as often the case for commercial available FISH-probes.

Also it is of importance to define the number of cells to be evaluated per test to be performed and to set cut-off levels for each probe. The latter especially has to be done in case of interphase-FISH studies, where it is important to distinguish real sub-clones from background noise; examples for cut-off rates can be found in Gebhart et al. (1993) or Liehr and Ziegler (2005). For the number of cells sometimes there are national guidelines, e.g. in Germany it is recommended to evaluate at least 30 interphase cells when performing the quick-FISH-test for the exclusion of the most common aneuploidies of the second pregnancy-trimester (http://www.medgenetik.de/sonderdruck/1998-319.PDF).

However, normally even for commercial probes no cutoff rates are provided. This is why, as the cut-off varies between different laboratories, users and tissue samples. Thus, laboratory internal cut-off rates must be determined before use of a probe in diagnostics. However, it must be stated that cutoff rates are practically only necessary in interphase molecular cytogenetics but not for metaphase FISH. One exception is, if exclusion of mosaicism shall be done by metaphase

FISH. Orientating cut-off rates were published for the aforementioned quick-FISH-test (Liehr and Ziegler 2005) and centromeric probes applied in interphase-FISH (Gebhart et al. 1993).

Samples

Samples have to be treated carefully and responsively during the whole procedure: i.e. a mix-up of sample has to be avoided by corresponding actions/ precautions; e.g. that always two people are present at critical steps of sample handling and that always only one sample is handled at one time for one step, if critical in terms of mixing-up. All steps have to be properly documented. Samples, slides and documentations have to be stored according to the national guidelines.

It is international consensus, that it is for diagnostic laboratories a quality issue to have a certain amount of turnover for their diagnostic cases. Below a certain amount of cases per year per technician a method cannot be performed routinely and in high quality. Also a maximum work load of technical personal should not be exceeded (http://www.eurogentest.org). Moreover, besides laboratory internal quality control it is recommended to take part external quality assessment programmes.

Evaluation and Issuing of a Report

For quality means, evaluation has to be double checked and confirmed by (at least) two different technicians and/or scientists. Result interpretation and issuing of a report underlies the individual regulations of each country. In general, the interpretation has to be done by an accordingly trained specialist. The time for issuing a final report is a quality issue. In our facility, starting from a cell pellet in Carnoys fixative, prenatal and tumor cytogenetic FISH-reports should be issued after 1 day to 1.5 weeks, postnatal ones within 1–3 weeks.

Karyotype Formula

At present it is matter of discussion if ISCN 2005 shall be used when issuing a (molecular) cytogenetic report. Mitelman and Rowley (2007) mainly criticize the changes in tumorcytogenetic nomenclature of ISCN 2005 compared to ISCN 1995. However, also the ish-nomenclature is at present not really well-engineered and reason for discussions (personal communication with F. Mitelman, Lund, Sweden). To achieve the main goal of a molecular cytogenetic report, i.e. to be understandable for the "customer" (= MD or patient), in our department, as in many others, tend to avoid the ish nomenclature. Instead a standard karyotype formula is given, adding

clear information which probes where applied to come to that result. Also a clear explanation of the obtained results is given in the result interpretation part.

To make the reporting problem obvious an example taken from ISCN 2005, p. 107. In this case an isodicentric Yq-chromosome characterized by two FISH-probes DYZ3 and DYZ1 ISCN 2005 recommends to write: 46,X,?i(Y)(p10).ish idic(Y)(q11)(DYZ3++,DYZ1-). Two different breakpoints are given here in that karyotype formula. Using the standard reporting formula the karyotype-would be written simply as 46,X,idic(Y)(q11) adding in the report under applied methods that GTG-banding and FISH with the two aforementioned probes were used to come to that result. ISCN 2009 recommends still the share.

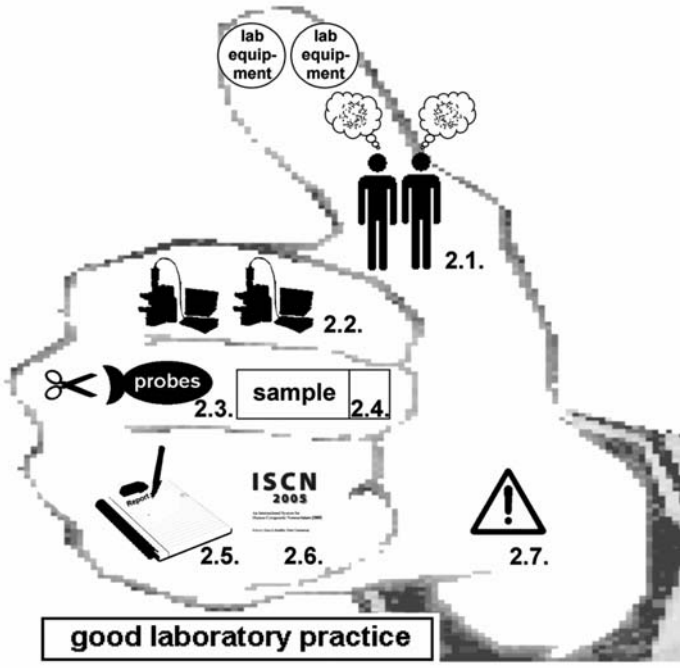

Fig. 1 Schematic drawing of what are important quality issues in molecular cytogenetics. Good laboratory practice is the basis. Special things to bear in mind are included in this scheme according to this chapter. Necessary are *Staff and Laboratory* (2.1.): Well trained personal with special knowledge of chromosomes and cytogenetics; lab equipment has to be on stock twice, particularly, *Microscope* (2.2.): two fluorescence microscopes, which have to be maintained especially for filters and lamps. *FISH-probes* (2.3.): For FISH-probes quality control has to be performed and cut-off rates must be defined. *Samples* (2.4.): A sufficient turnaround of samples and high quality sample handling must be guaranteed. *Evaluation and Issuing of a Report* (2.5.): Evaluation has to be double checked by two different persons and a report has to be issued in a certain timeframe. *Karyotype Formula* (2.6.): A karyotype formula should be provided. *Protection of the Environment and Staff* (2.7.): Toxic substances have to be treated properly

Protection of the Environment and Staff

Last but not least, nowadays one criterion for good quality should be aspects of environmental protection. Toxic substances, as present in every molecular cytogenetic procedure (e.g. formamide and formaldehyde, sometimes even xylene and cyanides), have to be discarded proper and according to national safety rules. This behavior also leads to a protection of health of the staff.

Conclusion

As summarized in Fig. 1 there are general rules of good laboratory practice and also some special ones to be followed to meet all criteria necessary for a high quality molecular cytogenetic laboratory. When setting up a new such facility it is always recommendable to ask for help and make training in other similar laboratories. Quality is nothing which is achieved once and then present for all future, but it is hard, continuous and daily work to keep and always enhance an achieved standard.

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Quality Issues in Biochemical Genetic Testing

Brian Fowler

Key Points

- External quality assurance (EQA) is important in assessing accuracy, reliability and comparability of results of quantitative biochemical genetic tests as well as diagnostic proficiency and metabolite pattern recognition.
- ERNDIM (European Research Network for evaluation and improvement of screening, Diagnosis and treatment of Inherited disorders of Metabolism) provides schemes on a Europe-wide basis due to the small number of laboratories in each country.
- Development of performance assessment criteria allows identification of improvements and is closely linked to accreditation of laboratories.
- There is considerable evidence that performance in biochemical genetic testing has improved since the introduction of ERNDIM schemes.

Keywords Inherited metabolic disorders · ERNDIM · Proficiency testing

Introduction

The first inborn errors of metabolism were described in the hallmark Croonian lectures by Garrod one hundred years ago (Scriver 2008). Subsequently the number of recognised inherited metabolic diseases (IMD) has dramatically increased from a few amino acid disorders in the 1940s to the hundreds of different disorders known today. This expansion of the scope of biochemical genetic testing (BGT) has

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paralleled technological advances such as quantitative ion-exchange chromatography, gas chromatography coupled with mass spectrometry, high performance liquid chromatography and tandem mass spectrometry alongside classical techniques of macromolecule identification, enzymology and molecular genetic analysis. The different groups of inherited metabolic disorders and the main methods used for their detection have been reviewed (Blau et al. 2008).

Analytical challenges in BGT relate to the occurrence of several hundred different analytes measured in single assays or in groups using separation techniques such as chromatography with detection systems of varying specificity. For example up to 200 different organic acids can potentially occur in urine and separation by gas chromatography must be accompanied by mass-spectrometric analysis for reliable analysis. Also the analytical challenges vary according to the clinical situation. The level of performance demanded for initial diagnosis with many fold increases of metabolites is less than that required for monitoring of treatment where action levels for treatment measures depend on accurate discrimination of smaller differences in concentrations.

The relative rarity of these disorders, the need for dedicated expensive equipment, concentration of experience in interpretation of results and close links to related clinical services requires optimal organisation in specialised centres, the number in individual countries depending on the size and geographical disposition.

Alongside reliability and validity of methods comparability of results within and between laboratories is essential because of agreed treatment thresholds of metabolite levels, the need for consensus cut off values in newborn screening, comparison of results in multi-centre studies and mobility of families between countries. Following detection in newborn screening programmes of inherited metabolic disorders which could be treated, as exemplified by phenylketonuria, it became necessary to increase the levels of accuracy, precision, reproducibility and harmonisation of laboratory analyses in this field using external quality assurance (EQA) programmes similar to those developed for clinical chemistry in the 1970s.

External Quality Control in BGT in Europe: The ERNDIM Foundation

ERNDIM (European Research Network for evaluation and improvement of screening, Diagnosis and treatment of Inherited disorders of Metabolism) was founded in 1994 with the aim of addressing quality issues in BGT. ERNDIM mainly works to provide EQA schemes but is also active in wider issues related to overall aspects and quality of services needed for adequate provision of BGT.

Although some national schemes existed prior to ERNDIM (e.g. Rattenbury 1990), EQA for BGT should be organised at the international level because there are too few provider laboratories in any one country to allow statistically meaningful evaluation of results within a scheme. EQA schemes are organised by ERNDIM according to current best practice. The schemes are mainly aimed at European laboratories although several from outside Europe also participate. Established

principles and guidelines (Sciacovelli et al. 2001) are followed in designing and operating ERNDIM schemes. As many aspects of the schemes as possible are harmonized such as the same numbers and frequency of samples distributed and submission of results and receipt of reports using the internet. Currently ERNDIM works in close partnership with two main types of provider. The Dutch Foundation for Quality Assessment in Clinical Laboratories Schemes (Stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek, SKML) is responsible for running the quantitative schemes and a number of academic centres organise the so called proficiency schemes which rely on a high degree of prowess at profile recognition. The scheme providers are governed by the Scientific Advisory Board and schemes are administered by the ERNDIM executive committee, which represents the ERNDIM Foundation Board (see http://www.erndim.unibas.ch/pdf/ssiem_structure.pdf for details of these bodies and the organisation of ERNDIM).

ERNDIM schemes are funded by subscription fees and it aims to be financially self sufficient through minimal administration costs and efficient subscription collection.

ERNDIM EQA Schemes

When ERNDIM was formed in 1994 schemes were provided for amino acids (88 participants), quantitative organic acids (51 participants), qualitative organic acids (38 participants), special assays (66 participants) and diagnostic proficiency testing in just one centre (Nijmegen, 20 participants).

Since then the capacity of existing schemes has expanded and new schemes have been added in response to demands for EQA in the various forms of BGT. This expansion has been greatly aided by the support of two EU Biomed grants. The original number of participants in 1994 of 123 has increased to 265 in 2008.

Different types of schemes are provided with 9 different schemes in all. Information on the various schemes with current numbers of subscriptions, aims of the schemes and the individual compounds tested are available on the ERNDIM website (http://www.erndim.org). Samples distributed in all schemes are validated in a reference laboratory.

Quantitative Schemes

The six different quantitative schemes are based on manufactured samples in which different concentrations of a range of metabolites are mixed together with a physiological matrix. The matrix for plasma is prepared by dialysis of a pool of control plasma. For urine pooled samples are collected from subjects in institutions who receive a very poor diet. Eight samples per year are distributed and results submitted by internet are processed to provide consensus values. In designing the content of samples emphasis is given to the inclusion of concentrations which are of clinical relevance including low as well as high levels.

Eight samples per year are prepared by adding 4 different concentrations of each of the respective compounds to lyophilised plasma or urine in duplicate. Participants analyse and submit results by internet for each sample spread over 8 months of the year. Reports for each sample are produced for the individual laboratories automatically showing the participant's own value compared with the median value for all laboratories. The values submitted by all laboratories and shown graphically as the percentiles can also be called up. There is also the facility for the Scientific Advisor to add comments within the report. The annual individual participants report summarises all 8 samples and indicates: (1) accuracy as the average of the eight values; (2) precision expressed as the coefficient of variation for the four duplicate samples; (3) linearity and (4) recovery, both calculated from the measured values compared with the added quantities. These are listed for each analyte for the participant and compared with medians for all laboratories. See Table 1 for an example of presentation of results of the amino acid scheme. The coefficient of variation between all laboratories is shown as an indication of comparability of results between different laboratories.

There is clear evidence of improvement of performance since introduction of the ERNDIM scheme as recently reported (Fowler et al. 2008).

Qualitative proficiency schemes (organic acids, acyl-carnitines) make use of natural samples from subjects with an inherited metabolic disorder or controls. Participants are obliged to analyse them and evaluate the overall metabolite profile to determine a diagnosis. The style of reports is carefully considered and participants are encouraged to tailor these to be understood by a non-specialist paediatrician working in a general hospital. Full details of the qualitative organic acid scheme have been recently reported (Peters et al. 2008).

Diagnostic proficiency testing schemes also use natural patient urine samples from patients with a specific inborn error of metabolism. Schemes are limited to 25 participants at most due to difficulties in obtaining large volumes of urine and the need to foster an intimate forum for discussion of results, including mistakes at the annual meeting of participants. Schemes are presently organised from University Hospitals in Amsterdam/Nijmegen, Basel, Lyon, Prague and Sheffield although organisation from a central EQA provider is being considered.

Six samples per year are distributed together with clinical information. Laboratories are required to perform the tests necessary to reach a diagnosis by analysis of one or more of amino acids, organic acids, mucopolysaccharides, oligosaccharides and purines and pyrimidines. A recently harmonized scoring system evaluates analytical performance (2 points), interpretative proficiency (2 points) and recommendations for further laboratory diagnostic tests (1 point) to give a maximum of 5 points per sample.

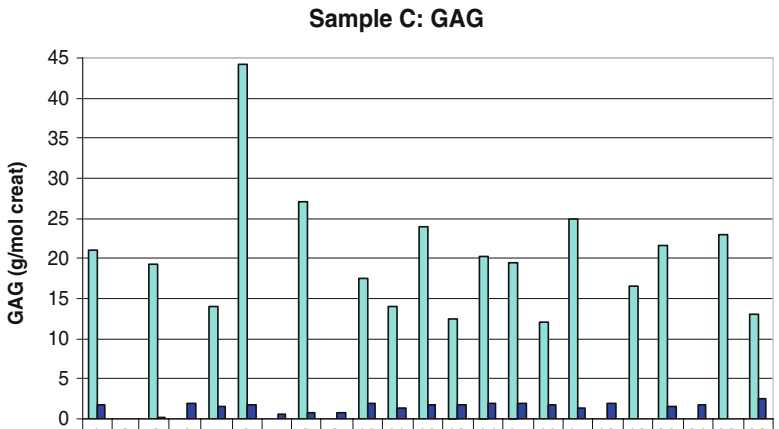
To illustrate the range of disorders covered in these schemes, diagnoses covered over the last 7 years from Lyon and Prague have included 16 amino acid, 15 organic acid, 7 energy metabolism, 5 mucopolysaccharide, 4 sphingolipid storage, 3 purine/pyrimidine and 1 peroxisomal disorders with some samples distributed more than once. Diagnostic proficiency has ranged from 28 to 100% with an average of 80%. Although overall trends in performance are difficult to quantify because of

Table 1 ERNDIM Amino acid EQA scheme: Details for representative amino acids from annual report

Annual report
Amino acids 2007

Analyte	Accuracy (Mean)		Precision (CV% duplicates)		Linearity (r)		Recovery (% added analyte)		Data all labs	
	Your lab	All labs	Your lab	All labs	Your lab	All labs	Your lab	All labs	Nr. of labs	Inter lab CV(%)
Alanine	473	446	1.7	4.8	0.9997	0.9981	100	95	204	8.5
alpha-Amino butyric acid	22.0	20.9	3.9	6.7	0.9970	0.9942	98	96	187	15.0
Arginine	165	156	6.2	5.1	0.9979	0.9987	99	94	201	14.2
Aspartic acid	24.1	32.9	6.4	7.0	0.1863	0.1667	19	23	197	20.3
Citrulline	165	156	7.8	5.6	0.9991	0.9995	105	100	198	13.7
Cystathionine	37.6	34.6	9.3	8.4	0.9975	0.9973	91	86	164	31.4
Cystine	46.0	45.4	6.6	6.7	0.9745	0.9765	56	59	182	11.6

CV, coefficient of variation



Lab no	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
GAG (g/mol creat)	21		19		14	44		27		18	14	24	12	20	19	12	25		17	22		23	13
Creatinine (mmol/l)	1.8		0.3	2.0	1.6	1.8	0.6	0.7	0.8	1.9	1.5	1.8	1.7	1.9	1.9	1.7	1.4	1.9		1.6	1.8		2.6

Fig. 1 Features of a representative report in the ERNDIM DPT scheme the findings in one sample from the DPT scheme organised from Basel are shown. MPS, Mucopolysaccharidosis; GAG, glycosaminoglycans; DS, dermatan sulphate; CS, chondroitin sulphate; HS, heparin sulphate; KS, keratan sulphate

differences in diagnostic difficulty with different disorders, evidence of improvement has recently been reported (Fowler et al. 2008). See also the experience from the Sheffield scheme, briefly reported by Bonham (2003). The figure shows the main features of a representative report for one sample (Fig. 1).

Scoring and Assessment of Performance

In order to be able to judge quality of performance in EQA, a robust and systematically grounded method of assessing participants' returns and scoring of them must be in place. The scoring system should be harmonised between different schemes as much as possible.

For quantitative schemes a web based system has been developed in which results for each analyte are computed to produce values for four parameters, accuracy, precision, linearity and recovery. These values are ranked for all laboratories and poor performance is assigned to values below the 2.5 percentile and above the 97.5 percentile for accuracy and recovery, to values above the 95th percentile for the coefficient of variation of results (precision) and to values below the 5th percentile for linearity. Acceptable performance is then assigned to an analyte only when no more than one parameter out of four is scored as poor.

For diagnostic proficiency and qualitative schemes, performance is scored for the individual samples as described above and the scores are totalled for each year.

The limit for satisfactory overall performance is agreed for the current year by the scientific advisory board and this is applied equally to each of the five DPT schemes.

A major step has been to produce certificates of participation for all schemes from 2007 onwards, which as well as confirming subscription include full details of the numbers of results submitted and indicators of performance achieved. Laboratories which fail to reach a satisfactory level of performance will be issued with a "warning" letter which will highlight any specific areas of weakness and offer advice on remedial action. In other words this should take the character of a "helping" letter aimed at initiating dialogue on identification of problems and possible remedies.

Web-Site Submission of Results

The website submission of results and generation of individual reports is already available for the six ERNDIM quantitative schemes. A current essential development is the development of an online system for submission of results and on-line reporting, for the DPT and other qualitative schemes.

A future possible development is the creation of so called virtual EQA whereby results of samples are mounted on the website and participants are required to interpret them as already described for cytogenetics (Hastings et al. 2008). This approach lends itself to several diagnostic challenges for inherited metabolic disorders such as evaluation of amino acid or organic acid profiles.

Pilot Schemes

Since 1994, ERNDIM has steadily added to the capacity of existing schemes and added to the range of EQA schemes in response to needs of testing laboratories and diagnostic advances. The need for new schemes for additional groups of metabolites is often highlighted and ERNDIM is active in supporting the development of new schemes together with potential scheme organisers. The first step in establishing a new scheme is to determine the potential number of laboratories. At least 25 participants are needed since a lower number makes reliable statistical ascertainment of results impossible. Then the practical feasibility and logistics of the scheme need to be tested during a pilot period which usually lasts for 2 years. Suitability and stability of samples have to be validated and the robustness of result presentation and reporting need to be tested. Only when these steps have been successfully undertaken can a new scheme be incorporated as an official ERNDIM scheme.

At the present time two pilot schemes are being run. A scheme for lysosomal enzymes, organised by SKML together with Dr. O. van Diggelen as scientific advisor, was begun in 2007 (see van Diggelen et al. 2008 for a brief interim report). Another one for disorders of glycosylation was initially organised within the Euroglycanet project (http://www.euroglycanet.org/) and was taken over as a pilot scheme operated by SKML together with Prof. R. Wevers in 2008.

Accreditation of Laboratories and EQA Schemes

Accreditation of laboratories which offer BGT plays an important role in providing reassurance for clinicians or patients who use such laboratory services. Generally accreditation systems follow the same principles applied to wider aspects of healthcare assessment (Donabedian 1998). These systems reassure users that: (a) adequate structures are available such as laboratory personnel, equipment and buildings; (b) suitable processes are used to guarantee reliable testing such as using standard operating procedures, internal quality control and participation in EQA; (c) critical audit of outcomes takes place (Bonham 2008).

Accreditation is organised differently in the various countries and is administered by organisations such as the Clinical Pathology Accreditation in the UK and the Foundation for the Promotion of the Quality of Laboratory Work and the Accreditation of Laboratories in the Health Service (CCKL Test) in The Netherlands. Regardless of national regulations and whether accreditation is optional or mandatory the standards to which these bodies refer are based on internationally agreed norms. These include ISO 9001:2000, which covers the overall aspects of quality management systems, ISO 17025:1999, which refers to aptitude in testing and calibration laboratories, or ISO 15189:2002 which particularly covers medical laboratories and includes post-analytical aspects and reporting of results.

Countries of the European Union have expressed commitment to maintaining uniformity of quality in BGT and support laboratory accreditation as the best way to accomplish this.

As well as laboratories it is important that the EQA scheme providers themselves and even the umbrella organisations responsible for administering and coordinating schemes should also follow the route of accreditation thereby greatly increasing the credibility of the total process of quality assurance. An important reference in this regard is the ISO/IEC 17043 norm which is currently under development.

The current Eurogentest project (www.eurogentest.org) seeks to coordinate activities on quality for BGT together with those for cytogenetic and molecular genetic testing. Sharing resources, guidelines and procedures should ensure a greater degree of harmonization and lead to more relevant accreditation standards for genetic testing especially with regard to all aspects of reporting of laboratory findings.

Further Measures Aimed at Improvement of Performance

A number of steps have been taken to try to improve performance in BGT and this is a continuous process. As well as the obvious benefit from participation in the EQA schemes themselves the value of further measures should be considered. Educational activities (see below), provision of expert guidance papers on quality issues and specific methods and development of reference materials and calibrators all contribute towards improving quality. A recent comprehensive book detailing a

wide range of methods relevant for BGT, (Blau et al. 2008), should be a valuable tool in helping to standardize procedures.

Training and Education

Further education of specialists is essential and ERNDIM has endeavoured to contribute towards this since its conception. From an early stage a number of workshops on topical diagnostic issues have been organised within the confines of the Society for Inborn Errors of Metabolism (SSIEM) annual symposium. Since 2001 these workshops have been integrated into a dedicated session open to all persons attending the SSIEM symposium and linked to parallel meetings for the participants of the different DPT schemes. These workshops have addressed clinical indications for testing, methodology questions and level of performance in relevant ERNDIM schemes for a particular group of disorders. Topics covered since 2000 are amino acids, mucopolysaccharides, organic acids, general aspects of EQA schemes (Fowler et al 2003b), acyl-carnitines, purines/pyrimidines, lysosomal enzymes, peroxisomal disorders and creatine synthesis disorders. Latterly the PowerPoint presentations have been mounted on the ERNDIM website and in addition they provide the basis for guidance documents on methodological issues for analysis of specific groups of metabolites as well as more general issues of quality. Currently mounted on the ERNDIM web-site (http://www.erndim.org/ "Training and Education") are the following: Theoretical aspects of QC in IEM and Method validation; Control of Accuracy and Precision; Amino Acid Analysis Recommendations; Biomed 2 Recommendations; Polymorphonuclear Leukocyte Preparation; Mixed Leukocyte Preparation; White cell cystine determination and the role of EQA ; Role of EQA in special assays for IEM. Additional documents in preparation include recommendations for the analysis of organic acids, mucopolysaccharides, purines/pyrimidines, lysosomal enzymes, acyl-carnitines and performance assessment in ERNDIM diagnostic proficiency schemes.

Training of biochemists in BGT is supported by ERNDIM. Although training programmes vary between countries, due to differences in the professional and institutional environment and varying incidence of individual diseases between countries many principles of good practice and analytical techniques can be shared. Also countries which plan to newly develop these services may benefit from exchange with those countries in which BGT is well established. With this in mind ERNDIM has developed an area of its website as a resource pool allowing call up of details of existing training programmes and web based resources and as a depository for information on the facilities and approaches to training in each individual country. Training resources such as training syllabuses, training logs and information about national training schemes are directly available from this site.

A new initiative is the organisation of training days for laboratory workers in collaboration with the Education and Training Committee (ETAC) of the SSIEM. The first of these was devoted to amino acid disorders and was held in parallel to one for clinicians adjacent to the annual SSIEM symposium in Lisbon in 2008.

ERNDIM / EUGT Directory of Laboratories

A directory of laboratories which perform BGT is a very important aid to specialist workers and geneticists in the field in increasing awareness about quality issues which should be paramount when they select laboratories for sample referral. This is especially needed for inherited metabolic diseases with the great diversity of individual tests often performed in a very few laboratories and not always available in every country. One role of the directory is as an assay finder for the individual or groups of metabolites, enzyme assays and mutation analysis referred to as analytes in our directory. A pull-down list currently contains approaching 500 different analytes. A second role is to provide full details of the listed laboratories including information on quality management and EQA participation. This directory has been established with support from a previous Biomed EU grant and has been further developed within the Eurogentest project.

A very simple registration procedure incorporates one off submission of details and allows validity checks of laboratories, especially of EQA participation. Presently of the estimated total of ca. 300 European laboratories there are about 130 with fully validated information in the directory. Moves to link the data with the Eurogentest QAu database and the disease oriented Orphanet web site are underway.

The Eurogentest Project and the Role of ERNDIM

BGT in general and EQA in particular are represented within the project by ERNDIM. This organisation is active in expansion of opportunities for BGT laboratories in the EU to take part in EQA, in improving quality of BGT by development of best practice guidelines especially in the use of internal and external quality control and working towards harmonisation with other genetic disciplines.

Examples of developments within the project include increasing capacity and scope of EQA for BGT by establishment of a fifth diagnostic proficiency testing scheme in Basel as well as the new schemes for lysosomal enzymes and congenital disorders of glycosylation mentioned above. A newly created network of National Representatives has developed guidelines for the complex issue of provision and organisation of the diverse range of BGT services needed for comprehensive diagnosis and management of patients in all countries in relation to population size and resources. Criteria for assessment and scoring of performance in EQA schemes have been developed in best practice meetings. Several educational activities have been consolidated as mentioned above and an ERNDIM website has been developed including the directory of laboratories and training and methodological guidance documents. Vital to the Eurogentest project are meetings with our partners responsible for EQA in cytogenetics and molecular genetics and accreditation experts aimed at promoting accreditation of both individual genetic EQA schemes and also the EQA umbrella organizations themselves. Relevant documentation which should aid all involved in the accreditation process includes generic checklists and quality manuals.

Conclusion

Quality issues in BGT have much in common with those in other types of genetic laboratory tests but also some differences. These are mainly related to the large number of different analytes and the combination of quantitative and qualitative measures and metabolic profile recognition. Activities aimed at raising quality of BGT such as those promoted by ERNDIM have been shown to help to improve patient services although challenges to continue to improve performance of laboratories and to increase awareness of users of BGT services of the importance of EQA remain.

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Emerging Technologies, Need for Quality Assessment

Egbert Bakker

Key Points

- Introduction of molecular genetics, both new disease specific tests and novel technologies, into the diagnostic service has been at an *ad hoc* and case-to-case basis for many years.
- Concentred efforts of producing uniform guidelines including all test conditions has been very beneficial for the field, and has greatly reduced the number of diagnostic errors caused by technical failure/problems.
- The last 4 years, a series of technologies both existing and new have been or are being evaluated and/or validated for diagnostic use. EuroGentest coordinated these activities to enable proper implementation of (novel) technologies into the genetic services.
- The industries need access to accredited clinical laboratories and to well-characterized clinical samples to produce new tests. And the diagnostic laboratories need validated tests, guidelines and specific training. Both could benefit from an evaluation/implementation program as set up within Eurogentest.

Keywords New technologies · Evaluation · Validation · Quality assessment · Guidelines

Introduction

The Human genome project has had and still has an enormous impact on the field of genetics and medicine. It greatly stimulates the development and dissemination of advanced DNA technologies.

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During the Eighties most molecular diagnostic laboratories arose within a research or academic setting, on the basis of their technical and/or on their disease specific knowledge. In the Nineties some molecular diagnostic service laboratories started to set up an internal quality system and felt the need to take part in External Quality Assessment (EQA) studies to demonstrate their competences. The Irish and Dutch molecular genetics laboratories joined the UK-NEQAS (United Kingdom National External Quality Assessment Service). From this collaboration in 1997 the EU- funded European Molecular genetics Quality Network (EMQN) sprouted, which enabled inter-laboratory test result comparisons for all European genetics laboratories. In 2003 the need for harmonization of clinical genetic services in Europe and the need for more laboratories to comply with a quality system increased and led to set up of a European project (coordinated by Cassiman, Leuven) called EuroGentest. This Network of Excellence (NoE) was funded for a period of 5 year (2005–2010) in the 6th Framework. EuroGentest further boosted the professionalization of Clinical Genetic Laboratories. Apart from setting up a registration system for diagnostic clinical genetic laboratories documenting their accreditation status and their participation in EQA studies, EuroGentest also covers: Education to inform both the patients and the health care professionals involved in the testing; Training for professionals; and Evaluation/implementation of novel technologies.

Up to 2003 the introduction of molecular genetic tests into the diagnostic service has mainly been at an *ad hoc* and case-to-case basis. Quality systems, proper evaluation and general validation procedures were often scarce especially in the implementation process of a novel technology. This has seriously delayed and hampered the proper introduction of new genetic tests in the molecular diagnostic laboratories and also caused increased financial expenses for many laboratories and research partners.

In this Chapter we will focus on the latter and demonstrate why proper evaluation, validation and implementation should best be concentrated at a National level or rather at a European level for example within EuroGentest. One of the aims of EuroGentest is to support and to guide the implementation of emerging technologies into diagnostic application. A rigorous test evaluation program, including beta testing in accredited laboratories, on selected well-characterized clinical samples, is used. By involving leading experts from research centres and industry EuroGentest developed some necessary infrastructure, tools, and resources to produce guidelines and procedures that will structure, harmonize and improve the overall quality of all genetic services within the EU.

Introduction of Molecular Genetic Tests, *ad hoc* Versus Concentrated

In the last two decades of the last century the introduction into the diagnostic service of both new disease specific tests and novel technologies has mainly been at an *ad hoc* and case-to-case basis. Discoveries obtained in the academia and university

hospital laboratories in the field of gene research, or molecular genetic testing often led to direct implementation into the diagnostic service. Either from own results or through adoption of published knowledge test procedures were introduced in the diagnostic laboratories. In house production of test kits was common practise for diagnostic laboratories. Most reagents and kits produced by the industry were labelled "for research purpose only". In general this approach worked well for many years and also accelerated the clinical use of the new knowledge. However, the laboratory specific diagnostic protocols introduce a huge diversity between laboratories in level and quality of the services offered.

One example of a rapidly spreading diagnostic application was the mutation scanning for both breast cancer genes (BRCA1 and BRCA2). Upon appearance of the gene sequence within the public domain (around 1995) many laboratories individually designed primers to set up the mutation detection for BRCA1 and BRCA2. Evaluation of the tests was preformed in house by simply the fact that mutations were detected. In some countries the laboratories combined forces and decided to use one common set of primers. Only when EMQN provided an EQA scheme for BRCA1 and BRCA2 (also see Chapter 27), it became clear that some laboratories missed specific mutations. Occasionally primers were showing allelic dropout in the PCR because they carried a polymorphic site in their sequence. All French laboratories, that used a commonly agreed upon primer set, failed in the BRCA EQA of 2002 (Mueller et al. 2004). This underlines the importance of EQA, external quality control should be an integral part of quality assessment in the laboratory, thus contributing to maintaining confidence in the reliability of genetic testing among patients and health professionals (Dequeker et al. 2001, Müller, 2001). On top of that now the whole genome is known, a proper test evaluation and validation should be performed prior to diagnostic use, see also Chapter 22 on the IVD. Furthermore, one also should keep in mind that possible population specific genetic differences might be present.

Another example of *ad hoc* introduction of a novel test was the introduction of a new Y-deletion kit by Promega in 1999. This kit was based upon a study by Kent-First et al. (1999) which claimed to have detected a fourth AZF locus (AZFd) involved in male infertility. A diagnostic kit consisting of 4 multiplexes was designed and put on the market claiming the detection of all deletions of regions involved in male infertility: AZFa, AZFb, AZFc and AZFd. In the same year a collaborative effort of the European Academy of Andrology (EAA), Belgian, Dutch, Italian and German molecular genetic laboratories had published guidelines for molecular diagnosis of Y-chromosomal micro deletions (Simoni et al. 1999). This because an earlier EQA in this field had shown that all labs tested different loci with a wide range of PCR based tests and conditions. These guidelines recommend the use of two multiplex reactions to reliably detect all deletions of regions involved in male infertility: AZFa, AZFb and AZFc.

When in 2001 a new Y deletion EQA was organised in a combined effort of the EAA and the EMQN, all laboratories that used the Promega kit failed to detect the AZFa deletion case. From then all laboratories were strongly advised to follow the EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal

micro deletions published again in 2004 (Simoni et al. 2004). These guidelines state that the AZFd locus in it self is not involved in male infertility, only if part of an larger AZFc deletion it will cause infertility. Recent data show that these best practice guidelines can be used in other populations; because also in Chinese men with azoospermia and severe oligozoospermia, the incidence of Y chromosome micro deletions and the frequency of the deletions of the three AZF regions are similar to those described previously in other populations (Li et al. 2008).

The concentred effort of producing uniform guidelines including all test conditions has been very beneficial for the field, and has greatly reduced the number of diagnostic errors caused by technical failure/problems. However, sample mix-up, interpretation or reporting mistakes, still occur and have to be dealt with by the individual laboratories through internal quality control (IQC), or ideally by implementation of a laboratory quality management system and accreditation (ISO151859) (see also Chapter 26).

Evaluation, Validation and Implementation of (Novel) Technologies

In the field of clinical genetics new technologies emerge constantly, some of which appear to have a strong potential for application in genetic testing. However these innovation often are introduced under time pressure, because the workload in the laboratory, the number of genes to be tested, which increase continuously, and the turn around time that should decrease.

Often representatives of companies come along with a new product or kit, and try to convince the laboratory scientist to test it, as this application is said to be better and/or faster than the currently used technology. This practice is common and as it turns out all these new tests, which are "for research purposes only" are being tested for free in many clinical labs and the company is performing their product testing in "the field". Unfortunately, implementation of these novel technologies is often hampered by the lack of complete evaluation of their clinical utility and technical performance in a diagnostic setting. Moreover, the uncoordinated introduction of tests in diagnostic laboratories all using different validation protocols, results in poor consistency in the exchange of technical performance and subsequent validation.

Over the last years molecular diagnostic laboratories have become more professional, in the sense that they have clearly separated patient care and research. In the UK there has been an initiative by the National Health Service to financially support 2 National Genetic Reference Laboratories (NGRL). These laboratories have over the last 5 years evaluated equipment, software and tests for all UK NHS funded diagnostic laboratories.

A EuroGentest (EGT) group (unit 5) has been formed to yearly scan the market by an open call requesting research centres and industry for their promising new diagnostic technologies. In a yearly Satellite workshop at the European Society of Human Genetics Conference the upcoming techniques have been presented. This

has been a great success for 4 years now. After an initial evaluation of the new technology some will be selected for further technical evaluation through one or more EGT laboratories. They will discuss, coordinate; integrate activities required for a complete evaluation. One ore more accredited laboratories will then perform the validation of technology in clinical diagnostic practice. EGT coordinated these activities and choose partners amongst a network of experts, and accredited diagnostic laboratories to ensure accurate and fast evaluation and implementation of new genetic tests.

Over the last 4 years, a series of technologies both existing and new have been or are being evaluated and/or validated for diagnostic use (see Table 1) by EuroGentest (EGT) laboratories (amongst which the 2 NGRLs).

The work involved in the process of evaluation up to diagnostic validation and preparing guidelines is often underestimated. When we, within EGT, started with the evaluation of the High resolution melting curve analysis (HRM), the plan was to evaluate the technology on three platforms (LightScanner from Idaho Technology, USA; RotorGene 6000 from Corbett, Australia and the LightCycler 480 from Roche, Germany) in parallel in three EGT laboratories (Leiden, Prague and Leuven). Soon it became clear the not only the chemicals (kits and/or dyes used) differed but also instruments and the analysis software. We had to split the efforts and choose for a more rigorous evaluation. Leiden had started with the LightScanner from Idaho Technology and fully focused on this for it's diagnostic use in BRCA1 mutation scanning. This implied starting from scratch by rigorously testing and evaluation of all primer sets in their performance in presence of an intercalating dye syber green. In total 58 sets optimal primer pairs were chosen. Idaho Technologies

Table 1 EGT technology, test evaluation/validation

Technique	Company	Coordination	Status, see website[a]
DNA-isolation	Gentra/Autopure	NGRL- Manchester	Implemented
DNA-isolation	Chemagen	EGT – Leuven	Implemented
FraX kit	Abbott	NGRL-Manchester	Implemented
PAP, ffDNA	BioKE	EGT-Leiden	Published Boon et al. (2007)
		NGRL- Manchester	Implemented
MLPA (BRCA1)	MRC-Holand	EGT – Leuven	Implemented
CSCE	ABI	NGRL-Wessex	Evaluated
HRM(BRCA1)	Idaho Technology	EGT- Leiden	Published Guidelines Stoep et al. (2009) Implemented
HRM (BRCA1/2)	Roche	EGT-Leuven	Evaluated
HRM (BRCA1)	Corbett	EGT-Praag/Wurzburg	Implemented
Alamut V1.2	Interactive Bio	NRGR- Manchester	Implemented
SNP-Array	Affymetrics	EGT-Leiden	Published Gijsbers et al. (2009) Implemented

[a] http://www.eurogentest.org/industry/

had to give their input in optimising the melt software so that for each fragment the optimal software setting for analysis was found and could be tested. In total 171 known variants and 197 controls were tested. These efforts lead to the selection of set of 40 HRM primer pairs optimal for HRM analysis of the BRCA1 gene. A selection of 10 of these primer-sets were subsequently tested in two other EGT laboratories (Leuven and Prague) on DNA samples, including 22 wt samples and 27 known variants, this to show reproducibility and inter-laboratory variability and robustness. These primer sets were also tested on different type DNA preparations to show the HRM high robustness in relation to the type DNA isolation protocol used. The final validation was performed on a blind set of 28 samples, which resulted in 100% sensitivity (no false negatives) at an average specificity of 98%, which indication a low false positive rate. Finally also a set of general guidelines for HRM set up was drafted (Stoep et al. 2009)

A second example is the evaluation and diagnostic validation of High-density Single Nucleotide Polymorphism (SNP) genotyping technology. Two different commercially available SNP array platforms were used: the Affymetrix system (GeneChip 262 K *NspI* and the Genechip 238 K *StyI)*, and the Illumina system (HumanHap 300 and HumanCNV 370 BeadChip), to detect copy number variants (CNVs) in a total 318 undiagnosed MR/MCA patients. Both systems and arrays performed equally on a subset of the patients and in 22.6 % of the samples abnormalities were found; including six CNVs, which overlap known micro deletion/duplication syndromes, eight CNVs, which overlap recently described syndromes, 63 potentially pathogenic CNVs (in 52 patients), four copy-number neutral changes, and two mosaic trisomies for an entire chromosome.

This study demonstrates that high density SNP array analysis will reveal a much higher diagnostic yield as that of conventional karyotyping. SNP arrays also have the potential to detect CNVs, mosaics, uniparental disomies (UPD) and loss-of-heterozygosity (LOH), all in one experiment. Furthermore, this study shows that two distinct SNP array platforms from different commercial suppliers can be readily used in a diagnostic setting (Gijsbers et al. 2009).

Up-Coming New Technologies; High-Though-put Sequencing Technologies as Diagnostic Testing Methods

The recently introduced high-throughput whole genome sequencing (WGS) technologies offers the unique opportunity to extend molecular genetic analysis and develop tailor-made medical re-sequencing approaches for molecular genetic diagnosis of heterogeneous genetic disorders. Therefore the focus, for the next few years, will be on high-throughput (also called next-generation) sequencing approaches.

The types of WGS technologies can be separated into two categories: (i) clonal cluster sequencing, and (ii) single molecule sequencing. Single molecule sequencing may require more research and development before it will be commercially interesting. Clonal cluster sequencing is commercially nascent and includes two

methodologies: sequencing by synthesis (Roche/454 and Illumina/Solexa) and sequencing by ligation (Applied Biosystems/Agencourt). Clonal cluster sequencing is not yet applicable to full mammalian genomes because of technical shortcomings such as the unreliable sequencing of homopolymers (a drawback of the sequencing by synthesis approaches), extreme difficulties in the interpretation of all sequence variations identified, as well as a lack of computational power for the interpretation of the huge amounts of sequence data obtained.

Most likely irrespective of the methodology chosen for sequencing some problems have to be tackled; 1st selection of genomic regions or selected genes (so-called mini-genomes) this will need an enrichment step prior to the sequencing process itself. Some technical solutions are ready to be tested such as enrichment by use of a chip approach (e.g. NimbleGene) or use of in liquid enrichment using beads (e.g. Agilent). The 2nd challenge will be to choose suitable analysis software; some new packages have become available allowing the analysis of data from the different methods (e.g SoftGenetics). In total for diagnostic application the upcoming technology does need more applied research before the techniques can be fully validated. Two new EU FP7 research projects have been granted in which amongst research centres also several EGT-partners, (Leiden, Leuven, Nijmegen, Prague etc.) are involved;

NMD-Chip (coordinated by Levy, Marseille) development of Chip based diagnostic testing methods for neuromuscular disorders started October 1st 2008, and TechGene (coordinated by Scheffer, Nijmegen) development of High-throughput diagnostic testing methods, started February 1st 2009.

Although these are research projects, with industry involvement, validation of the technologies is part of the scope. Direct involvement of EGT molecular genetic service laboratories will guarantee translation into a diagnostic product. They will be specifically involved in the coordination and integration of all activities required for complete technical evaluation, validation and subsequent implementation of new technologies into clinical practice.

Compared to the activities of EGT described in the former section, these projects are at the upstream level, and cover technologies that could never be validated with the resources, as they are available among the service laboratories or within the Eurogentest budget.

Concluding Remarks

Over the last decades molecular genetics has grown from research to a full clinical service, simultaneously UK-NEQAS and EMQN initiated and boosted the participation in external quality assessments schemes. In the last 5 years EuroGentest did put emphasis on the laboratory quality management in total; setting up a registration system for diagnostic clinical genetic laboratories documenting their accreditation status and their participation in EQA studies; providing Education to inform both the patients and the health care professionals involved in the testing; and last both

not least in evaluation/implementation of novel technologies. The need for a well structured approach with involvement of accredited genetic testing laboratories, industry and/or research laboratories to perform evaluation/ implementation studies for novel technologies is hopefully clear from this chapter. Continuation of this type of work is desirable, and could be possible if financed on a case-to-case basis. The industry, which needs access to an accredited clinical laboratory setting and to well-characterized clinical samples, and of the diagnostic laboratories, which needs validated tests, guidelines and specific training, could both contribute. Alternatively an independent organisation like the EU or EuroGentest (if continued) could help to set up an infra structure to perform these evaluations paid by the stakeholders.

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Genetic Counselling in Rare Diseases

Helena Kääriäinen

Key Points

- Genetic counselling is a communication process between appropriately trained person(s) and the patient/family members that deals with the occurrence or risk of occurrence of the disease
- Genetic counselling aims at providing full understanding of genetic and other aspects of the disease as well as support for coping and decision making related to the disease.
- Genetic counselling of rare diseases is optimally based on accurate etiologic diagnosis.
- Finding the causative genetic change (e.g. gene mutation) gives a useful tool for carrier testing, prenatal diagnostics and presymptomatic testing in families of the index patient.
- There are thousands of rare diseases (occurrence no more than 5/10,000) and numerous different life situations. Thus it is not possible in this chapter to draft a simple model for an ideal genetic counselling session; instead some of the different situations can be illustrated by examples.

Keywords Genetic counselling · Rare diseases · Pre-test genetic counselling · Post-test genetic counselling

What is Genetic Counselling?

The most widely accepted definition of genetic counselling was originally published by FC Frazer in 1974 and later slightly amended by BB Biesecker and KF Peters in 2001 (Frazer 1974; Biesecker and Peters 2001). Recently, EuroGentest, a five year

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Network of Excellence funded by European Commission (www.eurogentest.org), while creating European recommendations for genetic counselling related to genetic testing, used a slightly modified version of this definition which stands as follows:

"Genetic counselling is a communication process that deals with the occurrence, or risk of occurrence, of a (possibly) genetic disorder in the family. The process involves an attempt by appropriately trained person(s) to help the individual or the family to (1) understand the medical facts of the disorder; (2) appreciate how heredity contributes to the disorder and the risk of recurrence in specified relatives; (3) understand the options for dealing with the risk of recurrence; (4) use this genetic information in a personally meaningful way that promotes health, minimizes psychological distress and increases personal control; (5) choose the course of action which seems appropriate to them in the view of their risk and their family goals, and act in accordance with that decision; and (6) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder."

According to this definition, genetic counselling is a medical act performed by a highly specialized health care professional. It needs specific experience and ample time from the professional. It is also very demanding for the patient or counsellee as he or she is supposed to try to understand complicated medical and biological facts to be able to base future decisions on information that has really been understood. While all this is somewhat idealistic – the counsellor may lack time to go really deeply into the case and the counsellee may be unable to fully understand the message for emotional or intellectual reasons – it is the true aim widely shared in different guidelines and also among the professionals (Rantanen et al. 2008).

The reason for the ambitious goal to assist the counsellee in achieving full understanding of the situation is that the decisions made in connection or after genetic counselling are only sometimes "medical" but instead highly personal involving partnership, family planning, continuing or terminating pregnancy, future prospects related to education and profession etc. Thus such decisions can be made only by the counsellee, even though medical and legal aspects have to be taken into account as well.

Genetic counselling usually starts by the counsellee contacting or being referred to the genetics clinic where some preliminary preparations (asking family history, collecting consents and hospital files from relatives concerned) are usually made before the first visit, which in less complicated cases may remain the only visit to the clinic. The counselling session may take from 30 minutes to some hours. Afterwards, there may be genetic testing or other additional investigations, collecting more family history and, in case of rare diseases, discussion about the case with other colleagues at the clinic or elsewhere. There may be another (or more) counselling session(s), and finally the content of the counselling is summarised in a letter to the counsellee; this usually comprises one or two pages. The letter is sent also to the MDs treating the patient, if the counsellee so wishes. When the counselling concerning the individual is completed, the question of whether to inform the relatives is usually discussed and this may lead to cascade counselling of further family members.

Genetic counselling may be considered expensive, as it is time consuming. However, as an individual or a family does not need genetic services often, the total cost may not become very high. Genetic counselling can save money as it may help to find the correct diagnosis and stop other diagnostic investigations, it may give information for the family which helps them to cope with the situation, and it may help the physician to treat the disease more adequately (Godard et al. 2003a). In several European countries, for intance Nordic countries and UK, genetic counselling is part of public health care and the cost for the patient is very small. In some countries it may be offered also by private health care and the practices may vary.

Rare Disease

In European Union, a disease is defined as rare if it occurs in no more than 5 individuals out of 10,000. Some countries use a more strict definition (1/10,000 in Norway, 2/10,000 in Denmark, www.rarelink.org). In spite of these differences, the aim of picking out rare diseases as a special group is to recognize that this group of diseases needs special joining of forces, within and between national health care organisations, for improving their diagnostics and treatment. The widely used European database Orphanet (www.orpha.net) has information about some 5,717 rare diseases (February 2009), most of which are hereditary.

A rare hereditary disease may be inherited in autosomal recessive, autosomal dominant or X-linked (recessive or dominant) manner. In addition, the inheritance may be mitochondrial or caused by inherited chromosomal changes like translocations. In practice, when a rare disease appears as a sporadic case in the family, the mode of inheritance may remain unresolved. This creates extra challenge for genetic counselling.

In addition to having different modes of inheritance, rare diseases present extreme clinical heterogeneity. Some are severe, even early lethal, while others are well compatible with normal life. Some are easy to diagnose based on clinical features and findings (syndromes with specific features like Rubinstein-Taybi syndrome or diseases with specific biochemical findings like phenylketonuria). Genetic tests are available for a growing number of rare diseases and these may help in reaching a specific etiologic diagnosis. However, there still are numerous rare conditions for which genetic testing is not available either because the gene(s) involved are not known or the genetic background is too heterogeneous for testing in a clinical setting.

How to Reach the Diagnosis in Rare Diseases?

Specific treatment is seldom available for rare genetic diseases. It could be argued that a specific genetic diagnosis is thus not necessary: symptomatic treatment is available even without specific diagnosis.

However, patients and families with rare diseases benefit from a specific diagnosis in many ways. First, reaching the diagnosis makes a stop to the stressful process of trying to find the diagnosis. This often involves several visits to various specialist clinics, imaging and other (expensive) investigations, genetic tests with often prolonged waiting times and a lot of uncertainty and unanswered questions. When the diagnosis is set, both the patient/family and the physician are better equipped to concentrate to organizing the treatment, rehabilitation and follow up for the patient, including evaluating the educational, social and economical needs in the situation.

A specific diagnosis often sets the prognosis which gives a realistic background for planning the future. It also usually resolves the mode of inheritance and may offer possibilities to assess the risk of recurrence of the disease in near family, also for family planning purposes. Sometimes, early detection of other affected individuals may help in preventing the symptoms of the inherited disease, for instance in case of haemochromatosis or hereditary cancers.

As the specific diagnosis of rare diseases is often difficult to make, it makes sense to try to reach it in a most cost-beneficial way. Often, genetic consultation in a specialist clinic may speed up the diagnostic procedure by several months. An experienced clinical geneticist team may recognize the features of a rare disease easily and is usually able to choose the set of diagnostic investigations and tests in a cost-saving way and, in some cases, has the authority to tell that the disease remains for the time being without a specific diagnosis. Some elements of genetic counselling are usually intermingled already in such genetic consultation situations.

The tools that a genetics clinic can offer to diagnose a rare disease are careful clinical evaluation, thorough family history, databases created specifically for diagnosing rare diseases (for instance, London Medical Databases, www.lmdatabases.com), and above all the experienced team.

A genetic test, when available, verifies the diagnosis. In case of rare diseases, however, there has to be a candidate diagnosis and genetic testing is based on that. The test usually involves either a specific mutation, a set of “common” mutations in a certain gene or sequencing the whole gene. Finding a mutation usually confirms the diagnosis while not finding a mutation does not rule it out. Recently, test batteries have been developed which test a wide variety of genes/mutations related to a certain symptom (i.e. retinitis pigmentosa, see www.asperophthalmics.com). At present these, however, are rare and choosing a wise strategy for genetic testing is based on an experienced clinician, usually a clinical geneticist.

When is Genetic Counselling Needed?

Genetic counselling should be regarded as an integral part of the care for rare diseases. Often some information related to genetic counselling takes place integrated into the diagnostic work up. A separate genetic counselling session should be offered always, when either a rare disease has been diagnosed or it has become obvious that a diagnosis will not be reached.

In addition, the need for genetic counselling should be evaluated always when genetic testing is envisaged. Even in these situations, genetic counselling cannot be compulsory; medical acts are very exceptionally compulsory. It should, however, be offered and strongly recommended in most testing situations in the field of rare diseases, as explained below. If an individual insists on having a test without genetic counselling, the medical facts and possible consequences should be discussed by the clinician ordering the test. In these situations, non-genetics health care professionals have a responsibility to recognize their abilities and limitations with regard to provision of genetic services. Furthermore, both genetics and non-genetics health care professionals should not agree to testing without pre-test counselling in circumstances where doing so would go against their professional judgement. (Recommendations for genetic counselling related to genetic testing; www.eurogentest.org).

The need for and organisation of genetic counselling in genetic screening programmes (Javaher et al. 2010) goes beyond the scope of this paper. Briefly, pre-test information and post-test information has to be an integral part of the genetic screening programs, though the extent and content of information in these lower risk situations, and the professionals involved, may vary. In addition to this information, those who are found to be in a high-risk group for a rare disease, as a result of screening, should be offered genetic counselling.

In the following, need for genetic counselling is discussed in relation to situations where genetic testing is being planned due to some reason concerning the patient or his or her family, as genetic testing is the main focus of this book.

Diagnostic Setting

When searching for a diagnosis, several tests may be needed, including blood tests, X-rays and other imaging techniques, biopsies etc. If, for instance, a skeletal X-ray is being planned to reach exact diagnosis in case of a skeletal dysplasia, it generally is not considered necessary to offer extensive information and counselling discussion prior to the X-ray. A diagnostic genetic test can be considered to represent investigations of the same category and pre-test genetic counselling may be clarifying from the patient's point of view but cannot be considered obligatory. Patients should, however, always be aware of what investigations are performed to them and they should consent, usually verbally, to these investigations. Thus they should be told, minimally, what the test is for and what its implications are for the tested and for the family. If the test result is positive and a new diagnosis of a rare disease is established, the patient and the relatives should be offered genetic counselling. Even when the test result is negative, genetic counselling may be indicated.

Predictive Testing

Predictive testing in the field of rare monogenic diseases refers to genetic testing in a healthy high-risk relative for a specific later-onset disorder. The mutation in

the family leads to the disease or a considerably high risk for the disease (like in high risk familial cancers). Genetic counselling in predictive testing of late-onset monogenic diseases is a demanding task and will be discussed in detail in a separate chapter.

Carrier Testing in the Family and Carrier Screening Programs

Carrier testing means a genetic test that detects a gene mutation that will generally have limited or no consequence to the health of that individual. However, it may confer a high risk of disease in the offspring, if inherited, from one parent (in case of X-linked inheritance, autosomal dominant premutation or chromosomal translocation) or in combination with the same or another mutation in the same gene from the other parent (in case of autosomal recessive inheritance).

When a rare genetic disease is diagnosed in an individual, the risk of the disease in near relatives is always discussed in genetic counselling. In case of, for instance, X-linked recessive inheritance, the female relatives may have a high risk of having affected children as the sons of gene carriers have a 50% risk of inheriting the mutation. These female relatives, if informed, usually want genetic testing to verify or rule out their risk and to take it into account in their family planning. Usually, they are approached by a cascade approach where the result of the gene test in one relative is used as a possible indication to contact further relatives. Initially, the family members first inform the relevant (female) relatives and offer them a possibility to contact/be contacted by the genetics clinic. This usually leads to pre-test genetic counselling, possibly a genetic test and consequently post-test counselling where the implications of the test result are being discussed.

In case of autosomal recessive diseases the situation is somewhat different. A gene carrier is not at a high risk of having affected children. Those could be affected only if they inherited a non-functioning gene also from the other parent. As the frequency of gene carriers of rare diseases is usually very low (of the order 1:100 or less) the risk for offspring is generally so small, that one could argue whether active cascade testing can be considered worthwhile. However, if the disease is severe, there may be deep worry of its recurrence in the family and the relatives may insist of having the risk fully ruled out. Where extensive mutation test, enabling almost definite exclusion of recurrence risk, exists, this may be considered in spite of low a priori risk. Even though the testing in this kind of situations is performed to rule out a possible risk, not actually to detect it, genetic counselling before the test is strongly advised to avoid misunderstanding of the test result.

In some populations, certain autosomal recessive mutations may be rather common leading to reasonably high risk for an autosomal recessive disease in the near family and even in the general population. For instance in Cyprus, the frequency of thalassemia carriers is of the order 1:7 which has led to organisation of a nation wide screening program where carrier tests are offered independent of the family history (Godard et al. 2003b). In screening programs the situation differs clearly from the

family based testing as testing is systematically offered to the general population or a part of it (e.g. newborns, young adults, an ethnic group, etc.). Thus the reason for testing is not the worry of the individual but an offer from health care providers. In screening programmes, pre-test information and post-test information has to be an integral part of the program, though the extent and content of information in these lower risk situations, and the professionals involved, may vary. In addition to this information, those who are found to be in a high-risk group, as a result of screening, should be offered genetic counselling.

Sometimes, carriers of genes responsible for a rare disease may themselves be at risk of getting some carrier manifestations. In these situations the testing approaches predictive testing and genetic counselling prior to testing may become more complicated.

Prenatal Diagnosis

If there is high risk for having a severely affected child in a pregnancy, parents may choose to have the diagnosis during early pregnancy. When asking for this, their aim usually is to consider terminating pregnancy in case the fetus would be found to be affected. Legislations concerning induced abortions regulate this field and differ considerably, even within Europe. There are countries in which a pregnancy may be terminated (with permission of a special body) at any week of pregnancy if the fetus is very severely affected while in some other countries this is possible only up to a certain week of pregnancy (often around 20–25 weeks). Sometimes the parents do not intend to terminate the pregnancy but they want to be well prepared for the possible illness of their future child.

The family is identified as a high risk family, in case of rare hereditary diseases, usually by family history which reveals one or more affected individuals in the pedigree and leads to carrier testing of relatives. In case of an autosomal dominant disease in one of the parents, the risk for affected fetus is very high (50%) but the disease is rarely extremely severe as demonstrated by the fact that an affected young adult is planning parenthood. Autosomal recessive and X-linked diseases have a lower recurrence risk in the high risk families (25%) but the severity may vary from mild to extremely difficult, depending on the diagnosis. In case of mitochondrial inheritance, the risk may be up too 100% and the severity of the disease in the future child may be impossible to predict, based on prenatal testing. Each of these situations require their own, individually tailored counselling.

There are different methods to achieve prenatal diagnosis. Some of them are non-invasive (ultrasound, X-ray) while others require invasive taking of a sample (amniotic fluid or placental cells) which creates (a small) risk for termination of the pregnancy. A prenatal test can be performed using the sample, usually it is a genetic test aiming to detecting either a mutation, linked haplotype or chromosomal change. Prenatal diagnostic tests are performed during a pregnancy, where there is increased risk for a certain condition in the foetus. Pre- and post-test genetic

counselling for the prospective parents needs to be offered. The invasive techniques create an extra problem in pre-test counselling as evaluating the risk for an affected child in comparison to the risk for abortion caused by the testing procedure are difficult to explain and comprehend.

Preimplantation Diagnosis

Preimplantation genetic diagnosis (PGD) means testing the presence of a mutation, linked haplotype or chromosomal change in one or two cells of an embryo in a family with a previously known risk for a Mendelian or chromosomal disorder, in order to select the unaffected embryos to be implanted. Pre- and post-test genetic counselling for the prospective parents has to be offered and is often extremely demanding. The couple may feel the situation extremely contradictory as preimplantation genetic testing slightly reduces the likelihood for a pregnancy. PGD should be differentiated from preimplantation genetic screening (PGS), which aims at improved results of infertility treatment in families with no known genetic risks. In case of PGS, reproductive counselling by assisted reproduction professionals is usually appropriate (Soini et al. 2006).

Cystic Fibrosis as an Example

Genetic counselling in case of a severe autosomal recessive disease is chosen to exemplify the complexity of the different situations. This hopefully explains why clinical geneticists are unwilling to writing “cook-books” for genetic counselling in different diseases.

One of the most common among the group of rare diseases is cystic fibrosis. Its incidence is about 1/3,000 leading to estimated prevalence in Europe of about 1/8,000 to 1/10,000. This multisystem disease is caused by alterations in CFTR protein which leads to abnormal exocrine secretion. The secreted mucus in the respiratory tract has abnormal viscosity which leads to obstruction of the narrow respiratory ducts. This in term leads to bacterial infections and chronic lung disease. Similarly, the pancreatic excretion becomes abnormal which disturbs digestion. More rarely, symptoms arise from other organs as well. Treatment of this chronic disease manifesting already in newborns has greatly improved but in spite of that the disease severely affects the individual’s health and even life expectancy (www.orpha.net).

Earlier, the disease was diagnosed in symptomatic infants by measuring the chloride content of sweat. Even today, classic cystic fibrosis can be diagnosed by sweat testing. Diagnostic confirmation in non-classic cases is performed by a diagnostic genetic test.This is, however, complicated by the fact that more than 1,000 different mutations are known in CFTR-gene. The most common is delta F580 –mutation accounting some 70% of the cases, depending on the population. If a diagnostic test

reveals homozygous delta F580 –mutation, the diagnosis of "severe" cystic fibrosis is confirmed. If, however, the other or both mutation(s) are not delta F580, they may be difficult to detect and/or interpret. Some mutations are known to cause clearly milder phenotypes while in case of very rare mutations there may not be sufficient knowledge on their phenotypic correlations.

A diagnostic genetic test can be seen as part of the normal procedure to diagnose (or rule out) the disease in an infant with suspected cystic fibrosis. The family has to be informed about the genetic test (as in case of any tests) but genetic counselling may not always be necessary. Very rarely an exceptional family might not want any diagnosis to their child but would favour symptomatic treatment. Most doctors, on the other hand, would prefer an exact diagnosis for planning of the life-long treatment and rehabilitation. Thus the test may be considered as a self-evident part of the diagnostic procedure.

At some point, the family with a newly diagnosed cystic fibrosis baby will need profound information about the disease. This is important for understanding the cause and prognosis of the disease, the recurrence risk in future children as well as in other branches of the family and to achieve sufficient knowledge for the experience of personal control. This profound information is preferably given in a genetic counselling session. Especially, discussing possible future choices in family planning (e.g. terminating a future pregnancy) is something that the family's paediatrician should possibly not discuss as this may give the fault impression that the birth (and treating) of the present child would be somehow undesirable.

During genetic counselling the risk of carriership in the family is usually discussed. The parents of the index patient may be deeply worried about their other children (usually minors) being also carriers. The consensus in genetic clinics is not to test minors for conditions that need no treatment or other actions during childhood (Borry et al. 2009). In some countries such testing of minors is even forbidden by law. The parents may find this hard to accept as sometimes the uncertainty is considered even worse than disappointing knowledge. Usually this principle of postponing the testing to adulthood is well understood when carefully explained.

Of the other family members, for instance uncles and aunts of the index patient, some may want immediately genetic testing while others may not want to know about their risk of being carriers. Usually the difficult task of explaining the situation preliminarily to them is left to the relatives. In spite of the fact that the risk of finding other carrier couples in the near family is low, the need for the information may be very high.

If a relative, e.g. an aunt, is found to be a carrier as well, her partner may be tested. If he is found not to have delta F580 mutation or one of the other mutations that belong to the mutation testing package used, then his likelihood of being a carrier is very small but not ruled out. Depending on the rules of the health care system, even very wide mutation search may be performed. In practise, finding a mutation clarifies the situation, but not finding any mutation always leaves a theoretical possibility of an undetected mutation. Sometime finding a mutation associated with a phenotype clearly different from that of the index patient (e.g. vas deferens agenesis leading to azoospermia) may further confuse the situation. At worst case, in spite

of a low a priori risk, the worry may become unrealistically high and should be alleviated by skilful genetic counselling.

Sooner or later, there may be a pregnancy or plan for a pregnancy in the family or the other possibly identified risk couples. They may want to discuss preimplantation diagnosis, donated gametes or, more commonly, prenatal diagnosis. Again, genetic counselling pre- and post-testing is needed to help the couple to find decisions that best suit there values and life situation.

How to Organize and Evaluate Genetic Counselling in Rare Diseases?

Independent of the organisation of the health care system, rare diseases need special attention because their rarity creates problems in suspecting and diagnosing them, having the experience for treatment and follow up as well as in genetic counselling of the family and relatives. Diagnostic consultations as well as genetic counselling are tasks that the genetics clinics should be responsible for. In some health care systems, they may also have a role in treatment and follow up of rare diseases.

Genetic counselling is performed by genetics specialists (clinical geneticists and genetic counsellors/nurses) and these exist only in a small number of genetic centres, usually university centres. This leads to the unfortunate fact that, at least in sparsely populated areas, patients, families and counsellees may have to travel long ways to attend a genetic counselling session. The benefits of this kind of organisation, however, outweigh this harm as genetics clinic may thus have larger teams with possibility to share experience and even sub-specialize to a specific field within the clinic (e.g. cancer genetics). At present, a personal counselling session where the patient and counsellor are physically together is preferred to counselling on telephone or other remote methods.

In case of rare genetic diseases, genetic counselling is much easier if the exact diagnosis is known. Even when this is not the case, the probability information is essential. The context and the presentation of the risk information may influence subjective perception of the information and the subsequent decision.

Evaluating the success and quality of genetic counselling is complex not only because of the different approaches to genetic counselling, but also because it is difficult to define adequate outcome measures that are compatible with the aims of genetic counselling. How well do patients recall information? How has genetic counselling altered their plans? How have they in practice chosen to act on the basis of the information received? How satisfied are they with the process of genetic counselling? Have they experienced improvement in perceived personal control? Information, reproductive plans and reproductive behaviour cannot be considered as simple numerical measures of success or effectiveness of genetic counselling. Thus, some argue that a typical audit-approach for assessing the success or effectiveness of genetic counselling is not feasible and could give rise to misleading conclusions. (Godard et al. 2003a).

Based on all this, EuroGentest Unit 3 (Genetic services) has created an instrument for evaluation the quality of genetic counselling which can be applied in self assessment across different systems of genetic healthcare. It was developed in expert group workshops, including patient representatives, and discussed in an open workshop during ESHG Conference 2008. The decision was to emphasize the process instead of the outcome. The instrument consists of a set of standards and potential measurable outcomes for genetic counselling, including items from waiting times and physical clinical environment to access to peer support and continuing professional education, supervision of junior staff, and the actual communication with counsellees. The instrument can be approached at www.eurogentest.org.

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Genetic Counselling for Late-Onset Disorders

Gerry Evers-Kiebooms

Key Points

- Huntingon's disease is used as an example to discuss genetic counselling for autosomal dominant late-onset diseases before and after the availability of genetic testing.
- In the context of predictive testing it is of the utmost importance that a free informed choice is safeguarded. The origin and the practice of a multidisciplinary counselling approach for predictive testing is presented.
- The evaluation of the quality of genetic counselling for late-onset diseases is very difficult. It is suggested to integrate findings of longitudinal studies evaluating the psychological impact of predictive testing in the counselling approach.

Keywords Predictive testing · Huntington's disease · Psychological impact

Introduction

Most late-onset disorders are caused by environmental factors, genetic factors and their interaction. For some of these late-onset multifactorial diseases there exists a small monogenic subgroup and the pathogenic mutations have a high penetrance. This is the case for hereditary breast- and ovarian cancer (HBOC) and hereditary non polyposis colorectal cancer (HNPCC). Genetic counselling for these hereditary cancers is the topic of another chapter in this book.

The present chapter deals with genetic counselling for monogenic late onset diseases with autosomal dominant transmission, mainly neurodegenerative diseases

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that are currently untreatable and for which there usually are no preventive measures to prevent symptoms or to postpone the onset of the disease. The example of Huntington's disease will be used. Nowadays genetic counselling in this context is often related to genetic testing: diagnostic testing in patients with late-onset disease, predictive testing in their symptom free relatives, prenatal testing and preimplantation genetic diagnosis. Long before the availability of genetic testing for autosomal dominant late-onset diseases, individuals and families came for general genetic counselling.

Genetic Counselling Before the Availability of Genetic Tests for Late-Onset Disorders

Genetic counselling has been defined as a communication process which deals with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in the family. This process involves an attempt by one or more appropriately trained persons to help the individual or the family (1) to comprehend the medical facts, including the diagnosis, the probable course of the disorder and the available management; (2) appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives; (3) understand the options for dealing with the risk of recurrence; (4) choose the course of action which seems appropriate to them in view of their risk and their family goals and act in accordance with that decision; (5) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder. All these objectives are relevant in the context of genetic counselling for late-onset disorders. The content of genetic counselling as well as the frequency of genetic counselling sessions is tailored to the needs of those who come for counselling and are ultimately aimed at increasing personal control over the disease and its implications.

Till a few decades ago all persons belonging to families with Huntington's disease (HD) had to live their life without any possibility to know whether they would get the disease later in life or not. At that time a positive pedigree clearly showing the autosomal dominant transmission in a family was essential for establishing the diagnosis. At that time as well as nowadays the construction of a pedigree is a verbal and non-verbal communication process: it does not only allow to confirm the autosomal dominant inheritance of the disease running in the family, but it also gives insight in family dynamics. It gives information about important family events: death, suicide, marriage, divorce, loss… The process of pedigree construction gives insight in the medical, emotional and social impact of the disease and the increased genetic risk over two or more generations. During genetic counselling members of a family with HD do not only receive information about the autosomal dominant transmission but also about their own age specific risk. Notwithstanding the fact that the age specific risk decreases with increasing age, nobody could ever be completely reassured that he or she would never get the disease. As is clear from the definition, genetic counselling is not limited to "a

cognitive banquet of facts". Exploring experiences and feelings related to the hereditary disease, coping styles,... is inherent to the genetic counselling process. The communication of genetic information within the family is discussed as well as the available tools for fulfilling their "messenger role" (brochures, website, ...). In this context additional support by members of the genetic clinic may be offered when needed.

In addition to the fact that the disease of a parent is often perceived as a prefiguration of the own future, one of the dramatic aspects of HD is that at-risk individuals often have children before being informed about their increased risk and are afraid that they already have passed the disease to the next generation. Moreover many young couples are faced with a reproductive dilemma: a strong wish to have children combined with fear of transmitting the disease. Genetic counselling gives them the opportunity to express their feelings of shame, guilt and anxiety. Before the availability of genetic testing couples who wanted to prevent the transmission of HD to the next generation had less options than nowadays: adoption, artificial insemination if the prospective father is at-risk, egg cell donation if the mother is at-risk or refraining from having own children. Because of the high burden of HD many genetic centres paid special attention to genetic counselling for HD before the availability of genetic testing or were involved in supporting family associations for HD and that is still the case nowadays.

Genetic Counselling Related to Predictive Testing

Having a family history with an autosomal dominant late-onset disease means living with a burdensome uncertainty regarding their own future health as well regarding their descendants. Predictive testing for autosomal dominant late onset diseases detects whether the pathogenic mutation – detected in one or more affected family members by means of a diagnostic genetic test – is present or not in asymptomatic relatives and enables one to anticipate with a considerable scientific confidence future specific health risk of an individual. Predictive testing reduces the uncertainty of the tested person. On average half of the test applicants with a parent who has the pathogenic mutation will be informed that they will not get the disease in the future and that there is no risk that their offspring has or will have the mutation. This reassurance is very important. However a lot of uncertainties remain for the carriers of the pathogenic mutation because of the variable age at onset, the variable expression of the mutation or the uncertain efficacy of prevention and treatment, if available. For some late-onset diseases there is an additional source of uncertainty: the reduced penetrance defined as the percentage of persons with a pathogenic mutation who will become affected in the future. A particularly burdensome aspect is the fact that carriers of the pathogenic mutation have a 50% risk of transmitting the mutation to their children. All these uncertainties may be at the origin of hope as well as fear in the context of predictive testing and therefore an adequate counselling approach is needed.

It is of the utmost importance that a real choice about having or not having a predictive test is safeguarded. This choice should be a well-informed, free and personal decision of the test applicant without external pressure. This is the more true for neurodegenerative diseases because there usually is no medical reason to perform this type of test. The availability of predictive tests gives informed people the choice « to know » or « not to know », a decision with important short-, mid- and long-term consequences.

A general framework for organizing information around genetic testing has been presented by Kaut (2006). The multidimensional nature of the genetic context is conceptualized by combining biomedical, individual and socio-cultural characteristics with both immediate and future needs throughout the different phases in the course of a genetic scenario. The general framework was adapted to predictive testing by Mularczyk et al. (2007).

The individual characteristics of the counsellee should be viewed in the context of the family and cultural environment. Being a part of the predictive testing procedure, psychological counselling in the pre- and post-test period is concentrated on emotional support, facilitation of the decision making process and the communication with the family members. Counselling helps the predictive test applicants to process the information cognitively and emotionally.

Several relevant concepts and theories have been used to understand the process and implications of counselling or have served as an inspiration to develop research hypotheses. Evans (2006) and Brouwer-Dudok de Wit et al. (2002) used psychological theories to deepen the understanding of different psychological factors present in the context of predictive testing. Evans (2006) frames genetic counselling by the use of systemic and attachment theory. The family is the context of decision making, therefore it is important to understand the familial beliefs about and attitudes to the genetic disease. The counsellee's ability to control emotions and think about the problem is influenced by the attachment style. Moreover counsellee's but also counsellor's attachment style may impede establishing a secure-base relation between them. Brouwer-Dudok de Wit et al. (2002) analyzed the implications of predictive testing for Huntington's disease within a family life cycle framework. On the basis of different cases they presented how predictive testing and HD may interfere with the transition to the next stage of the family life cycle.

Research in genetic testing has paid much attention to health psychology theories. Gooding et al. (2006) reviewed the relevance of four health psychology theories in the context of uptake and psychological outcomes of genetic testing for adult-onset diseases. Two theories of health behaviour, the Health Belief Model (HBM) and the Theory of Planned Behaviour (TPB), although important in certain cognitive and behavioural domains, have limitations because of omitting the role of emotions. The other health behaviour theories, the Common Sense Model of Self-regulation (CSM) and the Transactional Model of Stress and Coping (TMSC), do not only take into account cognitive appraisal but also emotional issues related to health threats and emotional motivations to take health behaviours. For example in Leventhal's model coping with the health threat generated by cognitive processes and coping with emotional responses to the health threat may lead to different

behavioural reactions. The processes involved in emotional coping may be mutually interfering with or facilitating cognitive processes. Interference occurs if the response motivated by the emotional processes and the actions required to cope with the health threat generated by cognitive processes are incompatible. According to CSM and TMSC theories, the decision to apply for genetic testing is not just a health behaviour but also a way of coping with the stress. They view the stress and coping process as dynamic and consider reappraisal, whereas HBM and TPB ignore the feedback from prior health behaviours. Gooding et al. (2006) come to the conclusion that theories of stress and coping serve as a constructive framework to investigate the uptake and psychological outcomes of genetic testing for the adult-onset diseases.

Genetic Counselling for Predictive Testing for Huntington's Disease: A Model or Valuable Foundation for Other Diseases

When predictive testing for Huntington's disease (HD) became a reality – more than 20 years ago – this was an important milestone and a new challenge for families as well as for genetic counselors and other health care professionals. Because of the particular nature of predictive tests for (currently) untreatable late onset diseases, a large amount of international debate and consultation preceded the implementation of the first predictive tests for HD in clinical practice, initially indirectly by DNA-linkage and since 1993 by direct mutation analysis. Guidelines for predictive testing and counseling were elaborated by the International Huntington Association and the World Federation of Neurology and published in 1994. They were the result of an intense cooperation between families and healthcare professionals that already started shortly after the localization of the Huntington gene on chromosome 4 in 1983. Predictive test protocols in line with the international guidelines have been carefully established because the potential pitfalls were widely recognized before offering predictive testing as a clinical service. The guidelines aimed at protecting test applicants and at assisting clinicians, geneticists, and ethical committees as well as lay organizations to resolve difficulties arising from the application of the test. One of the guidelines precludes predictive testing of children on parental request: this type of test with far reaching consequences should not be carried out until the child has reached legal majority and is capable to make his own free decision. It is essential to respect the child's right not to know. However, some adolescents who are actively requesting HD predictive testing of their own accord pose a difficult dilemma. In this situation, adequate criteria are needed to assess the adolescent's decision making capacities in health issues.

Predictive test requests are often approached by a multidisciplinary team consisting of a clinical geneticist, a psychologist, a neurologist and/or a social worker or genetic nurse. The number of professionals involved may differ from one centre to another. During the pretest counselling sessions, full information is provided on HD and on the predictive test. The role and psychological meaning of the disease and the

test in the course of life of the testee are explored. It is the main aim of the pretest counselling sessions to help people to use sufficient time for reflection, to develop a scenario of their life after a favorable test result, after an unfavorable test result or without having a predictive test, and to make a free informed decision about having or not having a predictive test. After the disclosure of the predictive test result, short- and long-term emotional and social support is systematically provided during follow-up counselling sessions. The partner of the test applicant is encouraged to participate in all pretest and posttest counselling sessions. The number of pretest counselling sessions as well as the posttest follow-up, in particular the long-term follow-up are tailored to the needs of those tested. The multidisciplinary approach for predictive testing for Huntington's disease as outlined in the present chapter is completely in line with the "Recommendations for genetic counselling related to genetic testing" as formulated in the context of Eurogentest Unit 3.

Genetic Counselling for Predictive Testing for Other Autosomal Dominant Late-Onset Diseases

In the meantime the multidisciplinary approach to predictive testing for HD has been used as a model for predictive testing for other late-onset neurodegenerative diseases, such as autosomal dominant spinocerebellar ataxias (SCA), autosomal dominant amyotrophic lateral sclerosis, early-onset hereditary Alzheimer disease, hereditary Fronto-temporal dementia due to the progranulin mutation and other neurodegenerative diseases. It has also been a helpful starting point and valuable foundation for predictive testing for familial adenomatous polyposis (FAP), von Hippel Lindau disease and multiple endocrine neoplasia type 2 (MEN 2).

The increase of demands for cardiogenetic counselling and testing e.g. for hypertrophic cardiomyopathy results in a redefinition of the responsibilities of cardiologists and clinical geneticists. Genetic counselling is highly recommended before genetic testing. Some centres also opt for a multidisciplinary approach for predictive testing including psychologists and/or social workers. The fear of sudden death is the main concern in the context of psychological counselling in families with hereditary heart disease. Counsellees should also be helped to adjust their life-style as part of the risk management strategy.

Closing Comments

It is very difficult to evaluate the quality of genetic counselling related to predictive testing for late-onset disease, because there is discussion about the most appropriate outcome measures. There are instruments to measure parameters that are associated with the quality of genetic counselling (cf Helena Kääriäainen chapter "Genetic Counselling in Rare Diseases" in this book). So far there is no consensus about the way the quality as such can be evaluated.

A possible method to improve the quality of genetic counselling for late-onset disorders is to take into account and integrate the findings of longitudinal studies evaluating the psychological impact of predictive testing in a dynamic way. We refer to Evers-Kiebooms and Denayer (2008) for a short review of the impact of predictive testing on the tested persons and on the family system. Most information is available for HD. Overall getting certainty or being relieved from uncertainty is the most frequent reason to apply for predictive testing. Most quantitative studies did not reveal significant differences between the group of carriers and the group of non-carriers. About 10–15% of both carriers and non-carriers experienced psychological problems. Pre-test distress was a better predictor of post-test distress than the test result. Hypotheses to explain the low incidence of psychological problems are the use of careful protocols for pre-test and post-test counselling and the self-selection of the test participants. But we cannot rule out the hypothesis that the denial of distress by tested persons is also involved. However a recent cross-sectional study in France wherein an interview with a psychiatrist was included in addition to self report questionnaires and psychological tests, revealed depression in more than half of the carriers and also revealed that about one fourth of the non-carriers did not cope well with a favourable result (Gargiulo et al. 2009). Therefore they decided that psychological support is necessary for all testees regardless of the predictive test result.

A striking finding is that the evolution of psychological wellbeing over time is a function of the motives inspiring the application for predictive testing: for those who applied for the test without being able to specify concrete motives or expectations, the test result had a less beneficial effect than for those with specified reasons. In the former group the psychological distress reappeared after some years or even remained high after testing. This has implications for the counselling of this particular group of applicants.

Family planning is one of the major motives for predictive testing in couples at reproductive age. In a European collaborative study assessing the impact of the predictive test result on subsequent reproduction in the period before 2000 a significantly lower number of pregnancies was found in the carrier group as compared to the non carrier group (both with reproductive motives in the pretest period). The most frequently chosen option by carriers of the mutation was “no children”; prenatal diagnosis was the option of a small minority (Evers-Kiebooms et al. 2002). In a recent study of Decruyenaere et al. (2007) with a longer mean follow-up interval more than half of the carriers had chosen to have children with prenatal diagnosis (PD) or preimplantation genetic diagnosis (PGD). Reproductive decision making is complex for persons who received an unfavourable test result as well as for the majority of persons at increased risk for HD who do not apply for predictive testing. This has important implications for genetic counselling in general as well as for counselling related to PD or PGD. The latter should preferably involve genetic counsellors who are also experienced in pre-test and post-test counselling for predictive testing.

One should also keep in mind that the majority of persons at increased risk for HD do not apply for predictive testing. Many of them do not come for genetic

counselling but could certainly benefit from it. The same is true for families wherein the clinical diagnosis Huntington has been recently established by a neurologist and confirmed by a diagnostic DNA-test, in particular when they have little or no experience with HD. More multidisciplinary counselling could be helpful for these tested persons, their partner and their relatives. It also happens regularly that persons with subtile symptoms apply for predictive testing. Usually they get more exhaustive counselling when the "predictive test protocol" is followed. International Guidelines for diagnostic testing would be very helpful.

The psychological impact of predictive testing for other neurodegenerative genetic diseases or for hereditary heart disease is not yet well documented.

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Genetic Counselling for Common Diseases, Cancer Susceptibility as Paradigm

Shirley V. Hodgson

Key Points

- Inherited component of cancer risk may be subdivided into rare, high penetrance genes conferring a strong susceptibility to certain cancers, which may account for about 5% of cases, uncommon, moderately penetrant genes conferring a moderate risk increase, and common polymorphisms which alter disease risk a small amount.
- There are two types of genetic test for a strong inherited cancer susceptibility: a test for a mutation in an affected person (diagnostic) and a test for a known mutation in a family in an unaffected relative (predictive).
- There may be one of three outcomes of a diagnostic genetic test:
  (1) The test may reveal a pathogenic mutation, which explains the disease in the proband and allows genetic tests to be offered to their close relatives.
  (2) The test may not reveal a pathogenic mutation, so no genetic test will be available for close relatives, and no explanation will have been found for the cancer. However, other (probably lower penetrance) predisposing genes could still have contributed to the aetiology of the cancer.
  (3) A sequence change may be detected whose significance may not be clear, necessitating further tests to clarify this. Such variants are not uncommon.
- Genetic counselling for predictive and diagnostic testing follows clear protocols, including pre-test counselling with a discussion of the important consequences and options for management of a mutation carrier, the interpretation of results, and insurance and other relevant issues. The genetic test is followed by a results appointment and post-test counselling and support, as appropriate.
- Genetic testing for moderate risk susceptibility gene mutations are not in common use in the health service because the relative risk conferred is generally insufficient to warrant alterations in clinical management.

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Common disorders generally occur as a result of interacting genetic and environmental factors, and disease susceptibility is multifactorial. However, it is becoming increasingly apparent that in many conditions, such as inherited cancer susceptibility, the inherited component of risk may be subdivided into rare, high penetrance genes conferring a strong susceptibility to certain cancers, such as *BRCA1, BRCA2* and the genes causing Lynch syndrome (Hereditary non-polyposis colon cancer, HNPCC), which may account for about 5% of cases of the cancer, uncommon, moderately penetrant genes conferring a moderate increase in risk (e.g. conferring an odds ratio of 2–2.5), such as *CHEK2* and breast cancer, and common polymorphisms which alter disease risk a small amount (e.g. OR = <1.2) (Stratton and Rahman 2008). The latter are being identified in large case-control studies. (Pharoah et al. 2008). On their own these polymorphisms cannot usefully predict the susceptibility of an individuals to a certain disease, since many genetic and environmental factors will also have a bearing on disease susceptibility, but it is possible that in the future, individuals carrying several high risk variants will be identifiable, in whom the relative risk of a disease could be sufficiently elevated to warrant surveillance and preventative strategies. Thus a panel of such polymorphisms could be used for identifying patients at a significantly increased cancer risk, and offering screening and appropriate prophylactic measures based on such a risk assessment (Pharoah et al. 2008).

Genetic testing is classically for inherited mutations or chromosomal abnormalities which have high penetrance in causing disease. In this context, genetic tests may be divided into two main groups: the first includes tests for disorders which will inevitably develop, and where there is little prophylaxis that can be offered by current conventional therapy, such as Achondroplasia and Huntington's disease, and the second includes tests for genes conferring an inherited susceptibility to specific disorders, for which the paradigm is inherited cancer susceptibility. In the context of inherited cancer susceptibility, the latter group of disorders includes Lynch syndrome (Hereditary non-Polyposis Colorectal Cancer, HNPCC), and hereditary breast/ovarian cancer susceptibility due to inherited mutations in *BRCA1* or *BRCA2*. In these conditions it is not inevitable that an individual carrying a pathogenic mutation will develop cancer, but the probability that they will is significantly increased. There is good evidence that environmental factors influence whether cancer will develop in such individuals, and there are many surveillance and prophylactic options that can be offered to them to reduce their cancer risks.

In most healthcare systems there are thresholds for the risk estimates above which genetic testing for a cancer susceptibility is available in the health service (www.nice.org.uk/pdf/CG014Fullguideline.pdf; http://www.cancer.gov/cancerinfo/pdq/genetics/risk-assessment-and-counseling). The risk of detecting a mutation in a cancer predisposing mutation can be determined from the family history and from features of cancer in the affected individual. Thus early age at diagnosis and a strong family history of the same or related cancers indicates an increased risk of a genetic

predisposition, and certain characteristics of the cancers present are important. Thus, breast cancers with a "triple negative" phenotype (oestrogen and progestogen receptor negative and Her2-neu negative) are more likely to occur in women with germline *BRCA1* mutations, and colorectal cancers which are microsatellite unstable and proximally sited are commoner in Lynch syndrome. There are several computer programmes that can analyse pedigrees and give estimates of the likelihood that there is a mutation in the family (Kelly and Sweet 2007; Antoniou et al. 2008, Hampel et al. 2004), and these, and the "Manchester scoring" system can be used to help select families for mutation testing (Evans et al. 2004; Evans and Lalloo 2002).

Genetic Testing

The genetic counselling process for mendelian high-risk susceptibility gene mutations can be divided into two types of genetic testing situations: "mutation searching" diagnostic tests in an affected individual with a family history and/or other clinical features indicating that they have an increased chance of being a mutation carrier, and predictive testing, where an at-risk individual, who has an affected close relative with a known mutation, is tested to determine whether they have inherited the mutation or not. In the former case, an affected individual may present wishing to be tested because they want to know what the risks are for their children of inheriting a cancer susceptibility, and the test may also be requested because knowing that an individual has a germline susceptibility mutation may alter their management. Thus an affected woman found to carry a pathogenic *BRCA1* or *BRCA2* mutation might opt for more radical breast surgery, or oophorectomy (Weitzel et al. 2003; Tutt and Ashworth 2008), and subtotal colectomy might be recommended for early cancer in individuals with Lynch syndrome.

Cancers in patients who possess germline *BRCA1/2* mutations may be more susceptible to poly(ADP-ribose) polymerase (PARP) inhibitors, as they are unable to repair double strand breaks in DNA in the tumour due to the bi-allelic *BRCA1/2* mutations present in the tumour, and PARP inhibitors reduce the ability to repair DNA by an alternative mechanism. (Ratnam and Low 2007). Tumours with microsatellite instability, as in individuals with Lynch syndrome (caused by germline mutations in genes encoding DNA mismatch repair (MMR) enzymes) have greater resistance to cisplatin and 5-Fluoro-Uracil than MMR proficient patients (Papouli et al. 2004).

For these reasons, testing affected individuals may be performed for management indications, with little pre-test counselling, possibly because of time constraints, and the emotional impact of being informed that they carry a susceptibility mutation might be underestimated in someone already affected with cancer. Some mutation carriers may experience severe guilt feelings because they have handed on the mutation to their children, who may have developed cancer, so pre-test counselling should include a careful exploration of the reasons for having the test, the cancer risks in individuals carrying mutations in the gene tested, and the anticipated

impact of a positive, negative and uncertain result,. The surveillance, prophylactic and treatment options available to mutation carriers should be clearly addressed, and a strategy for management in the event of a positive result clearly outlined prior to testing. It is also helpful to discuss the way in which the results are to be conveyed, to whom, and any confidentiality constraints (Schwartz et al. 2004). Where a positive result was not anticipated, such a result can be unexpectedly upsetting in an affected individual, for instance, in a young woman affected with breast cancer but with no family history of cancer, or in a woman of Askenazi Jewish (AJ) descent with little family history of breast/ovarian cancer, tested for a founder mutation in the *BRCA* genes.

There may be one of three outcomes of a diagnostic genetic test:

(1) The test may reveal a pathogenic mutation, which probably explains the disease in the proband and allows genetic tests to be offered to their close relatives.
(2) The test may not reveal a pathogenic mutation. Where no mutation is detected, no genetic test will be available for close relatives, and no explanation will have been found for the cancer in that individual. However, it does not rule out the possibility that other (probably lower penetrance) cancer predisposing genes contributed to the aetiology of the cancer.
(3) A sequence change may be detected in the gene tested, whose significance may not be clear, necessitating further tests (e.g. segregation of the mutation with disease in the family, loss of the normal allele in tumour tissue, in silico and functional analysis of the variant, consultation with databases of mutations detected in other patients) to clarify this (Goldgar et al. 2004; www.genetests.org). Such variants are not uncommon. There is now a good deal of information available about such polymorphisms on websites, gleaned from the experience of other centres world-wide. In such cases it is important that the tested individual understands these results and their implications. The development of improved methods of mutation testing using sequencing has resulted in the detection of increasing numbers of such polymorphisms, and the uncertain nature of their implications is sometimes very difficult to explain to the individual tested. For this reason it is helpful to mention the possibility of detecting such a variant before the test is initiated. Clearly, when the pathogenicity of a variant is unknown, it cannot be used for predictive testing in the unaffected relatives in that family.

Predictive Tests

Where an unaffected individual presents for genetic risk assessment with a family history of cancer which suggests that there may be a highly penetrant cancer susceptibility gene mutation in the family, it is generally considered inappropriate to test the unaffected individual without knowing whether there is a detectable pathogenic mutation in the family. In order to identify the pathogenic germline

mutation in a family, it is necessary to obtain blood (or tissue) from an affected relative, with informed consent for testing for an inherited cancer susceptibility. The initial approach to this individual should ideally be made by the individual being counselled. It is important that the affected relative understands the nature of the tests being performed, its relevance to their own cancer risks and management, and the possible emotional impact of a positive or negative result. This should usually be achieved by arranging for the individual to be seen in a local genetics centre. When a pathogenic mutation is detected, the affected individual needs to agree to the release of their results to the family to enable predictive testing to be offered to at-risk individuals in that family. Occasionally, difficulties are encountered with this, and the ethical dilemmas involved in deciding whether to release genetic test information to at-risk relatives without the consent of the individual tested (thus breaking confidentiality) are complex. This may be resolved by further discussions with the family, and considering whether the interests of the individual or the family takes priority (McGivern et al. 2004;Costalas et al. 2003; Claes et al. 2003, Hughes et al. 2002, Smith et al. 2002; Sermijn et al. 2004; Daly et al. 2001; Parker and Lucassen 2003).

It is usually recommended that the genetic counselling process for cancer susceptibility predictive testing should follow the same pattern as for predictive genetic testing for disorders such as Huntington's disease, where there is high disease penetrance (Trepanier et al. 2004). It is preferable that a consultand's partner is in agreement with testing. Classically this process involves one or more pre-test sessions, during which the disorder and its inheritance is fully discussed. There should be a detailed explanation of the likelihood that the consultand will have inherited the mutation, the risks associated with carrying the disease –causing mutation, and the screening and prophylactic options available to mutation carriers to reduce their risks of cancer in the case of cancer-predisposing conditions. Issues such as implications for insurance cover, employment, and childbearing should be discussed. The counsellor should also explore how the consultand may react psychologically to either test result, their reasons for wishing to be tested, what they would do if found to have inherited the mutation, and who they would inform of their test results. In some families there are issues of confidentiality and release of information to third parties that should be clearly discussed before undertaking the tests.

Insurance issues with regard to genetic tests are still being debated. Currently, for policies under £500,000 there is a moratorium on insurers requesting genetic test results in the UK until 2014 (www.advisorybodies.doh.gov.uk/genetics/gaic/meetings05.htm). There is a new US state Genetic Information Non-discrimination Act protecting against discrimination against individuals because of their genetic test results.

In some cases, where the consultand is not the first-degree relative of the affected individual in the family, a positive test result in the consultand may indicate that the intervening relative is also a mutation carrier, and it is very important that this possibility is discussed prior to testing. There should be a clear decision about how the intervening relative is to be informed about the result, preferably to include genetic counselling of that individual at the same time as the consultand. In some cases

the consultand may wish to undergo testing and not inform the intervening relative, possibly because they are elderly or infirm, but sometimes because of poor family relationships. This can be a difficult counselling situation. Another counselling conundrum may arise when one member of an identical twin pair wishes to undergo predictive testing. Again, it is preferable that they both receive pre-test counselling at the same time, because the results for both would be expected to be the same.

The pre-test counselling session (or sessions) is usually followed after an interval by a further counselling visit to the clinic, at which time blood is drawn for the test if the individual still wishes to go ahead. The idea is that they will have had some time in the intervening period to reflect on the implications of the test, and will be prepared emotionally for the test results. In some cases, however, the individual wishing to undergo testing may feel that they have already deliberated sufficiently about the test to feel comfortable with going ahead with the test at the first counselling visit. At the time the blood is drawn, the consultand will be told when the results would be expected, and how they will be imparted. Often an arrangement is made for the results appointment at that time. Usually the results are given at a face-to-face meeting in a third counselling session, although in some cases they may be given by telephone or letter. In all sessions it is recommended that the consultand brings a confidant with them with whom they can discuss the implications of the test after the counselling session.

Individuals with a low-risk result may require post-test support because they can suffer from "survivor guilt", particularly if their close relatives have suffered or died from cancer. Individuals who have inherited the mutation should be offered support and a clear protocol for surveillance and possible preventative action. Patient support groups are well established for familial cancer conditions such as retinoblastoma, but other cancer predisposition support groups are less well developed, although there are some for breast and ovarian cancer susceptibility. "Carrier clinics" specifically for carriers of mutations in *BRCA1* and *BRCA2* have been set up in some genetic centres, where such individuals may be seen regularly and management issues can be addressed. Some patient support groups are arising from these. The Hereditary Breast and Ovarian Cancer Foundation (http://www.hboc.ca/) is devoted to women at increased genetic risk of breast and ovarian cancer.

The general rule that predictive testing is usually only performed when the pathogenic mutation in the family is known may sometimes be broken. For instance, where there is a strong family history of disease, e.g. breast cancer, with a high probability of a mutation being present in affected individuals in the family, or in families from certain ethnic groups such as Ashkenazi Jewish (AJ) people, where there is an increased chance of a founder mutation being present, an unaffected individual in the family may be tested in the absence of a known familial mutation. In AJ families, the at-risk individual may be tested for the three founder AJ *BRCA1/BRCA2* mutations only, and the absence of a mutation is reassuring since these mutations are the most likely cause of familial breast/ovarian cancer in individuals from this ethnic group. In such cases, counselling needs to include the implications of a possibly unexpected detection of a mutation, which can be a shock to someone unprepared for such a result. They should also understand that the receipt of a negative mutation

result cannot confidently indicate the absence of the familial genetic susceptibility in the individual tested, since it is not known whether the disease in the family was due to mutations in the gene tested or not. The test could have been, in effect, for the wrong susceptibility gene, and give an unrealistic perception of low risk. Such testing may be offered particularly in cases where the outcome would impact on management (e.g. where the consultand is requesting prophylactic surgery).

Systematic reviews of studies assessing the psychological impact of testing conclude that there is no evidence of adverse psychological outcomes in individuals who undergo predictive genetic testing. Most studies found that the level of distress, anxiety or depression in carriers was not significantly increased after disclosure of their positive result, and that non-carriers experience psychological benefits, such as significant relief, after disclosure of results. (Broadstock et al. 2000; Butow et al. 2003).

The risk of cancer in many predisposing conditions is often not significant until adult life, although this is not always the case (viz. early onset colorectal adenomas and cancer in Familial Adenomatous Polyposis), and cancer can sometimes develop in very young individuals with certain predisposing conditions (e.g. retinoblastoma). In cases where screening and prophylactic measures would not be initiated before adulthood, and genetic testing in childhood for such a susceptibility would not influence management, it is generally considered preferable to avoid testing in children. This is because a positive outcome could generate unnecessary anxiety at a time when no intervention would be advised, and it is argued that it would take away the autonomy of the child to decide whether to be tested or not. It is sometimes difficult to argue this point of view to anxious parents who find the uncertainty without testing very difficult to bear (Harris et al. 2005; Working Party of the Clinical Genetics Society, UK 1994). However, where surveillance would be initiated in childhood, predictive testing for such disorders is advisable in children.

Testing for Lower Penetrance Genetic Variants

Genetic testing for moderate risk susceptibility gene mutations are not in common use in the health service because the relative risk conferred is usually considered insufficient to warrant alterations in clinical management. Genome-wide scans for single nucleotide polymorphisms (SNPs) in large populations of cancer cases and controls have ascertained SNPs which confer a small increased risk of disease (e.g. Tomlinson et al. 2008). This may allow individuals to be typed for a panel of SNPs, which individually may only confer a relative risk of 1.2–1.3 but collectively could cause a small proportion of individuals to have a much more substantial increase in risk. In the case of colorectal cancer for instance, individuals with several such SNPs could have an overall relative risk >3, where colonoscopy screening might be offered. A similar situation is seen in breast cancer susceptibility, where about six common polymorphic loci have been identified in case-control studies, the high risk allele of each conferring odds ratios of <1.2 on average. Women with six high

risk alleles would have a significantly increased risk of breast cancer, and could be offered breast cancer screening earlier than in the general population, and women with several low-risk alleles could be screened from a later age (Pharoah et al. 2008). Such testing has not been clinically validated and is not currently offered in the health service.

Companies offering SNP risk profile services do not routinely offer pre- and post-test counselling and explanation of the results. Thus individuals informed that they possess a single SNP conferring increased disease risk may wrongly perceive this to be substantial, and may be unaware that the information does not take account of all other predictive factors (including other polymorphic loci, family history, and mutations in high-penetrance genes). Alternatively, one low risk SNP result could lead to false reassurance and risk-taking behaviour. Unregulated testing could lead to an increased workload for primary care practitioners, as patients may present requesting explanation of the results of the test, and access to further diagnostic testing.

Conclusions

Genetic testing for cancer susceptibility is a paradigm for testing for susceptibility to other common diseases. Such testing will become increasingly important as we understand more about the complex interplay of rare high penetrance gene mutations, uncommon variants of moderate penetrance, common low-penetrance variants and environmental and lifestyle factors in the causation of common diseases. The development of strategies for genetic counselling for such disease should take account of the importance of environmental risk factors and avoid the pitfall of genetic determinism. The provision of balanced information about the predictive value of different tests is extremely important, both for the wide variety of healthcare professionals who will be required to interpret test results, and for the individuals taking the tests.

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Genetic Counselling in Disorders of Low Penetrance

Christine Patch

Key Points

- Some aspects of genetic health care (non-directive counselling, risk assessment and practical and emotional adjustment to the disorder) are unchanged by the explosion in genetic knowledge.
- Three complex disorders: haemochromatosis, neural tube defects, schizophrenia, and their genetic counselling implications are discussed.
- The role of genetic services in genetic susceptibility testing is less clear.
- Accurate diagnosis, the ability to communicate the risk and precise risk estimation will remain important.

Keywords Genetic counselling · Susceptibility testing · Genetic tests

Development of Genetic Counselling

Genetic counselling is a relatively new field in health care, in the UK the first dedicated genetics clinic was established 1946. Models of delivery of genetic care vary across countries and jurisdictions, however increasingly non-medically qualified professionals are employed to deliver care in multidisciplinary teams. These may include genetic counsellors, nurses, psychologists or social workers. The development of genetic counsellors as a separate profession is recent but numbers are growing. There are Masters level programmes in many countries and a number of professional societies and registration boards. Although there is a large overlap between the roles of the medically and non-medically qualified members of the team

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the medically qualified practitioners will of course have the major role in diagnosis and treatment (Skirton et al. 2005).Traditionally the field of concern for genetic clinics has been rare syndromes which may or may not have a hereditary component, conditions where the primary aetiology is a single highly penetrant gene and identification of the subsets of common diseases caused by single genes. These situations have been discussed in more detail in previous chapters.

Although some of the expectations of the genomic revolution have been shown to have been unrealistic there has been an expansion of knowledge which has identified genomic risk factors and genes of low penetrance for common diseases. The role of genetic health services in counselling for these conditions is not yet clear. Much of the discussion to date has clustered around the genetic services associated with DNA based testing for these conditions (Khoury et al. 2008).

Evaluation of Genetic Tests

There is an emerging consensus on the necessity of considering clinical and scientific validity of tests as well as their usefulness in a clinical pathway before bringing them into use. There is still a debate as to the necessity for formal genetic counselling in these cases. It is suggested that there is no clear difference between genetic and non-genetic tests as the purpose for which the test is being used and the potential implications should define the components of the information and counselling that are provided. For example in the case of susceptibility testing for an increased or decreased risk of a condition in a healthy individual, it is rarely the case that the relative risk or familial implications would be so high that pre and post test counselling would be required. This of course is contrast to tests for single gene disorders such as Huntingtons disease where there is a consensus that full pre and post test counselling is necessary. This should be provided by a properly qualified individual according to professional norms. In a similar fashion to the first example, testing for a genetic susceptibility for adverse drug reactions or for the efficacy of a drug treatment in an individual with a given genotype will be ordered mainly by specialists other than clinical geneticists. The need for care by a genetic specialist may depend on whether the results have other implications than the decisions about the drug treatment for the person tested and his/her near relatives (Eurogentest 2009).

As is suggested in the previous paragraphs the debate around the role of genetic health services has been concerned with the use of genetic tests for health purposes. There is a burgeoning literature relating to the evaluation of genetic tests and the evidence required before tests are introduced into practice (Melzer et al. 2008). This is also discussed elsewhere in this book.

There should be a separation of evaluation of the analytical validity or the accuracy of the assay that forms the test from its clinical validity and utility. That is the relationship of the test result to the clinical outcome and the usefulness of the test result in a clinical pathway is different from its analytical accuracy. The evidence of

an association between a single or group of genetic markers and a health outcome may well only contain information on a small proportion of the genetic variation associated with that clinical outcome. This may have insufficient predictive value to provide useful health related information. Therefore even if the DNA analysis measures the polymorphism accurately it may have no clinical validity in terms of predicting a diagnosis or health state. There is considerable debate surrounding the level of scientific evidence from gene disease association studies that is necessary before tests based on those findings are developed and marketed (Janssens et al. 2008).

In order to assess the usefulness or clinical utility of a test the purpose of the test must be defined (Burke et al. 2007). The assessment of purpose will also help define the role of genetic health services in the delivery of the tests. Health services are generally directed towards reducing morbidity and mortality. However in the delivery of genetic health services a test result may provide information for personal decision making or simply knowledge about potential future health status without there necessarily being any action or therapy that is proven to ameliorate the outcome apart from the normal public health messages of taking more exercise, stopping smoking, eating a healthy diet etc.

Genetic Counselling in Disorders of Low Penetrance and Common Complex Diseases

One view of the role of genetic counselling in low penetrant disorders may be that there is no role and that it should not be the concern of specialist genetic health services. However definitions of genetic counselling do not define its domain very clearly. As detailed in Chapter "Genetic counselling in rare diseases" they tend to focus on the supportive and information giving element of the interaction between counsellor and client rather than the penetrance of the condition or relative risk of the condition. One widely accepted definition of genetic counselling is given below:

> Genetic counselling is a communication process that deals with the occurrence, or risk of occurrence, of a (possibly) genetic disorder in the family. The process involves an attempt by appropriately trained person(s) to help the individual or the family to (1) understand the medical facts of the disorder; (2) appreciate how heredity contributes to the disorder and the risk of recurrence in specified relatives; (3) understand the options for dealing with the risk of recurrence; (4) use this genetic information in a personally meaningful way that promotes health, minimizes psychological distress and increases personal control; (5) choose the course of action which seems appropriate to them in the view of their risk and their family goals, and act in accordance with that decision; and (6) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder (Eurogentest 2009).

Genetic counselling should always be based on a diagnosis that is as accurate as possible. This increasingly involves interpretation of complex genetic analyses. The activities that take place within a counselling session include:

Taking a family medical history which is necessary to provide reliable information.

Giving and interpreting genetic information with skill, presenting it in a non-judgmental way.

Supporting the patient or client particularly when they are making difficult decisions or at times of stress related to their genetic issues.

Three clinical scenarios will be used as examples to attempt to explore these issues in the context of low penetrant disorders, genetic counselling for the recurrence of a pregnancy with a neural tube defect, haemochromatosis and schizophrenia.

Neural Tube Defects and Genetic Counselling

Neural tube defects (NTD) have an incidence of approximately 1/1,000 in North American populations however the incidence is not constant over geographical area or time. The most common neural tube defects are:

Anencephaly or failure of closure of the rostral end of the neural tube leading to total or partial absence of the cerebral hemisphere and cranial vault.

Myelomeningocele, which is a failure of closure of the neural tube at the level of the vertebral column. The ranges of physical disabilities and effects may range from none to lifelong problems which depends on the location of the defect and the subsequent neurological damage.

While the appearance and effects of spina bifida and anencephaly differ, they are considered to be different manifestations of the same type of malformation, and are grouped under the term neural tube defect. Neural tube defects may form part of the spectrum of abnormalities associated with some rare single gene conditions such as Meckel syndrome or chromosome abnormalities such as trisomy 13 or 18 suggesting a genetic component. In the absence of a recognised syndrome, empirical data indicates that couples who have one child with a NTD are at greater risk of having a second child with a NTD than other couples in the general population. Following the diagnosis of one child with a NTD, the risk of NTD in each subsequent pregnancy for that couple is about 4%. However, the risk can be lowered to about 1% by maternal folic acid supplements. The mechanism by which folic acid has its effect is not clear and genetic factors may be important. Other environmental risk factors that are associated with an increased risk of neural tube defects include maternal diabetes and maternal teratogens such as anti-epileptic medication also give a risk of neural tube defects (De et al. 2006, Padmanabhan 2006).

Although non-syndromic neural tube defects are used as an exemplar of mutifactorial inheritance, counselling couples for recurrence risk has traditionally comprised part of the practice of genetic counselling services. The role of the genetic counsellor in partnership with the medical practitioner in this situation is as outlined above i.e. taking a clear family history, establishing if the congenital abnormality is part of a syndrome or is isolated, giving information on the recurrence risk based

on empiric data, supporting the couple in their decision making about future pregnancies and giving evidence based advice on actions that will reduce the recurrence risk.

The example of neural tube defects is used to illustrate that genetic services have traditionally had a role in counselling for recurrence risk where the aetiology is complex and the underlying mutifactorial and the genetic factors are not yet clearly elucidated. As outlined above it is clear there remains a role for genetic counselling according to the definitions previously given. Part of the rationale for this relates to the emphasis in the management of families on counselling for future reproductive decisions. This has traditionally been a domain of specialist genetic health services with an emphasis on non-directiveness and informed decision making.

Haemochromatosis

HFE related hereditary haemochromatosis (HHC) results from a genetic disorder of iron metabolism which leads to excessive intestinal absorption of iron and a progressive abnormal deposition of iron in the liver, heart, pancreas and other vital organs. Treatment is possible and effective by removing excess iron through venesection i.e. depletion of body iron by removing blood from the patient at regular intervals. Evidence for the benefits of treatment comes from observational studies which suggest that removing excess iron before organ damage restores normal life expectancy. The gene for HFE related haemochromatosis (HHC) was identified in 1996 which lead to a re-evaluation of the role of the genetic testing in both diagnosis and case identification. The carrier frequency is high in populations of Northern Europe as is the prevalence of homozygosity, however the disease itself remains rare (Bryant et al. 2008).

Some of the debate about genetic testing in HHC has centred on the penetrance of the gene mutations, that is, the probability that a person with two gene mutations will develop clinical consequences – disease. Claims have been made stating that the penetrance may be less than one percent (Waalen et al. 2005). This is in contrast to the 40% penetrance in male relatives of affected individuals reported in earlier studies. It is likely that a range of factors, many of which are unknown, determine the extent to which the phenotype is observed in a particular individual.

There is agreement that the clinical condition of haemochromatosis is the end result of a combination of genetic and environmental factors, not all of which have been described. The mutations associated with a risk of HHC are very common and therefore whilst they are a good diagnostic indicator in those already suspected of having haemochromatosis or in the context of family testing they are not useful for screening at the population level (Wood 2009).

Current clinical guidelines recommend family testing (Adams et al. 2000). However there is a lack of consensus as to which speciality undertakes this role and whether it is the role of genetic services. There is consensus that accurate evaluation of the risk of developing iron overload for any individual with a family history

depends on both the genetic status and the iron status and family cascade screening would appear to be a cost effective strategy for identifying cases for treatment.

HFE related haemochromatosis may be considered a complex disorder with a major recessively inherited genetic risk factor. A useful role of genetic health services may be to assist in interpretation of the laboratory results and also in family testing and cascade screening for relatives of affected individuals. HHC can be used to provide a clear example of how the purpose of a test defines it usefulness. Because the gene frequency is so high and the penetrance in the general population is low the genetic test is not considered useful in population screening however it is useful within a familial context and for diagnosis in suspected cases.

Schizophrenia

Schizophrenia is a complex disorder whose aetiology involves interactions between genetic and environmental risk factors. The heritability of schizophrenia is estimated to be in the range of 60–85%.The lifetime risk for schizophrenia, in most populations, is approximately 1% with the usual age of onset being between 16 and 30 years. It is therefore a major health problem.

One significant risk factor for developing schizophrenia is a positive family history. The relative risk (RR) to a first-degree relative of an affected individual is about 10 times the population risk, and the risk to the monozygotic twin of an affected individual is increased by approximately 50-fold. Risks for related disorders where psychosis may be a component also are elevated in families where an individual has schizophrenia as is depression in close relatives (Austin and Peay 2006). The description of the phenotype of schizophrenia is currently under discussion with results from genome research initiating a debate as to relevance of the diagnostic categories in psychiatric disorders.

Discoveries based on Mendelian genetics raised expectations that single genes would be identified as causal agents in schizophrenia and other psychiatric disorders. Although a few single genes for schizophrenia have been identified through the investigation of rare chromosome disorders, mutations of these genes in cohorts of patients are infrequent, indicating that they are not common risk factors for this disease. Association studies have suggested a large number of candidate susceptibility genes (Harrison and Weinberger 2005) Even though other susceptibility genes are expected to be identified in the near future, recent studies indicate that individual, rare, highly penetrant genetic variation may be just as relevant as the common variant of low susceptibility. More recently interest has been raised by the suggestion that copy number variation may also be significant indicating that rare recurrent CNV's are associated with schizophrenia (International Schizophrenia Consortium 2008). At the present time the findings from genome wide studies require careful interpretation and independent validation. The interpretation of results will crucially depend on the clinical and genetic definition of schizophrenia.

Currently, the risk of morbidity in schizophrenia is an empirical estimation based on the diagnoses in other family members and analysis of the family tree.

Genetic counsellors use estimates of risk, based on published reviews averaging epidemiological data from several studies, in order to try and inform families of the likelihood of the disease developing. Various commentators have suggested that although genetic counselling in psychiatric disorders is at present a rare activity, that potentially this may increase (Lyus 2007). Although it might be assumed that genetic counselling is only indicated if there are highly predictive genetic tests it is clear that risk prediction in schizophrenia will be an empiric assessment taking into account much epidemiological and personal data. There is interest amongst patients, their families and health professionals in risk assessment in psychiatric disorders although there are also ethical and social concerns (Austin 2005).

Accurate risk prediction in psychiatric disorders of complex aetiology such as schizophrenia is clearly at an early stage and with the current state of knowledge does not include genetic information. If, as some commentators suggest, there is a demand for information then genetic health services need to consider how to meet that demand in a clinically appropriate and ethically sensitive way. The basic principles of genetic counselling would still apply as outlined earlier.

From Research Into Clinical Use

The process of translation of scientific discovery to individual and patient benefit is commonly structured as a continuum. Khoury and authors outline a four phase model of translational research in genomic medicine (Khoury et al. 2007).

T1 scientific discovery to candidate health applications
T2 development from health application to evidence based guidelines
T3 translation of evidence based guidelines into health practice
T4 assessment of how those guidelines impact on population and individual health.

The majority of genomic research to date has focused on gene discovery and, in terms of translational research, methods for standardising the conduct and reporting of meta-analysis and systematic reviews of gene disease association studies have been a recent development. T2 research in genomics is currently focused on the development of new genetic tests in clinical practice. This may also include family history tools. This means translational research is still in its infancy.

This very systematic approach to developing health related applications from genomic research may however be in the process of being overturned with the advent of direct-to-consumer tests. Although there are no tests (to date) for schizophrenia some test panels do offer haemochromatosis testing and also analysis of polymorphisms in the MHTFR genes as part of a cardiac risk assessment. With the advent of these companies there is a potential shift towards individuals becoming managers of their own health information in a very personal way. There is much debate as to the appropriate regulatory and policy response with the focus

being on quality assurance of laboratories and procedures, appropriate information and advice and appropriate risk based assessment before marketing (Goddard et al. 2009, Human Genetics Commission 2008). How this model of provision will affect the development of genetic health services in the future is unknown.

Conclusion

In some ways the provision of genetic health services in the area of disorders of low penetrance is unchanged by the advances in the science. In the example of neural tube defects the emphasis is on non-directive counselling to enable reproductive decision making. In the example of haemochromatosis although the focus may be on appropriate case identification to initiate treatment the practical and emotional issues of extended family testing are familiar to those in genetic practice.

It is in the broader area of genetic susceptibility testing where the future is less clear and the role of specialist health care providers less certain. However what is certain is that there will remain a necessity for accurate diagnosis, the ability to communicate the risk in an appropriate and knowledgeable way and precise risk estimation whether these are based on empiric integration of multiple factors or risk estimation based on genomic analysis.

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Patient Perspectives on Genetic Testing

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Key Points

- For patients and families an accurate, timely diagnosis is key to understanding the situation in which they find themselves.
- Effective ethical genetic services deliver not just a diagnosis but also the information and support necessary for making informed decisions and making plans.
- The planning and development of genetic services must incorporate patient and family inputs if it is to focus on those aspects of genetic diseases that are of greatest significance to those affected.
- Regulation and legislation controlling the development and operation of clinical genetics in medicine must be appropriate and proportionate to the risks and benefits to be secured.

Introduction

Estimates vary as to the number of diseases and disorders attributable to a genetic cause, but an often quoted figure is in excess of 5-6000 http://www.ncbi.nlm.nih.gov/omim.While it remains the case that the vast majority of these conditions remain incurable, and that medical management of these affected is limited to palliative care and the treatment of symptoms, nevertheless the establishment of an accurate diagnosis remains of great importance to patients and to the families of those affected. Nevertheless genetic testing has over the past 10 years enabled far greater number of accurate diagnoses to be achieved.

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In those cases where interventions exist that will alter the course of the disease or condition the importance of an accurate diagnosis is self evident. A missed or misdiagnosis in these cases represents a lost opportunity, and allows the perpetuation of harm that might otherwise have been mitigated or even prevented. But accurate diagnosis can be no less important in those situations where no therapeutic intervention is yet possible. Knowing what has happened, and why, allows individuals and families to understand their situation, to inform themselves about their future prospects, to plan, and to make knowledge-based decisions to the extent that they wish and feel able to. This allows them to contact others in a similar situation, sharing experiences and practical advice and support where possible. It also helps to ensure that other (non-medical) services, such as those provided by Education and Social Care Agencies are able to make appropriate and timely inputs. All this allows those affected and their families to gain and retain a degree of control over their lives to the fullest extent possible, given their situation, the impact of their condition and the limitations it necessarily imposes on them.

Statham et al (2008, in Preparation) reporting the outcomes of the GOLD (Genetics of Learning Disability) study, comments that "having an explanation of what was going on within the family is more than just getting a diagnosis". This relates to the understanding of what was happening within the extended family, where a family gene had originated, how it worked and what the prognosis might be. Many respondents used words such as "why", "answers", and "information" (Haddow and Palomaki 2003).

Most health care systems in developed economies are based on the notion of solidarity. Interventions are provided on the basis of the need and out of a sense of our shared humanity, rather than as a consequence of the ability to pay, or other non-medical factors. The notion of equality is a strong ethical principle underpinning the provision of health care. For families with genetic conditions, the fact that "their" disease or disorder may be rare, difficult, perhaps expensive to diagnose, and requiring expertise available in perhaps only one to two laboratories in Europe, should not be an insurmountable barrier to a diagnosis.

If the rhetoric of a "needs-based" healthcare system is to be underpinned by the reality of timely, appropriate patient and family–friendly care, then benchmarks for evaluation need to be put in place. One such benchmark is the extent to which those with genetic conditions feel confident of benefiting from interventions that may be possible, rather than perceive that they may be seen as too difficult, too expensive or too unusual to warrant the investment of clinical time, energy and resources to sort out what could and should be done.

Feeling confident that accurate health care is a realistic right for those with genetic conditions also helps to endorse the trust and confidence of citizens and taxpayers that their expectations for care and support will be met, should they (or a family member) find themselves in need. It is also important, in the current climate where "patient choice" and "patient-centred health care" are both used by politicians as mantras to demonstrate their sensitivity to the importance that we all attach to health care, to use these concepts, and develop them into tools which will empower patients, enabling them to engage with clinicians and others as partners. This is the

case particularly with chronic genetic conditions, where there is no right answer, no quick fix, and charting a way ahead often means reaching a consensus as to the "least worst" rather than the "best possible" outcome. After all, few would opt to be affected by an intractable, life limiting genetic condition about which little is known and even less can be done. For those in situations such as this, a timely diagnosis, sensitively delivered with appropriate information, advice and support on hand, is often the start to the business of getting on with life, and not letting your existence be defined by your condition more than is absolutely necessary.

Patient Expectations of Genetic Service

Most patients and families will assume, when seeing a geneticist or a genetic counsellor to investigate the possible existence of a genetic 'problem', that the professional has the skills, knowledge, and competence to provide a proper professional service. They will also assume that the service infrastructure underpinning their clinical encounter is fit for purpose and properly resourced. While some patients may want to understand precisely how the information leading to their diagnosis is assembled – feeling this to be an important part of the process of assimilating this into their future expectations – others will take on trust that the assays used to establish the presence or absence of genetic changes resulting in disease are appropriate, and that the results are communicated to the clinician from the lab in a format that allows the correct interpretation of the risks and outcomes. This trust thus places a particular onus on those planning services to ensure that they are fit for purpose. This extends from the selection of the assays used to detect genetic changes (taking account of ethnic variations in the pattern of mutations in a given disease gene for example), to putting in place quality assurance systems to ensure that results are communicated and interpreted accurately and consistently. This will put the geneticist or genetic counsellor in a position where he or she can deliver accurate news to patients and families in a coherent, understandable manner, maximising the opportunity for patient benefit.

Once a diagnosis has been arrived at, patients will expect to be able to access information, advice and support that are potentially multi-layered in this structure and its complexity. Whilst some may be content to be relatively passive, trusting their doctor to do what is right, others will need to be much more active in understanding and planning what might happen, what can be done about it, and what needs to be done in order to make sure that the likelihood of plans being put into effect is maximised.

In these situations where an accurate diagnosis cannot be made, it is still important that families have access to appropriate clinical care. Contact with a clinical genetics service can help to ensure that individuals and families can be kept in touch with advancing medical knowledge, so that a diagnosis can possibly/potentially be made at a later date. It can also help to ensure that families can access the relevant social and educational support needed in a timely and accessible manner.

Most genetic diseases are complex, multisystem disorders. The organisation of care and support that reflects scientific possibility and best clinical practices, often involves planned intervention from a range of difficult clinical specialities, ideally in a logical, timely fashion designed to maximise health gain. However, anecdotal evidence would indicate that this is not always the case, and the services provided to families with rare genetic conditions are often partial, delayed and confusing. Families expect that clinical professionals will communicate with one another, and would like to see someone, probably the clinical geneticist, taking on the role of "ringmaster" – coordinating the order and timing of other clinicians' inputs to the best advantage for all concerned. Such a development would see efficient use being made of scarce clinical expertise, maximising patient benefit and delivering cost effective and clinically effective health care.

Such developments need not be expensive. As the Genetic Interest Group has shown in its 'Family Route Map' project (GIG 2008), patient support groups and interested clinicians can work together to develop sensible, feasible and user-friendly plans for optimizing care and support even in very rare conditions. If this can be accomplished in very rare conditions, how much more should it be possible for those with more common ones?

This integration of services, and the importance of appointing a "ringmaster" to oversee this, becomes increasingly urgent as possibilities for intervention in genetic diseases and of the need to provide support in a holistic manner continues to lag behind the leading edge of knowledge. As a result, this makes access to high quality care for patients dependent on well-planned systems, acting in support of clinical judgement and professionalism.

Patient Centred Service Development

Patients, families and their support organisations are well able to play a role in determining what their needs are, and how best to respond to them, as two recent projects have demonstrated.

Eurogentest

The EuroGentest project is a European Network of Excellence (contract no. FP6-512148-2004) which is encouraging the harmonization of standards and practice in all aspects of genetic testing across Europe. One of the main aims of the project is to develop accessible and informative information for patients and families about genetic testing. In order to ensure that the information developed is information that patients require, and not information that doctors think that patients require, research with patients and families to determine their information needs has been of paramount importance. A group of patient 'experts', made up of patient group representatives from across the EU, have played a fundamental role in determining

what information needs to be developed, and have inputted into the content of that information. The expert group have also ensured that this information focuses on the psychological and social aspects of genetic testing, as well as the core science. This is because so much of the material patients and families currently receive, particularly through the genetic clinic, fails to discuss this important aspect of genetics. Signposting towards good quality information sources and patient support groups is also key in providing good quality information. Through patient groups, families can be put in touch with other families, receive honest information and support, and can be directed towards social and educational services.

A series of eleven information leaflets have already been developed with the help of the EuroGentest 'expert' group and the series is currently being expanded. To ensure that this information is available to patients and families throughout Europe and beyond, translations into numerous languages (hopefully as many as twenty) is currently underway. These translations are being carried out by bilingual genetics students and genetic health professionals. This is to guarantee that the translations are of good quality, and that the medical explanations are clear and correct. Through initiatives like EuroGentest, high quality genetic testing information should soon be available to all who need it.

Eurogenguide

Eurogenguide is complementary to the larger Network of Excellence, EuroGentest. EuroGenGuide was devised in order to encourage patients to take the lead in decisions about their treatment, rather than being just passive recipients of what their doctor thinks is in their best interests in the narrow and purely medical sense. Taking a genetic test, or agreeing to allow samples taken from you to be used in research, are big decisions. In view of this it is crucial that individuals can make choices that they are happy with and to which they have freely given their consent. This notion of 'informed consent' is the central theme of the guide, and informs the nature and tone of the material contained within it.

EuroGenGuide is a two-part 'consumer manual' which will provide information about genetic testing, counselling and research across Europe. One half of the guide contains information written with the lay reader in mind and is aimed at patients, their relatives and carers, and also members of the public who may not be patients but who are considering donating biological samples to a DNA bank for research. The other half of EuroGenGuide consists of educational guidelines for health professionals. Both sets of information outline the kinds issues that are relevant to patients when they are taking a genetic test or participating in research, and this is especially important for those countries in Europe that do not currently recognise genetics as a distinct medical specialty.

As Europe becomes more closely integrated, and movement across the continent becomes easier, and as genetic technology continues to generate new tests and therapies, there should be fewer geographical or economical hindrances to being able to access treatments. However, treatments are of no use unless knowledge of them

can be channelled into those areas where it is currently lacking. The two halves of EuroGenGuide will form a complementary whole that will help to ensure that health professionals are educated about genetics, and patients can exert more control over their futures in being able to make informed decisions about taking advantage of the fruits of new genetic technology. Ultimately, it is hoped that in showing the potential benefits to health that can be achieved by European citizens in their choosing to find out about genetics and participate in research, new tests and therapies will continue to be developed and patients will be in a better position to act autonomously, fully understanding the issues that they are faced with.

Professional Development

In a fast changing arena of medical possibilities underpinned by rapid scientific and technological progress, a significant barrier to the implementation of new knowledge in clinical service delivery can be the lack of opportunity for systematic Continuing Medical Education (CME) or Continuing Professional Development (CPD). Both Eurogentest and Eurogenguide have addressed this issue, and in addition to the development of accessible, user friendly information for patients and families they have introduced opportunities for CME/CPD for clinicians and others involved to undergo appropriate education to acquire the relevant skills and knowledge.

EuroGentest have been working to identify minimum levels of competence for health professionals in Europe. The aim has been to develop competences that enable genetics education to be grounded in clinical contexts that are meaningful to learners, and that provide the basis for development of learning outcomes, and curricula for health professionals in primary, secondary and tertiary care settings.

These developments have also been parrelled by national initiatives such as the UK's National Genetics Education and Development Centre (NGEDC). The NGEDC is developing targeted programmes of education for different professionals including Medical Practitioners, Nurses, Pharmacists and Dieticians (NGEDC 2008).

Fitness for Purpose

The regulation of genetic tests as diagnostic devices (when marketed as commercial products) falls within the remit of the European Union's In-vitro Diagnostic Directive (98/79/EC). The focus of this legislation is on technical accuracy, and the level of scrutiny applied to claims made about this relates to an assessment of any harm to the patient arising from the procedure. Because genetic tests require the taking of a blood sample, or a cheek swab, they tend to be regarded as low risk procedures, and as such the regulatory framework relies mainly on self-reported data provided by the manufacturer. Most genetic tests do not use commercial kits but reply on in-house procedures in hospital molecular genetics laboratories. Quality

control rests on the accreditation of the laboratories concerned under a scheme such as National External Quality Assurance Scheme (NEQAS), in Europe, or Clinical Laboratory Improvement Amendments CLIA in the USA. Like the IVD directive, the focus is mainly on technical adequacy (i.e. does the test measure what is says it measures accurately?). However simply because something *can* be measured is not sufficient to justify that it *should* be measured, and if it is, that it will necessarily add something worthwhile to the outcomes of a clinical encounter.

There have been a number of attempts to address the deficiencies in current regulatory frameworks and to move consideration beyond the assay to encompass not just technical, but also contextual, issues as well. One of the best known of these is the ACCE framework developed in the USA by Wylie Burke and others (Statham et al. 2008)

The ACCE framework establishes criteria for the introduction of genetic tests into mainstream clinical practice based on pre-determined criteria to evaluate.

Analytical Validity
Clinical Validity
Clinical Utility
Ethical, Legal and Social Aspects

In other words, not only "does a given assay or test measure what it sets out to measure reliably?", but "is it relevant?", "can we use it to add value to other tools and mechanisms?", and "is it ethical to adopt it in practice?". This is clearly an advantage over the narrow focus of, for example the IVD directive, but it has been drawn up from the clinicians' perspective, and as such it neglects dimensions of testing and test availability that are highly significant from a patient and family perspective. These also create an ACCE framework, but in this instance it stands for;

Availability
Comprehendability
Compassionate
Equitable

In other words, the best test in the world is of little use if those who need it cannot get access to it. It is no good if it delivers information you cannot understand and take in. It is not helpful if the result of the test is given to the patient in a way that does not reflect and respect the pain and distress that receiving the information may cause, and which does not acknowledge that everyone needs an opportunity to find out what has happened to them/their family member – irrespective of rarity, difficulty, or other confounding factors!

Any genetic testing service which meets the technical and clinical criteria and the patient and family focussed ones or both these ACCE frameworks is likely to be providing high quality care and support to patients and families that they value and hold in esteem!

Conclusion

For patients and families living with genetic diseases, timely access to genetic testing is a critical element in what ought to be a package of integrated services and support from national health care systems. For the process of testing to deliver maximum benefit to those undergoing this procedure, we/families need to be able to have confidence in the accuracy and the validity of the information generated. This information needs to be delivered in a form that patients and families can assimilate and act upon, supported by information communicated in terms they can understand and in languages that they are comfortable with, as both Eurogentest and Eurogenguide have demonstrated. A diagnosis makes effective management of genetic diseases more likely, and timely access to high quality genetic testing services is crucial to achieving this.

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