Genetic Testing

A SURVEY OF QUALITY ASSURANCE AND PROFICIENCY STANDARDS

OECD

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Foreword

This report presents recommendations for action to assure the quality of human genetic testing and the proficiency of those that carry out such tests. It provides the first detailed information about the availability and extent of molecular genetic testing throughout OECD member countries as well as existing quality assurance practices in use in testing laboratories, including policies regarding samples and genetic data handling, and transborder flow of specimens. It also provides some insight into the level of proficiency of those offering genetic tests. It reports the results of a survey of 18 OECD countries, with responses from 827 laboratory directors. The survey was carried out between June and October 2003 in 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.

To guide the development and implementation of the survey, a steering group of experts and government representatives from the 18 participating countries was established (Annex C). Their work was invaluable and special thanks are due to Dr. Rob Elles (United Kingdom) who chaired the expert group and to Dr. Margaret McGovern, who acted as expert consultant to the OECD throughout the project. The financial support of Japan and of the European Commission is gratefully acknowledged. Dr. Elettra Ronchi of the OECD Secretariat was responsible for the co-ordination of this activity which took place under the supervision of the OECD Working Party on Biotechnology.

This is one of two reports emerging from this work. A summary of the OECD survey compiled by the OECD Secretariat, entitled "Quality Assurance and Proficiency Testing Schemes for Molecular Genetic Testing: Survey of 18 OECD Member Countries", is available on the OECD website at *www.oecd.org/sti/biotechnology*.

This publication presents the full results of the work, including methodology, and has been developed as a series of expert-authored chapters produced by the national experts that guided this project throughout. Chapter 1, drafted by Dr. McGovern, reports in detail on the methodology and the results of the survey. The remaining chapters report and discuss in depth results in the following five specific areas:

- Transborder flow of samples and of genetic data; rare diseases (Chapter 2, by S. Ayme and D. Taruscio).
- Report writing (Chapter 3, by I. Lubin and D. Barton).
- Consent, storage and confidentiality (Chapter 4, by G. Hoefler and J. Sequeiros).
- Licensing, accreditation, certification and proficiency testing/external quality assessment (Chapter 5, by R. Elles, E. Dequeker and C. Müller).
- Education and training (Chapter 6, by M. Somerville and U. Kristoffersson).

These chapters were drafted with input from other members of the OECD member country steering group for the work, which divided into task groups in these five subject areas. The chapters identify priority areas for internationally agreed good practice guidelines and co-operation.

The report was endorsed by the OECD's Working Party on Biotechnology and the Committee on Scientific and Technological Policy in accordance with procedures approved by the OECD.

Based on the results of the survey, OECD member countries reached agreement in 2004 to develop international best practice guidelines. The guidelines will set out minimum common principles and practices and will aim to facilitate mutual recognition across OECD countries of acceptable quality standards in molecular genetic testing.

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Summary

Introduction

The knowledge gained from the sequencing of the human genome, and the many related scientific and technical advances this has made possible, have led to a dramatic and rapid increase in the identification and characterisation of the genes and genetic variations underlying human diseases. One of the first practical applications of this knowledge has been the ability to develop genetic tests that identify disease-causing molecular variations or inherited mutations in individuals. In the past few years, the use of genetic testing to predict future disease risk or as an aid in diagnosing disease has grown steadily. Genetic testing is also just beginning to be used for prescribing drug therapy based on the genetic variation of the disease or of the individual. Testing is offered internationally, through both public and private sector genetic testing services, and there is evidence that human samples and related data are being exchanged across borders. This expanded use and "internationalisation" of genetic testing raises novel issues and is challenging current regulatory frameworks governing genetic services.

The OECD reviewed developments at an international workshop, "Genetic Testing: Policy Issues for the New Millennium", held on 23-25 February 2000 in Vienna, Austria. Workshop participants concluded that international frameworks needed to be established to apply genetic testing meaningfully, to assure its analytical and clinical validity, to protect the security, privacy and confidentiality of stored genetic information and to develop a level playing field in international trade of genetic services and products. A key recommendation from the workshop was to "develop internationally recognised and mutually compatible best practice policies for analytical and clinical validation of genetic tests, including quality assurance and accreditation of genetic services" (OECD, 2000).

Similar recommendations have since been articulated in other national and international forums, including the European Parliament, the European Commission, the Council of Europe, the US Secretariat Advisory Committee on Genetic Testing, the World Health Organisation (WHO) and UNESCO.

However, significant gaps in knowledge about the practices of molecular genetic testing (MGT) laboratories across OECD countries hindered the development of strategies for appropriate international action. Therefore, as a first step, OECD member countries agreed that it would be necessary to: "collect basic data to learn what quality assurance measures are being undertaken across OECD countries and in clinical laboratories that offer molecular genetic testing and to compare these practices" (OECD, 2000).

Thus, the OECD's Working Party on Biotechnology decided to carry out a survey to document and compare quality assurance (QA) practices in clinical MGT laboratories across OECD member countries. The results of the survey were intended to facilitate:

1. Identification of areas for international co-operation in developing standards, proficiency testing and interpretative guidelines.
2. Development of international good practice guidelines based on general principles.
3. International collaboration among disease-specific consortia, particularly for testing of rare diseases.

Following a pilot phase, 18 OECD member countries (Austria, Belgium, Canada, the Czech Republic, Finland, France, Germany, Ireland, Italy, Japan, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, United Kingdom and United States) participated in the survey, which ran from June to October 2003.

Study population

Each participating country nominated at least one expert to the survey steering group. Experts were either molecular genetic testing laboratory directors, or had expertise in and knowledge of national genetic testing policies and/or the operation of MGT laboratories. The steering group oversaw the selection of laboratories to be sampled. The net was cast deliberately wide in the pilot phase since for most countries information on where exactly MGT is carried out was unavailable. Only research laboratories that functioned as clinical laboratories and reported results back to patients or referring physicians were included in the survey. Of the 2 756 potential laboratory directors initially identified and contacted, 1 306 were finally included in the survey. Of these, 827 submitted a completed response.

Growth, configuration and organisation of genetic testing services

The survey confirmed the steady growth of genetic testing. The total number of samples processed increased from 874 608 in 2000 to 1 112 988 in 2001 and to 1 401 536 in 2002. Growth is not dependent on the setting (*e.g.* public or private) of laboratories. However, the commercial sector has the highest volume (on a per laboratory basis), as measured by samples processed in 2002.

A number of factors appear to determine testing volume, test menu, laboratory setting and service configuration. These are summarised and discussed in the following sections together with other key findings from the survey.

Close collaboration between clinical and laboratory services

As reported in Chapter 1, except in a few countries (Germany, Switzerland, Japan and the United States), most MGT laboratories are located in the public sector, either in public hospitals or several other research settings. This delivery structure dates back to the mid-1980s, when clinical molecular genetic laboratories were first established. At that time genetic testing was limited to carrier detection and prenatal diagnosis for a few conditions and was mainly performed in academic clinical centres. These laboratories were often directed by the same professionals who cared for the patients and were closely associated with clinical genetic counselling services, a university or other research facility. Public hospital and research laboratories were (and still are) more likely to offer tests for clinically complex, newly characterised or difficult-to-diagnose rare diseases. This often requires a close working relationship between laboratory staff and clinicians to ensure that the testing offered can transfer from research to clinical practice and is appropriate for a specific indication or an individual patient. As a result of these factors,

genetic testing laboratories in most OECD countries have developed either within, or in close proximity to, clinical genetics services.

Technology

Some aspects of the technology platforms used in MGT laboratories are common between different tests, but others are highly variable. Many molecular genetic tests designed to determine if specific mutations are present start with the amplification of specific segments of the genome by the polymerase chain reaction (PCR), followed by mutation detection using a direct or indirect method. More comprehensive analysis of genes, particularly when the precise underlying mutation is unknown, is accomplished by sequence analysis. The survey confirmed that PCR and sequencing were performed in the great majority of laboratories and that laboratories may use a wide range of approaches for mutation analysis. Reagents for these procedures are mainly produced in-house and so potentially prone to variability.

Commercial laboratories generally provided the more common tests, based on stable technology, for which the clinical diagnosis is straightforward. Commercial laboratories also provide a service in general much different from one in which testing is intimately linked to clinical service. Of the tests included in the survey, cystic fibrosis testing, as well as alpha-1-antitrypsin (AAT) deficiency testing, were the only tests more likely to occur in the commercial (independent) setting than in all other settings. These tests are high-volume, well-established MGT tests. In contrast, Connexin 26, haemophilia A and Rett syndrome testing are more likely to occur in the research setting The survey shows that testing based on the BRCA1 and BRCA2 mutations is primarily available in research institutions, though a private sector body, Myriad Genetics, holds approximately 20 patents on the use of the two genes and has developed automated tests to detect the presence of mutations. This company is an example of how biopharmaceutical companies that are dedicated to the discovery of genes related to major diseases may diversify to become providers of specialised genetic testing services.

Referral systems and gatekeeping arrangements

Many of the OECD member countries see a need for mechanisms to regulate genetic testing provision and access, particularly of predictive or presymptomatic testing. One such mechanism is to require that tests be accessed only through an appropriate gatekeeper. The level of expertise needed in a given gatekeeper may vary according to the test concerned. In some circumstances a family physician may have sufficient expertise to prescribe a certain genetic test, while in other cases a genetic counsellor, clinical geneticist or other specialist may need to be involved.

In the 18 countries participating in the survey, the most important sources of samples to MGT laboratories are the clinical geneticists and physicians. Responsibility for making genetic tests available may also be assigned to a national (or regional or provincial) health authority or institution. In such cases, the institution provides an additional layer of oversight that is intended to combine the authority and the expertise to evaluate whether a test accurately identifies a genetic factor and whether there is, for a specific population, a net benefit. The UK Genetic Testing Network[1] is an example of such an authority. In Ireland the National Centre for Medical Genetics is the "gatekeeper" in the sense that it

1. *www.genetictestingnetwork.org.uk*

decides which MGT to offer in-house and acts as a referral centre to other domestic or foreign laboratories for all other MGT.

Service funding agencies may also act as gatekeepers. In the United States, the reimbursement mechanism varies and requires the test to be ordered through a participating health-care provider and a plan that covers the particular test ordered. Therefore, payers of services also serve as gatekeepers to access genetic testing. In only three of the 18 participating countries (Germany, the Czech Republic and the United States) patients can request genetic testing directly from laboratories.

Funding and uptake of genetic tests

At least some measures to control the costs of health care, including genetic testing services, are taken in all 18 countries that participated in the survey. There is considerable convergence in the policies adopted, although the methods may differ according to the way in which a country's health-care system is organised and financed. Currently, measures to contain costs of genetic testing operate, as in all other sectors of health care, by acting on supply or on demand.

Such cost containment measures acting on supply include introducing expenditure ceilings through prospective budgets for public testing facilities, limits on trained human resources for testing and as qualified gatekeepers, limits on the availability of certain technologies and controlling prices paid for genetic tests. The most common measure acting on consumer demand is cost-sharing and exclusion of the test from coverage (although this can act also to limit supply).

In many OECD countries most or all of these measures are applied to contain or regulate the provision of genetic testing, including whether genetic testing can be provided both within public and private sectors. For example, in many countries, the average public laboratory receives a standard budget for each sample, independent of the type of sample or the work required.

Public and private health insurers play a significant role in defining patient and provider use and access to genetic tests. In most OECD countries, public insurance reimbursement of genetic tests is conditional on medical referral and in many countries also on testing in an officially recognised genetic testing centre.

Geographical disparity in the range of genetic tests available

In an ideal world, with no cost and resource constraints, tests that provide genuine net health benefit at reasonable cost would be included in the public health insurance systems, but this is not always the case. The reality of the situation is much more complicated and there is considerable geographical disparity in the range of genetic tests available across OECD member countries. For example, in 2001, 273 diagnostic tests were available in the United Kingdom, 250 in the Netherlands, 214 in Spain (Ibarreta *et al*, 2004) and 751 in the United States (Yoon *et al,* 2001).

There is no clear evidence that explains the disparity in availability of genetic tests in different countries, although the plethora and variety of demand-side mechanisms in place is likely to play a role. Given the importance of resource allocation decisions in health care, there is a surprising lack of empirical studies on availability and access to genetic testing. Notably, with few exceptions (*e.g.* the recently established Gene Dossier process in the UK) there are no clearly established formalised or systematic procedures

nor internationally shared criteria to determine when potential tests are ready to move from the research phase to a clinical laboratory setting. The transfer of genetic tests from research to services may thus still be considered a "grey zone" influenced by a number of factors inherent to the process of research and delivery of health care, the nature of the test and the target disease. This generates specific regulatory challenges for all OECD countries, particularly given the "internationalisation" of genetic testing.

Neither is there clear evidence that the increasing availability of patents on genetic tests directly restricts access, though a previous study by Cho *et al* (OECD, 2002), had suggested a negative impact on access, cost and quality of tests as well as on information sharing between researchers. The OECD survey sought to cast further light on the interactions between patents and access to genetic tests. The majority of laboratory directors reported that patent licenses affected the cost of the test. Ten percent of laboratories had ceased offering a test because of a patent issue. Directors cited the inability to secure a patent license, the high cost of the royalty fee and unacceptable terms of the licensing agreement as reasons not to offer a patented test.

As the number and variety of genetic tests increase, so will the need for data on their analytical validity, clinical validity and utility. Discussions concerning criteria to establish the validity and utility of genetic testing are at an early stage in many OECD countries. There is thus an opportunity for countries to establish a process that facilitates the development of mutually compatible methods for collecting data to evaluate the uptake, use and impact of new genetic tests and enables more rapid and widespread access to new beneficial tests in a manner consistent with the provision of a positive environment for innovation in this area.

The growth of genetic testing networks

More than 10 000 genetic disorders have been catalogued by Online Mendelian Inheritance in Man (OMIM) (McKusick, 1998) to date, and about 1 700 of these have been ascribed to specific mutations in the human genome. The large number of genetic disorders, combined with the need to design a specific set of diagnostic assays for each, precludes any one clinical molecular genetic laboratory from offering a complete range of diagnostic tests for all known genetic conditions. To cope with this problem, networks and consortia have been and are being established within and between countries.

The OECD survey shows that cross-country referral has become relatively common, particularly for rare disorder testing. Data shows that specimens are frequently sent to another country to be tested. Transborder flow involves the majority of laboratories, and is particularly significant in Belgium, France, Italy, Spain, United Kingdom, Germany, and the United States. In 2001, a total of 18 000 samples crossed OECD countries' borders.

These data indicate that cross-country exchange of samples, allied to the availability of sometimes small number of laboratories worldwide offering specific specialised services, is leading to "internationalisation" of genetic testing for medical and research purposes.

However, the capacity to access genetic testing on an international scale both increases the availability of testing and raises significant policy issues. The issue of greatest concern is the lack of internationally agreed good practices for quality assurance in MGT, including protection of the privacy of individuals' genetic information and specimen handling and processing.

Handling of samples and data

The majority of surveyed laboratories store samples indefinitely. This is a common practice as it allows for review and verification should this become necessary. It is in the interest of the patient and family members. A number of concerns arise from long-term storage of patient samples primarily in relation to confidentiality, privacy and consent issues. The survey included questions addressing laboratory practices on these issues.

Just over half of laboratories required documentation of written informed consent before any genetic testing was performed. Much genetic testing in these laboratories occurs within the governance framework of public health systems. In such circumstances, laboratories may not document informed consent but consider that it is the referring doctor's role to discuss the significance of tests and to record the discussion and consent in the patient's notes. Nonetheless, in countries with specific guidelines or procedures on informed consent for MGT, the proportion of laboratories requiring a copy of the informed consent form prior to any genetic testing is higher than in countries without guidelines.

There was a low positive response rate for written policies on confidentiality of genetic testing results. In particular, there appears to be no difference in the confidentiality practices of laboratories performing pre-symptomatic and predisposition testing including in those countries where there are clear and specific confidentiality requirements concerning such testing. As the authors of Chapter 4 suggest, this constitutes an area in which international co-operation to guide practice appears necessary, particularly, to accommodate transborder flows of samples. Security of stored samples and data can only be achieved by clear-sighted recognition of what needs to be secured or which information needs to be restricted and by which appropriate risk analysis. There is little evidence of current clear practical guidance on these issues for laboratories.

Risk management

Errors in genetic testing may have very serious, even irreversible implications, particularly in the area of predictive testing. For this reason, all OECD countries have mechanisms in place to reduce and/or manage risk from inappropriate and inaccurate testing and to assure the quality of MGT procedures. In general, the "toolkit" in place for ensuring quality in MGT laboratories is not very different from those used for general diagnostic laboratories. However, as discussed in Chapter 5, implementation of these instruments in the context of molecular genetic testing presents specific challenges.

The survey assessed the status of MGT centres with regard to whether they were subject to external permission (licensing), external audit (accreditation and certification) and proficiency testing (PT) or external quality assessment (EQA) schemes designed to compare laboratories' analytical performance. These instruments are regarded as important indicators of performance and quality and can all be applied to regulate MGT practice although some are more effective than others.

The survey results show that QA requirements have not penetrated diagnostic MGT laboratories across OECD countries to a significant degree or with any consistency. It also reveals that a number of the terms used in the survey (for example, the difference between licensing and accreditation) are largely unfamiliar to laboratories. In particular, directors from almost every country provided erroneous responses when asked if licensing was required in their country. Yet licensing is required by half of the countries

participating in the survey, although the conditions that apply to the requirement may vary significantly.

Determinants of laboratory personnel competence

The levels of competence of the laboratory personnel who provide and interpret clinical molecular genetic tests are a crucial factor. In particular, they should possess expertise in the technologies employed (to test for sequence variations), knowledge of the potential limitations of the tests used, and understanding of what the test result may mean for the clinical condition referred.

A comprehensive multinational assessment of competence presents challenges, however, particularly because of the variations in requirements among countries. This is of concern given the relatively high numbers of laboratories reporting transborder flows of specimens for genetic testing. The survey both confirmed the existence of such between-country variations and created an opportunity for cross-analysis to learn which possible variables or determinants are most closely associated with quality assurance and competence of laboratory personnel, generally defined as an adequate combination of academic achievement, technical training and experience. To achieve this minimal set of quality indicators, the core activities which together represent determinants of competence are: *i)* result reporting; *ii)* education and training, and *iii)* laboratory practices.

Survey results were assessed against quality indexes based on good practice components for the three activities. The core good practice components for results reporting and education and training were derived from an overview and comparison of a number of guidelines available across OECD countries. The specific core elements for laboratory practices were identified and agreed upon by country experts during discussions relating to the survey instrument.

Generally, cross analysis of results indicates that accreditation status is the most important predictor of higher laboratory QA practice, followed by a director with formal training in molecular genetics, and participation in PTl Accreditation was defined in the survey's glossary as a "formal recognition of the competence of a laboratory by an authoritative organisation". Its association with higher quality and performance in general suggests that accreditation of MGT laboratories is an important means to assure quality.

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Résumé

Introduction

Les connaissances acquises dans le cadre du séquençage du génome humain et les nombreuses avancées scientifiques et techniques que ce dernier a permis se sont traduits par des progrès spectaculaires et rapides dans l'identification et la caractérisation des gènes et des variations génétiques associés aux maladies humaines. L'une des premières applications concrètes de ces acquis a été la conception de tests génétiques qui mettent en évidence des variations moléculaires ou des mutations héréditaires qui sont à l'origine de maladies chez les individus. Depuis quelques années, ces tests sont de plus en plus utilisés pour anticiper un risque de maladie future, ou bien à l'appui du diagnostic. Ils commencent aussi à être employés pour prescrire des thérapies médicamenteuses à partir de la variation génétique qui caractérise la maladie ou le patient. Les tests peuvent être réalisés dans de nombreux pays, par des prestataires relevant aussi bien du secteur public que du secteur privé, et il est avéré que des échantillons humains et les informations les concernant s'échangent par delà des frontières. Cette exploitation accrue et cette « internationalisation » des tests génétiques soulèvent des problèmes nouveaux et remettent en question les cadres réglementaires tels qu'ils s'appliquent aujourd'hui aux services génétiques.

En 2000, l'OCDE s'est penchée sur la situation à l'occasion d'un atelier international intitulé « Tests génétiques – Les enjeux du nouveau millénaire », organisé à Vienne (Autriche) du 23 au 25 février. Les participants ont conclu qu'il était nécessaire d'établir un cadre international pour tirer parti des tests génétiques, garantir leur validité analytique et clinique, protéger la sécurité, la vie privée et la confidentialité des informations génétiques stockées et pour égaliser les conditions de concurrence dans le commerce international des services et des produits génétiques. L'une des principales recommandations formulées lors de l'atelier était la suivante : mettre au point des « pratiques exemplaires, reconnues à l'échelle internationale et mutuellement compatibles, pour la validation analytique et clinique des tests génétiques, y compris l'assurance qualité et l'agrément des services génétiques » (*Tests génétiques – Les enjeux du nouveau millénaire*, OCDE, 2000).

Depuis, d'autres instances nationales et internationales ont formulé des recommandations similaires, dont le Parlement européen, la Commission européenne, le Conseil de l'Europe, le Comité consultatif sur les tests génétiques du ministère de la Santé des Etats-Unis, l'Organisation mondiale de la santé (OMS) et l'UNESCO.

Cependant, des lacunes importantes dans la connaissance des pratiques des laboratoires qui réalisent des tests de génétique moléculaire dans les pays de l'OCDE empêchaient de concevoir des stratégies visant une action appropriée à l'échelle internationale. C'est pourquoi les pays membres de l'OCDE ont estimé qu'il était nécessaire, dans un premier temps, de « recueillir des données de base pour savoir quels sont les systèmes d'assurance qualité (…) en vigueur dans les pays de l'OCDE et dans les laboratoires de biologie qui proposent des tests de génétique moléculaire et pour comparer ces pratiques » (OCDE, 2000).

Le Groupe de travail sur la biotechnologie de l'OCDE a donc décidé de conduire une enquête pour réunir des informations sur les pratiques d'assurance qualité des laboratoires de biologie qui réalisent des tests de génétique moléculaire dans les pays membres, et pour les comparer. Les résultats de l'enquête étaient censés faciliter :

i) la mise en évidence des domaines où développer la coopération internationale en vue de concevoir des normes, des méthodes de contrôle des compétences et des critères d'interprétation.

ii) la formulation de lignes directrices internationales sur les bonnes pratiques, fondées sur des principes généraux.

iii) la collaboration internationale entre consortiums propres à chaque maladie, notamment pour l'étude des maladies rares.

A l'issue d'une phase pilote, dix-huit pays membres de l'OCDE (Allemagne, Autriche, Belgique, Canada, Espagne, Etats-Unis, Finlande, France, Irlande, Italie, Japon, Norvège, Portugal, République tchèque, Royaume-Uni, Suède, Suisse et Turquie) ont participé à l'enquête, qui s'est déroulée de juin à octobre 2003.

Composition de l'échantillon

Chaque pays participant a désigné au moins un expert au groupe de pilotage de l'enquête. Les experts étaient des directeurs de laboratoires pratiquant des tests de génétique moléculaire ou bien avaient une expérience et des connaissances concernant les politiques nationales en matière de tests génétiques et/ou le fonctionnement des laboratoires en question. Le groupe de pilotage a supervisé la sélection des laboratoires devant constituer l'échantillon. Il a délibérément établi une très longue liste au cours de la phase pilote, car dans la plupart des pays, aucune information ne permettait de savoir où exactement étaient pratiqués les tests de génétique moléculaire. Seuls ont finalement été retenus les laboratoires de recherche faisant office de laboratoires d'analyse et remettant les résultats aux patients ou à leur médecin référent. Sur les 2 756 directeurs de laboratoires identifiés et contactés à l'origine, 1 306 ont été inclus dans l'échantillon. Parmi eux, 827 ont répondu à l'enquête.

Essor, configuration et organisation des services de test génétique

L'enquête a confirmé le développement régulier des tests génétiques. Le nombre total d'échantillons traités est passé de 874 608 en 2000 à 1 112 988 en 2001 puis à 1 401 536 en 2002. Cet essor n'est pas fonction des caractéristiques des laboratoires (publics ou privés, par exemple). Cependant, c'est le secteur commercial qui affiche le volume le plus important (par laboratoire), si l'on se réfère aux échantillons traités en 2002.

Plusieurs facteurs déterminent le nombre de tests pratiqués, l'éventail des analyses proposées, les caractéristiques des laboratoires et la configuration des services. Ils sont synthétisés et examinés dans les sections suivantes, de même que d'autres résultats importants de l'enquête.

Collaboration étroite entre services cliniques et laboratoires

Comme l'indique le chapitre 1, sauf dans quelques pays (Allemagne, Suisse, Japon et Etats-Unis) la plupart des laboratoires qui pratiquent les tests de génétique moléculaire appartiennent au secteur public, et relèvent d'hôpitaux publics ou de diverses autres structures de recherche. Cette structure date du milieu des années 80, lorsque sont apparus les premiers laboratoires d'analyse de génétique moléculaire. A cette époque, les tests génétiques étaient limités au dépistage de mutations et au diagnostic prénatal de quelques maladies et ils étaient surtout pratiqués dans des centres d'analyse universitaires. Ces laboratoires avaient souvent pour directeur un membre du personnel soignant et étaient étroitement associés aux services de conseil génétique, à une université ou à une autre institution de recherche. Les hôpitaux et laboratoires de recherche publics étaient (et sont toujours) plus susceptibles de proposer des tests pour des maladies rares difficiles à diagnostiquer, caractérisées depuis peu et entraînant un tableau clinique complexe. Cela exige souvent une collaboration étroite entre le personnel de laboratoire et les cliniciens, de manière à assurer la transmission entre la recherche et la pratique clinique et à ce que chaque test soit adapté à une indication spécifique ou à un patient particulier. En conséquence, dans la plupart des pays de l'OCDE, les laboratoires qui pratiquent des tests génétiques se sont développés soit au sein des services de génétique médicale, soit à proximité.

Technologie

Certains aspects des plates-formes technologiques utilisées dans les laboratoires qui pratiquent les tests de génétique moléculaire sont communs aux différents tests, tandis que d'autres varient beaucoup. De nombreux tests destinés à déterminer la présence d'une mutation spécifique commencent par l'amplification de segments précis du génome moyennant une PCR (réaction en chaîne de la polymérase), suivie de la recherche de la mutation par une méthode directe ou indirecte. Une étude plus complète des gènes, en particulier lorsque la mutation en cause n'est pas connue avec précision, est réalisée au moyen d'une analyse de séquence. L'enquête a confirmé que la PCR et les analyses de séquence étaient pratiquées dans la grande majorité des laboratoires et que ceux-ci pouvaient utiliser un large éventail de méthodes pour analyser les mutations. Les réactifs employés dans ces procédures sont pour l'essentiel produits sur place et sont donc susceptibles de varier.

De manière générale, les laboratoires privés pratiquent les tests les plus courants fondés sur une technologie stable, pour lesquels le diagnostic clinique est simple. Les services qu'ils assurent sont généralement très différents de ceux où les tests sont étroitement associés aux prestations cliniques. Parmi tous les tests pris en considération dans l'enquête, le dépistage de la mucoviscidose, ainsi que le diagnostic du déficit en alpha-1-antitrypsine, sont les seuls qui sont plus susceptibles d'être pratiqués par les structures commerciales (indépendantes) que par toutes les autres. Ces tests sont très fréquents et bien établis. A l'inverse, les tests de mutation du gène de la connexine 26, de l'hémophilie A et du syndrome de Rett sont quant à eux plus susceptibles d'être pratiqués dans les structures de recherche. Il ressort de l'enquête que les tests fondés sur les mutations BRCA1 et BRCA2 sont principalement proposés par les institutions de recherche, bien qu'une entreprise du secteur privé, Myriad Genetics, détienne une vingtaine de brevets sur l'utilisation de ces deux gènes et ait développé des tests automatisés pour détecter la présence de mutations. Cet exemple montre que les laboratoires biopharmaceutiques qui

se consacrent à la découverte des gènes impliqués dans les principales maladies peuvent se diversifier et devenir fournisseurs de services spécialisés de tests génétiques.

Systèmes de référents et mécanismes d'aiguillage/filtrage

Beaucoup de pays de l'OCDE estiment nécessaire de mettre en place des mécanismes pour réguler la fourniture de tests génétiques et l'accès à ceux-ci, en particulier lorsqu'il est question de tests prédictifs ou présymptomatiques. L'un de ces mécanismes consiste à exiger que ces tests ne puissent être prescrits que par des professionnels agréés à cet effet. Le niveau de qualification nécessaire peut varier en fonction du test en question. Dans certaines circonstances, un médecin de famille peut être suffisamment compétent pour prescrire un test génétique donné, tandis que dans d'autres, il se peut qu'un conseiller en génétique, un généticien clinicien ou un autre spécialiste doive être consulté.

Dans les dix-huit pays qui ont participé à l'enquête, les échantillons envoyés aux laboratoires de tests de génétique moléculaire ont le plus souvent pour origine les généticiens cliniciens et les médecins. La responsabilité de la mise à disposition des tests génétiques peut aussi incomber à un organisme ou à une institution de santé nationale (ou régionale/provinciale). Dans ces cas, l'institution en question constitue un filtre supplémentaire, qui est censé disposer à la fois de l'autorité et de la compétence nécessaires pour déterminer si un test caractérise avec précision un facteur génétique et s'il existe ou non, pour une population spécifique, un bénéfice net. Le UK Genetic Testing Network [1] en est un exemple. En Irlande, c'est le National Centre for Medical Genetics qui assure un aiguillage, au sens où c'est lui qui décide quel test génétique proposer en interne et fait office de centre référent au service des autres laboratoires, irlandais ou étrangers, pour tous les autres tests de génétique moléculaire.

Les organismes de financement des services peuvent eux aussi jouer le rôle d'aiguilleur. Aux Etats-Unis, le mécanisme de remboursement varie et pour en bénéficier, il faut que le test soit prescrit par un prestataire de soins de santé conventionné et qu'il fasse partie des prestations prises en charge. Dans ce cadre, les organismes qui paient les services filtrent aussi l'accès aux tests génétiques. Les patients ne peuvent demander eux-mêmes un test génétique à des laboratoires que dans trois des dix-huit pays étudiés (Allemagne, Etats-Unis et République tchèque).

Financement et utilisation effective des tests génétiques

Dans la totalité des dix-huit pays qui ont participé à l'enquête, au moins certaines mesures sont prises pour maîtriser les dépenses de santé, y compris les coûts des services de tests génétiques. Les politiques adoptées convergent nettement, même si les méthodes diffèrent parfois selon les modes d'organisation et de financement des systèmes de santé des divers pays. Actuellement, les mesures de maîtrise des coûts des tests génétiques consistent à agir soit sur l'offre, soit sur la demande, comme dans tous les autres secteurs des soins de santé.

Les mesures qui agissent sur l'offre comprennent le plafonnement des dépenses des établissements publics de tests au moyen de budgets prospectifs, la limitation des effectifs humains formés à la réalisation des tests et compétents pour assurer un filtrage, la limitation de la disponibilité de certaines technologies, et le contrôle des prix des tests

1. *www.genetictestingnetwork.org.uk.*

génétiques. Pour agir sur la demande, la mesure la plus commune est la participation du patient aux frais et la non-prise en charge des tests (qui peut aussi être considérée comme une mesure de limitation de l'offre).

Dans beaucoup de pays de l'OCDE, toutes ces mesures ou une partie d'entre elles sont appliquées pour maîtriser ou réguler la fourniture de tests génétiques. Par exemple, la réglementation détermine si ces tests peuvent être ou non pratiqués aussi bien dans le secteur public que dans le secteur privé. Ainsi, dans de nombreux pays, les laboratoires publics « ordinaires » reçoivent un budget standard pour chaque échantillon, quel que soit la nature de ce dernier ou la tâche à effectuer.

Les assurances santé publiques et privées jouent un rôle important dans la définition de l'utilisation des tests génétiques par les patients et par les prestataires de services, et de l'accès à ces tests. Dans la plupart des pays de l'OCDE, le remboursement par le système public est subordonné à la prescription par un professionnel référent et, dans beaucoup d'entre eux, à l'obligation de faire réaliser le test dans un organisme officiellement autorisé.

Disparités géographiques dans la gamme des tests disponibles

Dans un monde idéal, sans contraintes de coûts ni de ressources, les tests qui procurent un avantage net véritable en termes de santé à un coût raisonnable seraient pris en charge par les systèmes publics d'assurance santé, mais tel n'est pas toujours le cas. La réalité est beaucoup plus complexe et il existe des disparités géographiques considérables dans la gamme des tests disponibles dans les différents pays membres de l'OCDE. Par exemple, en 2001, 273 tests de diagnostic étaient disponibles au Royaume-Uni, 250 aux Pays-Bas, 214 en Espagne (Ibarreta *et al.*, 2004) et 751 aux Etats-Unis (Yoon *et al.,* 2001).

Cette disparité est difficile à expliquer avec certitude, même si la multitude et la variété des mécanismes de maîtrise de la demande en vigueur ont probablement une incidence. Etant donné l'importance des décisions concernant l'affectation des ressources dans le domaine de la santé, il est curieux que les études empiriques sur la disponibilité des tests génétiques et l'accès à ceux-ci fassent défaut. Notamment, à quelques exceptions près (la procédure du « dossier génétique » mise en place récemment au Royaume-Uni, par exemple), il n'existe pas de procédure officielle ou systématique clairement établie, ni de critères internationaux permettant de déterminer à partir de quel moment un test est prêt à passer de la phase de recherche à la phase de l'application médicale. Cette transition entre la recherche et la prestation de service peut donc toujours être considérée comme une « zone grise » sous l'influence de plusieurs facteurs inhérents au processus de recherche et de fourniture des soins de santé, à la nature du test et à la maladie ciblée. Cela soulève des problèmes réglementaires particuliers dans tous les pays de l'OCDE, notamment dans le contexte de l'« internationalisation » des tests génétiques.

Il n'est pas non plus clairement établi que l'augmentation du nombre de brevets sur les tests génétiques restreigne directement l'accès à ces derniers, bien qu'une étude de Cho *et al.* (OCDE, 2002) conclue à un impact négatif sur l'accès aux tests, leur coût et leur qualité, ainsi que sur le partage des informations entre chercheurs. L'enquête de l'OCDE visait entre autres à en apprendre davantage sur les interactions entre brevets et accès aux tests génétiques. La majorité des directeurs de laboratoire a indiqué que les licences sur les brevets avaient des retombées sur le coût des tests. Dix pour cent des laboratoires ont cessé de proposer un test à cause de problèmes de brevet. Parmi les raisons invoquées pour ne pas proposer un test breveté, les directeurs indiquent

l'impossibilité d'obtenir la licence nécessaire, le coût élevé de la redevance à verser et les conditions inacceptables de l'accord de licence.

A mesure qu'augmenteront le nombre et la variété des tests génétiques, la nécessité d'obtenir des données sur leur validité analytique, leur validité clinique et leur utilité s'accentuera elle aussi. La réflexion sur les critères à retenir pour établir la validité et l'utilité des tests génétiques n'en est qu'à ses balbutiements dans beaucoup de pays de l'OCDE. Cette situation offre aux pays la possibilité de mettre en place une procédure qui facilite la mise au point de méthodes mutuellement compatibles de collecte de données d'évaluation de l'adoption, de l'utilisation et de l'impact de nouveaux tests génétiques, et qui permette un accès plus rapide et plus large à de nouveaux tests bénéfiques, ce dans des conditions qui seraient en même temps propices à l'innovation dans ce domaine.

L'essor des réseaux sur les tests génétiques

Plus de 10 000 troubles génétiques ont été répertoriés à ce jour par Online Mendelian Inheritance in Man (OMIM) (McKusick, 1998), et quelque 1 700 d'entre eux ont été attribués à des mutations spécifiques dans le génome humain. Du fait du grand nombre de ces troubles, conjugué à la nécessité de concevoir un ensemble particulier de tests de diagnostic pour chacun d'eux, aucun laboratoire d'analyse n'est à même de proposer une gamme complète pour toutes les affections connues. Pour surmonter ce problème, des réseaux et des consortiums se mettent en place dans les pays et entre eux.

L'enquête de l'OCDE montre qu'il est devenu relativement courant d'adresser un patient à un organisme étranger, notamment lorsqu'il est question de diagnostiquer une maladie rare. Les données indiquent que des échantillons sont fréquemment expédiés dans un autre pays pour y être soumis à des tests. Ces flux internationaux concernent la majorité des laboratoires et sont particulièrement importants en Allemagne, en Belgique, en Espagne, aux Etats-Unis, en France, en Italie et au Royaume-Uni. En 2001, 18 000 échantillons ont ainsi traversé les frontières des pays de l'OCDE au total.

Il ressort de ces données que les échanges internationaux d'échantillons, associés au fait que certains services très spécifiques ne sont parfois assurés que par un petit nombre de laboratoires dans le monde, se traduisent par une « internationalisation » des tests génétiques pratiqués à des fins médicales et de recherche.

Cependant, si la possibilité de faire procéder à des tests génétiques à l'étranger accroît leur disponibilité, elle soulève aussi des problèmes non négligeables. Le plus important tient à l'absence de bonnes pratiques définies à l'échelon international en matière d'assurance qualité des tests de génétique moléculaire, notamment en ce qui concerne la protection de la confidentialité des informations génétiques sur l'individu, et la manipulation et le traitement des échantillons.

Manipulation des échantillons et des données

Dans leur majorité, les laboratoires interrogés stockent les échantillons indéfiniment. Courante, cette pratique permet de procéder à un réexamen ou à une vérification en cas de besoin. Elle est dans l'intérêt des patients et des membres de leur famille. Ce stockage à long terme des échantillons prélevés sur les patients soulève néanmoins plusieurs problèmes, notamment en ce qui concerne la confidentialité, le respect de la vie privée et le consentement. L'enquête comportait des questions sur les pratiques des laboratoires à ce sujet.

Un peu plus de la moitié des laboratoires ne procèdent à aucun test sans avoir obtenu par écrit le consentement éclairé de la personne concernée. Nombre des tests en question sont pratiqués dans le cadre de la réglementation appliquée par le système de santé publique. Dans ces circonstances, les laboratoires peuvent considérer qu'il ne leur appartient pas d'obtenir le consentement éclairé de la personne, mais que c'est au médecin référent d'en parler avec elle et de consigner l'entretien et son consentement dans son dossier. Toutefois, dans les pays où il existent des lignes directrices ou des procédures sur le consentement éclairé spécifiques aux tests de génétique moléculaire, la proportion de laboratoires qui demandent une copie du formulaire de consentement avant de procéder à un test est plus élevée que dans ceux où ces directives n'existent pas.

En ce qui concerne les règles écrites sur la confidentialité des résultats des tests génétiques, le taux de réponses positives est faible. En particulier, il ne semble pas y avoir de différences entre les pratiques de confidentialité des laboratoires qui réalisent des tests présymptomatiques et celles des laboratoires qui réalisent des tests de prédisposition, y compris dans les pays où il existe une réglementation claire et spécifique à ces tests. Selon les auteurs du chapitre 4, il s'agit d'un domaine où une coopération internationale paraît s'imposer en vue d'orienter les pratiques, compte tenu notamment des flux transfrontières d'échantillons. La sécurité des échantillons et des données stockées ne peut être assurée que moyennant une analyse lucide de ce qui doit être protégé ou des informations dont la diffusion doit être restreinte, et moyennant une analyse de risque adaptée. Il ne semble pas exister actuellement d'orientations pratiques claires sur ces questions à l'intention des laboratoires.

Gestion des risques

Les erreurs dans les tests génétiques peuvent avoir des conséquences graves et parfois irréversibles, notamment lorsqu'il s'agit de tests prédictifs. C'est pourquoi tous les pays de l'OCDE ont mis en place des mécanismes visant à réduire et/ou gérer les risques induits par des tests inadaptés ou inexacts, et à garantir la qualité des procédures de test de génétique moléculaire. Globalement, les instruments en place pour assurer la qualité dans les laboratoires qui pratiquent des tests génétiques ne sont pas très différents de ceux qui s'appliquent dans les laboratoires de diagnostic en général. Cependant, comme l'indique le chapitre 5, la mise en œuvre de ces instruments dans le contexte des tests de génétique moléculaire pose des problèmes particuliers.

L'enquête détermine si les centres de tests de génétique moléculaire sont soumis à des autorisations externes, à des contrôles externes (accréditation et certification) et à un contrôle des compétences ou à des dispositifs d'évaluation externe de la qualité conçus pour comparer les performances des laboratoires en matière d'analyses. Ces instruments sont considérés comme des indicateurs importants de la performance et de la qualité, et ils peuvent tous être employés pour réglementer les pratiques dans le domaine des tests de génétique moléculaire, bien que certains soient plus efficaces que d'autres.

Les résultats de l'enquête montrent que l'assurance qualité est encore peu réglementée dans les laboratoires de diagnostic des pays de l'OCDE et que la situation varie de l'un à l'autre. Ils révèlent aussi que plusieurs termes employés dans l'enquête sont loin d'être familiers aux directeurs de laboratoire (par exemple, la différence entre autorisation et accréditation ne semble pas claire). En particulier, dans presque tous les pays, des directeurs ont donné une réponse erronée à la question de savoir si une autorisation était nécessaire sur leur territoire. Pourtant, elle est obligatoire dans la moitié des pays qui ont participé à l'enquête, même si les conditions d'obtention peuvent varier sensiblement.

Facteurs déterminant la compétence du personnel des laboratoires

Le niveau de compétence du personnel qui, dans les laboratoires, pratique et interprète les tests de génétique moléculaire est un facteur déterminant. En particulier, il doit maîtriser les technologies employées (pour analyser les variations de séquence), connaître les limites potentielles des tests utilisés et savoir ce que les résultats du test peuvent signifier pour l'état clinique concerné.

Cependant, il est difficile de procéder à une évaluation plurinationale complète des compétences, notamment en raison des disparités que présentent les réglementations des différents pays. Cela pose un problème étant donné le nombre relativement élevé de laboratoires qui font état de flux transfrontières d'échantillons à soumettre à des tests. L'enquête confirme l'existence des variations entre pays et crée l'occasion de procéder à une analyse transversale en vue de découvrir quels variables ou facteurs déterminants sont le plus étroitement corrélés avec l'assurance qualité et la compétence du personnel des laboratoires, généralement définie comme la conjugaison adéquate entre le niveau d'études, la formation technique et l'expérience. Pour obtenir cet ensemble minimal d'indicateurs de qualité, les activités fondamentales qui, ensemble, représentent les facteurs déterminants de la compétence sont les suivants : *i)* la communication des résultats ; *ii)* l'enseignement et la formation et *iii)* les pratiques de laboratoires.

Les résultats de l'enquête ont été évalués à l'aune d'indices de qualité fondés sur les composantes des bonnes pratiques, pour chacune des trois activités. En ce qui concerne la communication des résultats et l'enseignement et la formation, les composantes essentielles des bonnes pratiques ont été déduites de l'examen et de la comparaison de plusieurs lignes directrices applicables dans les pays de l'OCDE. Dans le cas des pratiques de laboratoire, elles ont été caractérisées d'un commun accord par les experts des différents pays au cours des réflexions sur l'enquête.

De manière générale, il ressort de l'analyse transversale des résultats que l'accréditation est le facteur prédictif le plus important d'un niveau élevé des pratiques d'assurance qualité des laboratoires, suivie de la présence d'un directeur titulaire d'une formation structurée en génétique moléculaire, et de la participation à un système de contrôle des compétences. Dans le glossaire établi pour l'enquête, l'accréditation a été défini de la manière suivante : « reconnaissance officielle de la compétence d'un laboratoire par un organisme investi de l'autorité nécessaire ». Son association avec un niveau supérieur de qualité et de performances en général indique qu'elle constitue un moyen important pour garantir la qualité dans les laboratoires qui pratiquent des tests de génétique moléculaire.

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Chapter 1

QUALITY ASSURANCE IN MOLECULAR GENETIC TESTING: RESULTS OF A SURVEY OF 18 COUNTRIES

Introduction

This chapter discusses the methods used for and reports the results of a survey carried out in 18 OECD member countries. The survey was designed to assess quality assurance (QA) practices in molecular genetic testing (MGT) laboratories. Information was collected on: personnel qualification; handling of samples and related data, including informed consent; confidentiality policies; result reporting; and specimen retention. In addition, information was collected on transborder flow of specimens and the impact of patents and availability and quality of tests.

Methods

Steering committee

A group of experts was nominated by the 18 OECD countries to serve on the steering committee for the project. Each country nominated at least one expert who was either an MGT laboratory director or had expertise and knowledge about national policies and/or the operation of such laboratories. These experts, who were the national contacts, met twice during the survey development process and twice to discuss survey results. They also interacted extensively on a web-based electronic discussion group established for the project and via conference calls. The group of experts also formed sub-groups to discuss in depth various aspects of the survey results and to identify areas of interest for further statistical and policy analysis. These are addressed in subsequent chapters.

Study population

The identification of potential MGT laboratory directors in the 18 member countries of the OECD that participated in the survey was the responsibility of the expert(s) from each country. Since it was not known in most countries exactly where MGT was being carried out, the goal of the identification process was to cast a wide net in order to identify potential directors. Therefore, the experts were asked to assemble a list by systematically contacting the genetics and clinical laboratory professional societies in their respective countries, and by using all other national or regional resources that list such laboratories (*e.g.* GeneTests, European Molecular Quality Network [EMQN], etc). Table 1.1 provides details about the methods employed by each country. Using this approach, 2 756 potential MGT laboratory directors were identified and a list of their e-mail or facsimile numbers was compiled for subsequent delivery of the questionnaire. Recipients of the questionnaire were asked to complete it if they were the laboratory director *(i.e.* had responsibility for the MGT laboratory and for the interpretation and reporting of results). Those who did not have such responsibility, or who were not performing MGT, were asked to indicate this in their response to the e-mail invitation.

Such individuals were eliminated from the database of potential directors and excluded from the study population for the purpose of calculating response rate. In addition, for directors to participate in the survey, their laboratories had to perform one or more of the following types of MGT: diagnostic testing to identify individuals and/or foetuses affected with or carriers of monogenic disorders; pre-symptomatic testing for monogenic disorders; predisposition testing for susceptibility genes; tests to establish genotypes known to be associated with adverse drug reactions.

Table 1.1. Method(s) used to identify potential directors

Country	Method(s)
Austria	Austria has an accreditation system for labs. Therefore, laboratory directors were identified from the Austrian database of licensed laboratories. Contact with professional societies was also made.
Belgium	Contact was made with all federations and associations of private diagnostic laboratories (human genetics, haematology, clinical chemistry), and the society for the study of inborn errors and metabolism.
Canada	Experts were contacted in the various provinces and asked to identify the directors of laboratories offering genetic testing.
Czech Republic	Clinical biochemistry and genetics associations were contacted. There is no official directory of labs in the Czech Republic.
Finland	The heads of the relevant national associations were contacted. In addition, the national registers and the "Labquality" database were used.
France	French directors were identified from the database *www.orpha.net*.
Germany	The relevant national organisations (German Society of Human Genetics, Laboratory Medicine, Internal Medicine, Gynaecology and others) were contacted and asked to provide lists of potential lab directors. In addition, European public databases were also searched (EDDNAL, orphanet).
Ireland	An invitation was sent to all pathology labs in Ireland and to members of the Irish Society of Human Genetics. The contact for those who wished to participate was then provided.
Italy	All representatives of the Societies of Biochemistry, Human Genetics, Pathology, Haematology and Clinical Biology were contacted and invited to submit a list of potential directors.
Japan	A list of national hospitals and commercial laboratories was provided. They are under the control of different sections of the Japanese Ministry of Health, Labour and Welfare (MHLW).
Norway	There are only seven laboratories in Norway that offer MGT and the directors of these labs were all included in the list.
Portugal	A list of the directors of all laboratories and associations that announce MGT was compiled. The list was obtained from professional societies including the Portuguese Society of Haematology, and the Portuguese Association of Clinical Pathologists.
Spain	The list was compiled from the databases of the Spanish Association of Human Genetics, Institute of Health Carlos III, the National Catalogue of Spanish Hospitals, the Spanish-Portuguese Group of the international Society of Forensic Haemogenetics and the information published in a survey of the European Commission Joint Research Centre's Institute for Prospective Technological Studies (IPTS).
Sweden	Directors of the five regional genetics labs in Sweden, of the two national reference centres for metabolic diseases, of all clinical chemistry labs identified in a 2002 Swedish survey as performing genetic tests, and of all clinical chemistry labs participating in molecular proficiency testing offered by EQALIS were included.
Switzerland	The National Agency for Education and Science organised a small meeting of relevant professional organisations, including pathologists and geneticists, to identify lab directors
Turkey	The Turkish Scientific Council database of genetic testing laboratories was used to identify potential directors.
United Kingdom	Lab directors were identified from the following professional societies: Clinical Molecular Genetics Society (CMGS), British Society for Haematology, Haemophilia Genetics Lab Network, Royal College of Pathology, Association of Clinical Biochemists and British Society for Inborn Errors of Metabolism and Biochemical Genetics Network. The CMGS Web site was searched. Directors of CMGS laboratories were asked to give names of MGT labs in their areas.
United States	MGT laboratory directors listed in GeneTests were included as well as other lab directors that participated in a previous 1999 survey.

Survey development

The survey questions were developed by the group of national experts. A closed and open-ended survey was developed to collect data about: laboratory setting; personnel qualifications, training, and years of experience, including employment or affiliation with genetics professionals; types and source of specimens and number of specimens accessioned, including details related to on- or off-site collection, storage and transborder flow; types of testing services provided; methods used for analysis; standard operating procedures (SOPs); reporting practices; policies regarding informed consent and confidentiality of results; certification and licensing status; participation in PT programmes; and QA practices of the laboratory. The first question on the survey asked the country in which the laboratory was located in order to permit breakdown of results by country for later analysis.

The laboratory settings were defined as: public hospital, private hospital, public non-hospital-based, private non-hospital-based or independent (*e.g.* commercial, commercial manufacturer of reagents, non-commercial reference laboratory (non-governmental-affiliated, employed by health clinic) or research. Directors that indicated they operated in a research setting were also asked if they functioned as a clinical laboratory (*i.e.* reporting results back to referring physicians or patient). If they did not function as a clinical laboratory, but only as a research laboratory, their responses were not included in the database or in the subsequent analyses of the data. For the types of testing services provided, directors were asked to choose from a list of 32 common MGT analyses. The list was agreed upon by the country experts and was derived in part from the responses to a pilot survey that identified commonly performed tests.

Defined options were provided for all items with the exception of the number of specimens accessioned each year, the number of technicians employed, and the percentage of the total number of specimens accessioned that are received from outside the country, each of which required the director to write in the appropriate number. The option to write in additional responses was provided for the following items: further description of the setting for research labs; the types of laboratory professionals employed by the laboratory; the roles affiliated clinical or medical geneticists play in the laboratory operations; the highest degree of the person with ultimate responsibility for the laboratory; the academic discipline of the degree of the director; the minimum degree required for a genetic counsellor employed at the laboratory and of molecular testing personnel; the training requirement for technicians; the types of specimens accepted; barriers to the receipt of specimens from other countries; reasons why the lab might refer a specimen to another located outside of its country; barriers to the referral of specimens to other countries; methods used for analysis; individuals to whom laboratory reports are issued; who obtains the informed consent from patients; policy of the laboratory with regard to specimens for which informed consent has not been obtained; the length of retention of specimens; accreditation system or authority that has accredited/certified the laboratory; proficiency testing (PT) programmes the laboratory participates in; reasons why the laboratory does not participate in PT; reason why the laboratory is not certified/accredited; influence of patents; and reason why the laboratory does not offer patented tests. The write-in responses were analysed to determine if any actually fit into a predefined category of the survey. If so, the responses were added to the total for the specified items. The remaining write-in responses were catalogued and are summarised in the data tables under the heading "other". It should be noted that since these were additional responses that had to be written in by the director, it is possible that the number of responses may not reflect actual practice (*e.g.* write-in responses for method used were

provided by only 8% of directors whereas it is very likely that nearly all use methods that were not listed).

To provide guidance to respondents about the meaning of some of the terminology used in the survey that was found to be problematic in the pilot, a glossary was included/embedded in the survey questions. The terms included in the glossary and the definitions provided were as follows:

- *Monogenic disorders:* disorders that result from mutations in a single gene. Examples: sickle cell disease, Tay Sachs disease.
- *Genetic counselling services:* services that offer a dialogue with patients and the provision of information about genetics risks and/or testing prior to and after genetic testing.
- *Esoteric testing:* testing for rare diseases, non-routine testing.
- *Accessioned:* information about the specimen entered into the laboratory data system during which a unique identifier is assigned
- *Licensed:* granted permission from a governmental agency to operate a laboratory.
- *Accredited:* formal recognition of the competence of a laboratory by an authoritative organisation (for example, CAP).
- *Susceptibility genes:* genes known to predispose to specific disorders or conditions. Example: BRCA1/2.
- *CAP:* College of American Pathologists.
- *CPA(UK):* Clinical Pathology Accreditation (UK).
- *Proficiency testing:* may also be called *External Quality Assessment (EQA)*. This usually involves the distribution of samples to participating laboratories by an external agency. The results of tests on these samples are checked and form a measure of laboratory performance.
- *CORN:* Council of Regional Networks.
- *EMQN:* European Molecular Genetics Quality Network.
- *UKNEQAS:* UK National External Quality Assessment Schemes.
- *Turnaround time:* the time from the day the laboratory receives the specimen to the day the result is reported back to the referrer.

Validation of the survey instrument

Validation of the survey instrument was achieved by: *i)* utilising previously validated items from a similar survey conducted in MGT laboratories in the United States; *ii)* conducting a pilot survey among 164 directors in nine member countries to identify items requiring clarification; *iii)* analysing three item pairs that would reflect internal inconsistencies during completion of the survey, which revealed a low (<2%) level of internal inconsistency, and *iv*) use of a decision tree embedded in the survey that prevented respondents from skipping questions and automatically skipped questions that should not be answered based on a prior response (*e.g.* directors who indicated a research setting would have to answer the follow-up questions about their research setting prior to

proceeding to the next question, and those who responded that they were not in a research setting would automatically skip these questions).

The aforementioned pilot survey identified a number of questions requiring rewording to account for regional differences in health-care systems and terminology. The pilot survey also identified a number of areas of interest for which additional questions were developed for the larger survey. For example, 72% of the 164 responding laboratories indicated that they received specimens from outside their city or region, and 45% received specimens from other countries, with international receipt of specimens reported by at least one laboratory in eight out of the nine participating countries. This finding suggested the importance of collecting more detailed data on international referral of specimens, such as the reasons for doing so, the number of specimens involved, and the barriers, if any, that affect the ability to do so.

Assessment of the "representativeness" of the survey results for each country was also attempted. The data set was broken down by country, and the individual country responses were analysed in a variety of ways by the national contact points to determine if the responses were representative. A question-by-question analysis of the responses was compiled to determine if the responses seemed to be in line with what was commonly known about MGT services within the country.

Contact of potential laboratory directors

In most countries, potential directors were contacted by e-mail and invited to participate in the Web-based survey. In most cases, the e-mail invitation also included a letter from the country representative requesting participation. Within the e-mail invitation was a specific URL that linked the respondent to the Web site hosting the survey. Embedded within the URL was a unique identifier that permitted tracking of respondents for the purposes of calculating response rate. In Spain, the survey was distributed as a document by regular mail, and the responses to the survey were subsequently entered into the study database. In Belgium, invitations were distributed via facsimile.

In all cases, complete confidentiality was ensured; individual response sets were not identifiable and could not be traced back to the respondent. Three sets of e-mail reminder notices were sent to non-responders over a four-month period. National representatives in most countries also helped to increase response rate by contacting the non-responding laboratories and requesting their participation. Respondents could start the survey on the Web site, save their responses if necessary, and return to complete the survey later.

Prevention of duplicate entries

A number of measures were employed to prevent duplicate entries from the same director or laboratory. To prevent the same individual from submitting more than one entry, once a URL had been used to submit a completed survey, the Web system would not permit another survey submission from the same URL.

Attempts to identify duplicate entries from two different individuals working at the same laboratory were also made. Specifically, since the list of potential directors was culled from a variety of sources, the possibility existed that two individuals from the same laboratory might have been invited to participate. In addition, it was possible that a laboratory would have co-directors, each of whom responded to the survey.

Therefore, although instructions to the survey explicitly requested that the survey be completed only once and by the laboratory director, the database was analysed to ensure that duplicate responses had not been received from the same laboratory through two types of analysis: *i)* performing a global comparison of the responses from the labs within individual countries to determine if there were any completely overlapping responses; and *ii)* comparing the responses from each country for a smaller subset of items. This second analysis was undertaken because the first strategy might have missed some duplicate entries since the survey contained both closed and open-ended questions, and two individuals in the same lab might have answered the open-ended questions differently.

The constellation of items included for the second method were: the types of testing offered, laboratory setting, whether or not technicians are employed by the laboratory, test menu, the method used for DNA isolation, whether or not there are SOPs, whether or not the lab participates in PT, and whether or not the laboratory performs any prenatal or pre-implantation testing. The items were selected on the basis of the range of responses in the entire data set and to represent different sections of the survey. In particular, items for which the majority of respondents answered in the same way would not have been informative for this analysis and were not included (*e.g.* whether a report is issued).

The first analysis (*i.e.* global comparison of response sets) did not identify any sets of completely identical responses. However, the second analysis revealed 38 sets of responses with identical answers for at least six of the eight items queried. These 38 sets of responses were further analysed to determine the percentage of identical responses for all closed questions included in the survey. Those with 80% or more identity were further analysed to determine the degree of agreement for the open-ended responses. Those with substantially similar responses to the closed and open-ended questions were determined to be duplicate responses. This resulted in the removal of 27 sets of responses from four countries, and indicated a low level of duplicate responses (3%). The remaining 11 sets of data differed in substantial ways for the open-ended questions and were left in the database.

Calculation of result reporting and QA best practice indices

The reporting practices of laboratories were assessed through a series of questions related to the critical elements included in the final report. A reporting quality index was developed to simplify the analysis of the factors influencing reporting practices. The index (see Chapter 3 for more details) was developed based on the identification of elements that were graded according to whether they were: *i)* "basic" items or pieces of information without which the report could be misleading, dangerous or of no use; *ii)* "specific" items or pieces of information that modulate the basic information; and *iii)* "also useful" items or pieces of information that add to the effectiveness of the report (Table 1.2). The grading of items was agreed by debate among the steering group members until consensus or near-consensus was reached.

An essential minimal set of general QA practices of laboratories was identified using questions based upon best practices that were agreed upon by the country experts for inclusion in the survey. Best practices were also identified for two specific techniques commonly used in MGT laboratories: PCR and sequencing. The specific items to include were debated and agreed upon by the country representatives. A QA index was then calculated for each laboratory based on the response of the director to the individual best practices items developed for general QA, PCR and sequencing (Table 1.3). Each best practice item was assigned a value of 1. The total QA index of each laboratory was expressed as a percentage calculated by dividing the number of QA best practices used by

that laboratory by the total number of best practice items that would apply based on the methods used by the laboratory.

Statistical analysis

The aggregate and country-specific data were analysed by descriptive statistics and by frequency distributions. Pair-wise comparisons of responses were made using the Students t-test, and statistical significance was defined as $p<0.05$. The significance of differences in the reporting and QA indices with respect to various predictors was evaluated using the one-way Analysis of Variance. For comparison of a small number of pre-specified comparisons (generally for three groupings), pair-wise comparisons were performed without adjusting for the number of comparisons. For comparisons suggested by the responses, Scheffe's method of multiple comparisons was used. The differences detected with 80% power ranged from 4% to 7% depending on the number in each group, and the number of groups. Correlation of the percentage of labs offering a particular type of analysis with the prevalence of the relevant disease was calculated using Pearsons correlation coefficient.

Table 1.2. Report index

Report item	Value	% respondents meeting standard
Two unique identifiers	3	100
Genotype and/or haplotype identified for the individual	3	95
Date of birth of the patient	2	88
Reason for testing or disease locus tested	2	89
Statement on the limitations of the test	2	78
Signed by the laboratory director	2	84
Implications of the results for other family members	2	61
Date of report	1	99
Sample collection date	1	86
Suggestions for further testing	1	82
Maximum index	19	

Table 1.3. Quality assessment index

QA best practices	% respondents meeting standard
General QA	
Standard operating procedures exist	94
SOPs are reviewed by director	82
Laboratory report is issued	95
Report is reviewed by director	84
Turnaround time data is collected	81
PCR	
Procedures to minimise contamination are in place	93
A blank with all PCR components except for target DNA is included as a negative control	96
Controls that contain all common alleles are included in analyses that rely on the detection of sequence variation	90
Size ladders that cover the range of the expected results are included during the electrophoresis for analyses that detect differences in fragment size	90
Appropriate controls are included to ensure correct interpretation for analyses that rely on the detection of a change in electrophoretic mobility	99
DNA sequencing	
The full genomic sequence for genes being sequenced are available in Genbank	92
Both strands of the DNA region are analysed	85
Standard loading formats are used to orient gels and prevent sample mix ups	90
Timing, voltage requirements and separation characteristics of the gel apparatus are standardised for each individual set-up	90
Readings of the gels are verified using second strand and/or second aliquot sequencing	87
Positives are confirmed by sequencing a second aliquot	75
The report notes the exact base change and location by nucleotide position as referenced in Genbank, and the corresponding position change in the protein using standard nomenclature	95
Base differences are correlated with known functional changes, clinical reports and other relevant data	96
When a base alteration has not been previously described, the report states that the nature and significance of the change may be unclear	94
If sequencing was confined to the coding regions the report states that mutations in the promoter or intragenic regions would not be detected	72
The report states that sequencing will not detect large gene deletions or duplications	60
When no mutations are detected the report includes a disclaimer that the sensitivity of the test is <100%.	80

Results

Study population

Table 1.4 lists the countries that participated in the survey and provides details about the response rate. Of 2 756 potential laboratory directors contacted, 360 were no longer at the laboratory contact provided, 733 were not directing a MGT laboratory, 177 were not doing any of the testing specified, 159 were professionals who either were not the laboratory director or who had been identified as at a laboratory that had already responded (see above for details on removal of duplicate entries), and 6 declined to respond. Thus, the final number of potential directors included in the survey was 1 306 (Table 1.4). Of these, 827 submitted a completed response for an overall response rate of 63%. The range of response rates among the different participating countries was 20% to 91%.

Table 1.4. Country responses

Country	E-mail contacts	No longer at lab	Not doing MGT	Not doing testing specified	Duplicates	Declined to participate	Final # labs	Responded	Response rate
Austria	68	7	6	5	11	0	39	34	87
Belgium	364	49	214	5	57	0	39	8	20
Canada	108	17	13	11	3	0	64	29	45
Czech Republic	48	6	8	4	1	0	29	12	41
Finland	14	0	0	0	0	0	14	6	43
France	298	32	65	23	2	0	176	103	58
Germany	539	103	160	49	53	6	168	128	76
Ireland	13	0	2	0	0	0	11	10	91
Italy	335	43	103	18	22	0	149	121	81
Japan	11	0	0	0	0	0	11	7	64
Norway	7	0	0	0	0	0	7	5	71
Portugal	70	0	0	0	0	0	70	27	38
Spain	100	n.a.	n.a.	n.a.	0	n.a.	100	73	73
Switzerland	300	67	119	42	10	0	62	31	50
United Kingdom	128	n.a.	n.a.	0	n.a.	n.a.	113	72	64
United States	325	36	43	20	0	0	226	141	62
Sweden	16	0	0	0	0	0	16	9	56
Turkey	12	0	0	0	0	0	12	11	91
Total	**2 756**	**360**	**733**	**177**	**159**	**6**	**1 306**	**827**	**63**

Laboratory setting

Of the directors, 56% (n=464) indicated that their laboratory was in a public hospital setting (range 8-100%); 8% (n=66) a private hospital setting (range 0-62%); 4% (n=33) public non-hospital-based (range 0-55%); 12% (n=99) private non-hospital-based or independent (*i.e.* commercial) (range 0-57%); and 20% (n=165) a research setting (range 0-75%) (Figure 1.1). All countries had at least one responding lab in the public hospital setting, and 7/18, 12/18, 13/18 and 14/18 had labs in the private hospital, public non-hospital, independent and research settings, respectively (Table 1.5). Therefore, there was considerable variability among countries with regard to setting. The research labs that participated functioned as clinical laboratories since they reported results back to patients or referring physicians. Among the research labs, 32% offered testing only as part of a research study, 57% were associated with a university, 19% were government-funded and 14% were privately funded.

Figure 1.1. Distribution of laboratory setting among all respondents

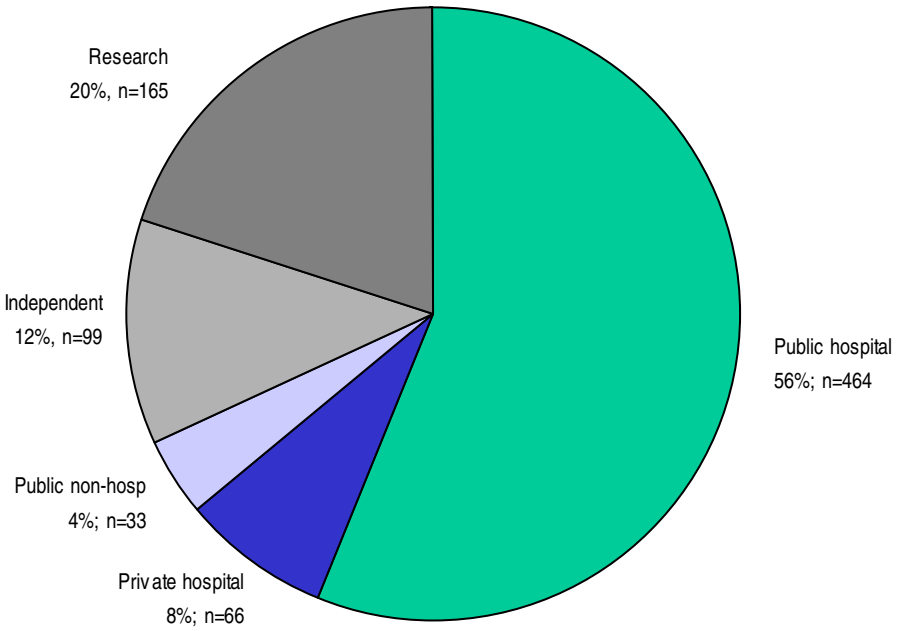


Table 1.5. Distribution of lab setting by country

Country/number of respondents (n)	Public hospital (%)/n	Private hospital (%)/n	Public non-hospital-based laboratory (%)/n	Private non-hospital-based or independent (%)/n	Research (%)/n
Austria (n=34)	73/25	0/0	3/1	3/1	18/7
Belgium (n=8)	38/3	62/5	0/0	0/0	0/0
Canada (n=29)	76/22	0/0	3/1	3/1	18/5
Czech Republic (n=12)	8/1	0/0	0/0	17/2	75/9
Finland (n=6)	83/5	0/0	17/1	0/0	0/0
France (n=103)	81/83	6/6	4/4	4/4	6/6
Germany (n=128)	39/50	5/6	2/3	32/41	22/28
Ireland (n=10)	60/6	0/0	10/1	0/0	30/3
Italy (n=121)	43/52	9/11	<1/1	5/6	42/51
Japan (n=7)	28/2	0/0	14/1	57/4	0/0
Norway (n=5)	100/5	0/0	0/0	0/0	0/0
Portugal (n=27)	15/4	0/0	55/15	15/4	15/4
Spain (n=73)	52/38	7/5	3/2	18/13	20/15
Sweden (n=9)	89/8	0/0	0/0	0/0	11/1
Switzerland (n=31)	61/19	0/0	0/0	32/10	6/2
Turkey (n=11)	73/8	0/0	0/0	18/2	9/1
United Kingdom (n=72)	81/58	1/1	1/1	7/5	9/7
United States (n=141)	16/22	38/54	4/6	20/28	22/31

Personnel qualifications

All but three laboratory directors who responded to the survey had one or more doctoral degrees, 74% (n=612) were certified or registered to practice clinical laboratory medicine by an officially recognised body (*e.g.* board certification in specialty; qualification by government), and 67% (n=554) had received formal training in molecular genetics (Table 1.6). The mean number of years of experience directing a clinical laboratory was 10.5 years with a range of one to 31 years. Most directors (93%, n=769) provided on-site supervision of the laboratory operations. In addition to the director, many laboratories also employed a variety of other doctoral level professionals (Table 1.7).

Among the laboratories, 72% (n=595) were affiliated or associated with a clinical or medical genetics unit that provided genetic counselling services (*i.e.* cognitive genetic services to patients prior to and/or after genetic testing), and 75% (n=620) employed or were associated with physicians who provided genetic counselling services. Only 21% of labs (n=173) employed non-physician professionals to provide genetic counselling. These 21% were located in 15 countries, although the majority (88%, n=153) were located in Canada (n=18), the United Kingdom (n=26), Italy (n=33) and the United States (n=76). No respondents in three countries (Belgium, Portugal and Turkey) reported the employment of non-physician genetic counsellors. The majority of laboratories (94%, n=776) employed technicians who performed the actual patient testing (range 1–56, mean=5.5, median=4). Of these 91% (n=706) had minimal educational and training requirements for technicians (Table 1.8).

Table 1.6. Directors' qualifications

	% of respondents	n
Highest degree awarded		
Medical [qualification equivalent to the United States] MD degree	42	347
PhD or equivalent	49	405
MD/PhD	9	72
Masters degree or equivalent	<1	3
Academic discipline of the highest degree		
Medicine	51	347
Genetics	22	182
Molecular biology	14	116
Biology	12	99
Biochemistry	11	91
Clinical lab science	4	33
Chemistry	3	25
Medical technology	1	8
Certified or registered to practice clinical laboratory medicine		
Yes	74	612
No	16	215
Formal training in molecular genetics		
Yes	67	554
No	33	273

Table 1.7. Laboratory professionals employed by laboratories in addition to the director

Qualification	% of labs	n
Clinical geneticist with a medical qualification	23	190
Clinical cytogeneticist with a medical qualification	8	66
Clinical cytogeneticist with a PhD	12	99
Clinical molecular geneticist with a medical qualification	18	149
Clinical molecular geneticist with a PhD	32	265
Geneticist with a PhD	21	174
Pathologist with a medical qualification	11	91
Clinical chemist with a medical qualification	10	83
Clinical chemist with a PhD	13	106

Table 1.8. Minimum qualifications for technicians

	% of respondents	n
Qualification		
Bachelors degree or equivalent	41	339
Masters degree	9	74
Specific qualification for medical technologists	43	356
PhD or MD	1	83
Other	6	50
Training requirement		
In-house (at the bench) training	92	761
Previous experience at another molecular genetic testing facility	42	347
Research experience	31	256
Formal training by a professional organisation	19	157

Specimens

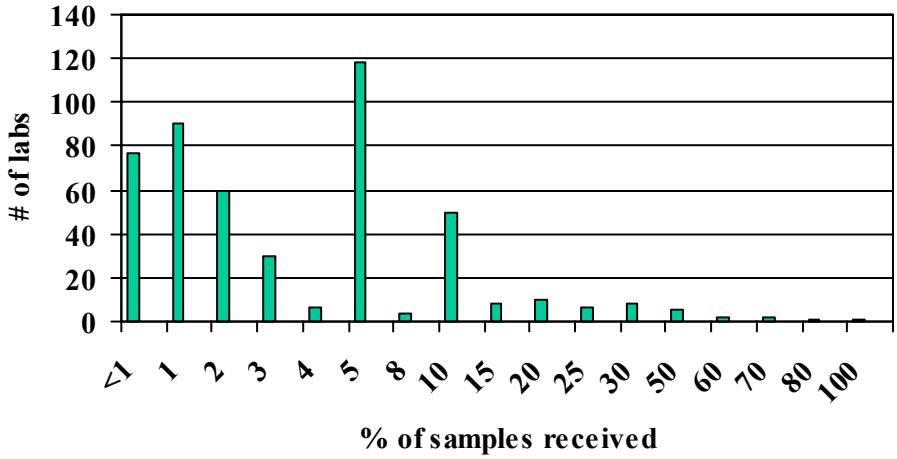
Specimens were collected both on and off site by 80% of laboratories, whereas 6% only collected specimens on site and 14% only received specimens from off site. A broad range of specimen types was used for analysis (Table 1.9).

Table 1.9. Specimen types received by laboratories

Specimen type	% of respondents	n
Whole blood	95	786
Post-mortem (tissues or fluids)	44	364
Mouthwash or buccal smear samples	34	281
Dried blood spots	28	231
Organ tissue	51	422
Cultured fibroblasts	47	389
Foetal blood	36	298
Direct amniotic fluid	38	314
Cultured amniocytes	50	413
Chorionic villus cells	49	405
Guthrie cards	26	215
Other response written in:		
Paraffin blocks	3	25
Extracted DNA	3	25
Bone marrow	2	17
Hair bulbs	1	8

Notably, 64% of respondents (n=529 labs), including laboratories in every country participating in the survey, indicated that their laboratory received specimens from outside of the country (overall mean=2.5% of all specimens received). Furthermore, labs in all settings received transborder specimens. However, the percentage of samples received from outside the country borders ranged from <1% of the total laboratory volume to 100% of the volume in one laboratory (Figure 1.2). In 2002, over 18 000 specimens crossed borders.

Figure 1.2. Distribution of the percentage of specimens received across borders



Of those receiving transborder specimens, 73% (n=357) reported that these were received for rare diseases or esoteric testing (range 28-100%), and 23% (n=121; range 0-100%) were for testing offered only as part of a research study. Among all respondents, 27% indicated that there were barriers to the receipt of transborder specimens, including difficulties for reimbursement (66%), liability issues (22%), complexity of the paperwork involved (27%), and compliance with regulatory requirements of other countries (21%). Other less frequently cited barriers were problems with specimen integrity (3%) and customs requirements (2%). Similarly, 60% of directors indicated that they referred specimens to laboratories in other countries. The reasons for such referrals included: the test was not performed in their laboratory (71%); the test was not offered by any lab in their country (83%), the test was offered as part of a research study (62%), cost of the test (8%), and the test is patented and only offered outside of the country (4%). Twenty-eight percent of directors indicated there were barriers to their receipt of transborder specimens, including: difficulties with reimbursement for services (69%), liability issues (15%), and complexity of required forms and documents (24%). Less frequently cited barriers were local regulations that prohibit such referral (1%) and customs regulations (1%).

Respondents were also asked to indicate which countries they received specimens from. For this question, a list of countries was provided (Table 1.10). Among the laboratories that stated that they received transborder specimens, the percentage of all labs that received such specimens from each country listed is detailed in Table 1.10, along with the list of countries that had labs stating that they receive specimens from each of the 30 countries inquired about. For example, among labs that receive transborder specimens, 18% had received a specimen from Australia, and these 18% of labs were

located in Canada, Finland, France, Germany, Ireland, Italy, Sweden, Switzerland, the United Kingdom, and the United States.

Of interest, the majority of laboratories (72%, n=595) indicated that they retained specimens referred for MGT indefinitely (Table 1.11). Laboratories in the independent setting were less likely to retain specimens indefinitely (37%) than any other setting, *i.e.* public (72%) or private (74%) hospital labs and labs in the public non-hospital (83%) and research settings (73%). Also of interest, labs that indicated they retained specimens indefinitely were not more likely than those that did not to have a requirement for informed consent (p=0.1).

Table 1.10. Countries from which transborder specimens were received

Country	% of labs receiving specimens from country/(n)	Countries receiving specimens
Australia	18/89	Canada, Finland, France, Germany, Ireland, Italy, Sweden, Switzerland, UK, USA
Austria	17/84	France, Germany, Italy, Spain, Switzerland, UK, USA
Belgium	25/123	Austria, Canada, France, Germany Ireland, Italy, Spain, Switzerland, UK, USA
Canada	17/84	Austria, Finland, France, Germany, Italy, Switzerland, UK, USA
Czech Republic	9/44	Austria, France, Germany, Italy, Portugal, Spain, Switzerland, UK, Sweden
Denmark	12/59	Austria, Canada, Finland, France, Germany, Italy, Sweden, Switzerland, UK, USA
Finland	9/44	Austria, Canada, France, Germany, Italy, Sweden, Switzerland, UK, USA
France	24/118	Austria, Canada, Finland, Germany, Italy, Norway, Portugal, Spain, Sweden, Switzerland, UK, USA
Germany	30/148	Austria, Canada, Finland, France, Italy, Spain, Sweden, Switzerland, UK, USA
Greece	19/94	Austria, France, Germany, Italy, Sweden, Switzerland, UK, USA
Hungary	12/59	Austria, Finland, France, Germany, Ireland, Italy, Spain, Sweden, UK, USA
Iceland	2/10	Germany, Norway, Sweden, Switzerland, UK, USA
Ireland	15/74	Austria, Canada, Finland, France, Germany, Sweden, Switzerland, UK, USA
Italy	27/133	Austria, Belgium, Canada, Finland, France, Germany, Portugal, Spain, Sweden, UK, USA
Japan	7/34	Austria, Canada, France, Italy, UK, USA
Korea	1/5	Germany, Switzerland, UK, USA
Luxembourg	2/10	Canada, France, Germany, Switzerland, UK
Mexico	7/34	Canada, France, Germany, Spain, Switzerland, USA
Netherlands	18/89	Austria, Belgium, Canada, Finland, France, Germany, Italy, Portugal, Spain, Sweden, UK, USA
New Zealand	9/44	Canada, France, Germany, Switzerland, UK, USA
Norway	10/50	Finland, France, Germany, Ireland, Italy, Sweden, Switzerland, UK, USA
Poland	11/54	Austria, Canada, France, Germany, Italy, Sweden, Switzerland, UK, USA
Portugal	18/89	Austria, France, Germany, Italy, Spain, Sweden, Switzerland, UK, USA
Slovak Republic	7/34	Austria, France, Germany, Italy, Spain, Switzerland, UK, USA
Spain	25/123	Austria, Canada, Finland, France, Germany, Italy, Portugal, Sweden, Switzerland, Turkey, UK, USA
Sweden	13/64	Austria, Canada, Finland, France, Germany, Italy, Norway, Switzerland, UK, USA
Switzerland	16/79	Austria, Canada, France, Germany, Italy, UK, USA
Turkey	21/103	Austria, Canada, France, Germany, Italy, Portugal, Spain, Sweden, UK, USA
United Kingdom	31/153	Austria, Belgium, Canada, Finland, France, Germany, Ireland, Italy, Portugal, Spain, Sweden, Switzerland, USA
United States	34/168	Austria, Belgium, Canada, Finland, France, Germany, Ireland, Italy, Norway, Portugal, Spain, Sweden, Switzerland, UK

Table 1.11. Retention of specimens

Length of time specimen is retained	% of laboratories	n
< 30 days	6	51
1 to 6 months	12	102
1 to 10 years	6	50
10 to 30 years	3	29
Indefinitely	72	595

Types of testing being offered

Diagnostic testing to identify individuals and/or foetuses affected with or carriers of monogenic disorders, pre-symptomatic testing for monogenic disorders, predisposition testing for susceptibility genes, and establishing genotypes known to be associated with adverse drug reactions to prescription drugs was offered by 61% (n=504), 31% (n=256), 35% (n=289), and 9% (n=74) of laboratories, respectively. Of the 32 genetic tests listed, cystic fibrosis, factor V Leiden, and Fragile X syndrome were the most commonly offered (Table 1.12). In addition, cystic fibrosis testing, as well as alpha-1-antitrypsin deficiency testing, were more likely to occur in the independent setting than in all other settings (p values 0.023 and .0012, respectively). Similarly, BRCA1/2 testing, Connexin 26, haemophilia A and Rett syndrome testing were more likely to occur in the research setting (p=0.001, 0.42, 0.009, 0.012, respectively). With the exception of sickle cell disease testing, public non-hospital labs were less likely to offer every other test asked about than all other settings. There was poor correlation of the percentage of labs offering a particular type of analysis with the prevalence of the disease (R^2=-.043, p<.001) although this observation may be due in part to the fact that some of the disorders listed (*e.g.* Tay Sachs disease and sickle cell disease) have an ethnic predilection which has led to the establishment of screening programmes. For example, although Tay Sachs disease is very rare in the general population (prevalence of <1:100,000), the carrier frequency of this disorder is 1:25 among the Ashkenazi Jewish population, for which prenatal carrier screening is recommended.

Number of specimens accessioned

The total and mean number of specimens accessioned by laboratories increased substantially in each of the three years inquired about (2000, 2001 and 2002). The mean number of tests per lab was 1 064 in 2000, 1 354 in 2001, and 1 705 in 2002. Similarly, the total number of specimens accessioned increased from 874 608 in 2000 to 1 112 988 in 2001 and 1 401 536 in 2002. The mean and total number of specimens accessioned by setting for 2002 is detailed in Table 1.13. Independent labs tended to be higher volume than all other settings, although the greatest number of specimens was accessioned in the public hospital setting. There was no significant correlation between the growth in testing over the three years inquired about and the setting of the labs (r = 0.1027); rather similar incremental increases were noted for each type of setting.

Table 1.12. Percentage of laboratories offering specific molecular genetic tests

Prevalence in general population	Disorder	% of labs offering test (n)	% public hospital	% private hospital	% public non-hosp	% independent	% research
> 1:2 000	Factor V Leiden	28 (231)	29 (134)	30 (20)	18 (6)	31 (31)	24 (40)
	BRCA1/2 hereditary breast/ovarian cancer	14 (116)	9 (42)	18 (12)	3 (1)	18 (18)	26 (43)
	Y chromosome deletions	14 (116)	13 (60)	12 (8)	3 (1)	34 (34)	8 (13)
	Alpha-thalassemia	6 (50)	5 (24)	4 (3)	9 (3)	7 (7)	8 (13)
< 1:2 000, > 1:10 000	Cystic fibrosis	27 (223)	28 (130)	27 (18)	3 (1)	51 (51)	14 (23)
	Fragile X syndrome	22 (182)	21 (97)	23 (15)	3 (1)	28 (28)	25 (41
	Huntington disease	12 (99)	11 (51)	5 (3)	0 (0)	14 (14)	19 (31)
	Duchenne/Becker muscular dystrophy	12 (99)	11 (51)	12 (8)	3 (1)	16 (16)	14 (23)
	DFNB1 (Connexin 26)	9 (74)	7 (32)	8 (5)	6 (2)	10 (10)	15 (25)
	Alpha-1-antitrypsin	9 (74)	10 (46)	3 (2)	9 (3)	21 (21)	1 (2)
	Charcot-Marie-Tooth	9 (74)	9 (40)	7 (5)	0 (0)	9 (9)	12 (20)
	Sickle cell disease	7 (58)	8 (37)	7 (5)	21 (7)	8 (8)	<1 (1)
	Neurofibromatosis I	4 (33)	2 (9)	7 (5)	0 (0)	6 (6)	8 (13)
	Marfan syndrome	2 (16)	6 (3)	1 (1)	0 (0)	1 (1)	7 (11)
	Tuberous sclerosis II	1 (8)	4 (2)	1 (1)	0 (0)	1 (1)	2 (4)
	Tuberous sclerosis I	1 (8)	4 (2)	1 (1)	0 (0)	1 (1)	2 (4)
< 1:10 000, > 1:100 000	Angelman syndrome	16 (132)	16 (74)	15 (10)	0 (0)	22 (22)	16 (26)
	Prader Willi	16 (132)	16 (74)	15 (10)	0 (0)	22 (22)	16 (26)
	HNPCC	12 (99)	12 (57)	12 (8)	0 (0)	14 (14)	12 (20)
	Myotonic dystrophy Type I	12 (99)	11 (53)	9 (6)	0 (0)	12 (12)	17 (28)
	Achondroplasia	9 (74)	9 (42)	10 (7)	0 (0)	10 (10)	9 (15)
	Spinal muscular atrophy	9 (74)	10 (46)	5 (3)	0 (0)	10 (10)	9 (15)
	Haemophilia A	7 (58)	2 (11)	15 (10)	3 (1)	8 (8)	17 (28)
	Rett Syndrome	5 (41)	2 (10)	1 (4)	0 (0)	4 (4)	14 (23)
	Haemophilia B	4 (33)	4 (18)	1 (4)	0 (0)	1 (1)	6 (10)
	Myotonic dystrophy Type II	4 (33)	4 (17)	10 (7)	0 (0)	1 (1)	5 (8)
	Glucose 6 phosphate dehydrogenase deficiency	2 (16)	<1 (4)	3 (2)	3 (1)	8 (8)	<1 (1)
< 1:100 000	Familial adenomatous polyposis	11 (91)	10 (46)	11 (7)	3 (1)	7 (7)	18 (30)
	Gaucher disease	5 (41)	4(18)	6 (4)	0 (0)	10 (10)	5 (9)
	Tay Sachs disease	3 (25)	2 (11)	1 (1)	0 (0)	7 (7)	4 (6)
	Niemann Pick disease types A and B	2 (16)	1 (5)	4 (3)	0 (0)	1 (1)	4 (7)
	Incontinentia Pigmenti	1 (8)	4 (3)	1 (1)	0 (0)	1 (1)	5 (3)

Table 1.13. Mean number and total of specimens accessioned by setting for 2002

Setting	Mean number of specimens accessioned	Total number of specimens
Public hospital	1 457	670 220
Private hospital	1 603	105 798
Public non-hospital	1 058	34 914
Independent	4 440	439 560
Research	921	151 044

Table 1.14. Methods used by MGT laboratories

Method used	Percentage of laboratories	n
Polymerase chain reaction	97	802
Direct mutation analysis using a PCR based technique	81	670
DNA sequencing	72	595
Direct mutation analysis using sequencing	69	571
Indirect mutation analysis using PCR technique*	52	430
Direct mutation analysis using Southern blot	47	389
Linkage analysis using microsatellites	42	347
Imaging using silver stain, Ethidium bromide or other systems	37	306
Real-time PCR	32	265
Imaging using fluorescent label	26	215
Reverse dot blot	24	198
Imaging using radio label	16	132
Linkage analysis using other markers	11	91
Minisequencing	9	74
DNA chip analysis	6	50
Other responses written in:		
Protein truncation	2	16
MALD-TOF	1	8

Methods used

Laboratories used a wide range of methodologies for clinical analysis (Table 1.14), including both direct and indirect (*e.g.* SSCP, DGGE, DHPLC, etc.) methods. PCR and sequencing were performed in 97% and 72% of labs, respectively. There was also variability in the system used for DNA isolation, including automated systems using commercial reagents (9% of labs), non-automated systems using commercial reagents (47%), and non-automated system using in-house reagents (25%).

Directors also were asked to identify the source of reagents used in their laboratories. Since many reagents used in MGT are not available commercially, reagents developed and produced in house (so-called "home brew" reagents) are commonly used. Indeed, the majority of labs used both commercial reagents and reagents prepared in house (81%), with only 14% of labs indicating they rely entirely on commercial test kit systems. The

distribution of the setting of the last subset of laboratories did not differ from that of laboratory settings overall (p=0.139).

Reporting practices

Laboratory reports were issued by 95% (n=786) of laboratories, and 84% (n=660) of laboratory directors signed and/or verified reports prior to their release. The only variable that correlated strongly with the 5% of labs that did not issue a report was the research setting (R^2=0.6532). For the laboratories that issue reports, the specific items included are summarised in Table 1.15.

Overall, the mean reporting score (see the section on methods for the derivation of the score and Chapter 2 for an in-depth discussion) was 16.4 (standard deviation[SD] 2.6) with a range of 14 to 19. Although there was no statistically significant difference in report scores among laboratories offering different types of testing (*e.g.* predisposition, pre-symptomatic and pharmacogenetic testing) (p>0.1), there was a significant difference in the mean reporting score among labs in different settings, with research labs having a lower mean report score than all other settings (Table 1.16) (p<0.05). Differences in the scores among labs in the other four settings were not statistically significant. Similarly, labs accessioning <150 samples per year had statistically lower mean report scores than labs accessioning any of the other three ranges selected. Other factors associated with lower report scores were labs with SOPs for few or no procedures (p=0.001) and labs that were not licensed (p=0.048) and did not participate in proficiency testing (p=0.013). Pair-wise comparisons also identified affiliation with a clinical or medical genetics unit, director with formal training in molecular genetics, collection of turnaround time data, and performance of prenatal testing as factors associated with better scores (p=0.003, 0.002, 0.007, and 0.001, respectively).

Table 1.15. Items included in laboratory test reports

Item	% of laboratories that include the item	n
Sample collection date	86	676
Name of patient	97	762
Date of birth	88	692
Unique laboratory identification number	88	692
Date of report	99	782
Reason for testing or disease locus tested	89	700
Genotype and/or haplotype identified for the individual	95	748
A statement on the limitations (sensitivity/specificity limits of accuracy as appropriate) of the test result	78	613
Suggestions for further testing when appropriate	82	644
The implications of a positive result for other family members?	61	479

Table 1.16. Analysis of relevant factors versus means reporting index

Laboratory setting	Mean reporting index
Public hospital	18.32
Private hospital	18.61
Public non-hospital-based laboratory	18.72
Private non-hospital-based or independent	18.68
Research	17.42
# samples accessioned	
<150	16.91
151-500	18.33
501-1500	18.74
>1500	18.22
SOP policy	
Yes for all procedures	18.27
Yes for most procedures	18.91
Yes for a few procedures	16.54
No	16.10
Lab licensed?	
Yes	18.45
No	16.45
Participate in PT?	
Yes	18.74
No	16.87

Of the labs that prepared reports, 98% (n=770) issued them to the referring physician; however, some also indicated that they may issue a report directly to a patient (15%, n=118), another referring health care professional (22%, n=173), including genetic counsellors, and the reference laboratory that referred the sample (4%, n=13).

Informed consent and confidentiality

Overall, 57% (n=474) of laboratories required a copy of the informed consent document (*e.g.* a document describing the test and its benefits and limitations) to be provided to the lab prior to testing for at least one analysis offered, and 63% (n=523) had a specific written policy about confidentiality of genetic testing results. Among labs that required informed consent, only 13% would reject a specimen unaccompanied by the consent, with most (69%) indicating they would accession the sample and contact the referring physician to obtain the required documentation. There was a trend for public non-hospital labs, independent labs and research labs to be more likely than private and public hospital labs to require informed consent (Table 1.17), although these differences were statistically significant only when research labs were compared to all other settings ($p<0.01$).

Table 1.17. Requirements for informed consent versus setting and type testing

Setting	Percentage of respondents requiring consent
Public hospital	48
Private hospital	57
Public non-hospital	61
Independent	66
Research	77

Licensing and proficiency testing participation

Directors of 91% of laboratories reported that they were licensed for diagnostic testing, although only 55% (n=455) indicated that licensing was required in their country. It should be noted that directors from every country, with one exception, provided discrepant responses when asked if licensing was required in their country; this suggests (see Chapter 5) either that the term "licensing" is not uniformly understood, or that directors are uncertain about the licensing requirement. In addition, 56% (n=465) indicated that their lab was accredited/certified by a recognised agency or accrediting body. The accreditation system or authority most commonly cited for having accredited/certified the laboratory was sponsored by the government (31%, n=142), followed by CAP (25%, n=118) and CPA (13%, n=62). As expected, there were significant regional differences in the systems used. For example, although CAP was cited by 25% of respondents, all of these laboratories were located in only five of the 18 countries surveyed. Similarly, CPA was cited by labs in only four countries. Among labs that were not accredited/certified (44%, n=362), the reasons given included the fact that accreditation was not mandatory (46%, n=167) and cost (64%, n=232).

Among the labs, 74% (n=616) participated in a PT programme (Table 1.18). Among those that did not, the reasons given included cost (9%, n=20), the lack of a relevant programme for the testing performed in the lab (65%, n=137) and insufficient personnel resources to participate (31%, n=65). The majority of labs maintained turnaround time data (81%, n=670).

Table 1.18. Participation in proficiency testing

Proficiency testing programme	Percentage of laboratories participating	n
Inter-laboratory exchange of specimens	30	182
CAP	22	137
EMQN	20	123
German scheme	18	111
CF Thematic Network	14	87
UKNEQAS	13	81
Italian scheme	10	64
EAA/EMQN	5	30
CORN	1	11
Other*	4	25

* "Other" includes LabQuality, OQUASTA, QMPLA, OMAQMP (Ontario Scheme), EQUALIS Sweden, ISS Project, RCPP, ISS Roma, Instad, QMPLS, Spanish Scheme, EUQALIS.

Patented tests

Patented tests were offered by 65% (n=537) of labs. Patent licences affected the cost of the test for 70% of these labs (n=376), and the number of tests performed for 28% (n=150); 10% of labs (n=82) indicated that they had ceased offering a test because of a patent issue. Among the 35% (n=290) of labs that did not offer patented tests, the most common reason was that the lab had not yet wanted to add a patented test to the test menu (79%, n=229), although other directors cited the inability to secure a patent licence (3%, n=9), the high cost of the royalty fee (7%, n=20) and unacceptable terms of the licensing agreement (7%, n=21) as reasons not to offer a patented test.

Quality assurance practices of the laboratories

The responses to questions related to the performance of PCR analysis revealed a high rate of adherence to the minimum practice standards that were identified by country experts (see list of QA best practices in Table 1.3). However, 7% (n=56) of the 802 labs that utilised PCR did not take adequate steps to prevent contamination, which can result in erroneous results, and 10% (n=80) did not include all relevant controls, which can result in incorrect interpretations. The latter finding may be due in part to the lack of commercial availability of appropriate control materials. In contrast, responses to the DNA sequencing section revealed that a substantial number of the 595 laboratories that utilise this method did not fulfil the minimum requirements identified. For example, 15% (n=89) of respondents did not analyse both strands of the DNA, and 25% (n=149) did not confirm positive results by sequencing a second aliquot. Deficiencies in the reporting of sequencing results were also identified. These included the failure of a substantial number of labs (40%, n=238) to note on the report that the technique would not detect deletions and duplications, or that mutations in the promoter or intragenic regions would not be detected (28%, n=167).

In order to compare QA practices with other variables, a QA index was calculated for each laboratory (see the above section on methods for the derivation of the index). Overall, the mean QA index was 86.27% (SD 13.44) with a range of 64% to 100%. Pair-wise comparisons of the QA index with variables that were not included in its derivation were carried out and revealed a significant association with four variables (Table 1.19): a director with formal training in molecular genetics, affiliation of the laboratory with a genetics unit, accreditation of the laboratory, and participation in PT. Results of multi-variate analysis indicate that accreditation status is the most important predictor of QA index, followed by a director with formal training in molecular genetics and participation in PT.

Accreditation was defined in the survey's glossary as "formal recognition of the competence of a laboratory by an authoritative organisation". Its association with a higher quality index suggests that accreditation of MGT laboratories is an important way to assure quality. Similarly, the finding that participation in PT programmes was associated with a higher quality index appears reasonable and provides an indirect validation of the scoring scheme. Laboratories participating in PT had in place a mechanism to respond to identified deficiencies, leading to improvements in laboratory quality. The fact that directors with formal training in molecular genetics were a significant predictor of the QA index is also an important observation. It is possible that directors with formal training are more aware of professional guidelines for the good performance of molecular genetic techniques and have incorporated these into their laboratory practice. Directors educated in other disciplines may need additional training to ensure quality in MGT techniques.

Finally, the association of a higher QA index with a clinical or medical genetics unit may be related to the fact that the index included items that would lead to greater clinical utility of results. For example, a QA item included under the sequencing section was that the report should correlate a detected change with known functional changes and clinical reports.

Variables that were not significantly associated with QA index included: country (p=0.131), laboratory setting (p=0.208), receipt of transborder specimens (p=0.062), laboratory requirement for informed consent (p=0.558), policy on confidentiality (p=0.632), retention of specimens (p=0.216), licensing status (p=0.736), and degree of the director (MD vs. PhD, p=0.701). The lack of a relationship between the requirement for informed consent and the presence of a confidentiality policy and QA index is notable. This result indicates that although the need for informed consent and confidentiality of genetic testing results has been identified as important patient management and clinical issues, labs that had these safeguards in place did not have significantly better QA indices. Therefore, laboratory practices with regard to patient management issues do not necessarily correlate with higher laboratory QA practice. Finally, the lack of significant association with the laboratory setting suggests that laboratories in all settings performed at similar levels with regard to the minimum standards identified.

Table 1.19. Variables that correlated with the mean reporting index

Director with formal training in molecular genetics	**Mean QA index (%)**	**p value**
Yes	88.04	<0.005
No	82.86	
Laboratory is affiliated or associated with a clinical or medical genetics unit		
Yes	87.56	p=0.003
No	83.31	
Laboratory is accredited		
Yes	89.51	p<0.005
No	83.75	
Participate in PT?		
Yes	88.00	p<0.005
No	83.80	

Chapter 2

TRANSBORDER FLOW AND RARE DISEASES

Introduction

Rare diseases are, by definition, diseases that occur infrequently in the population.

Although individually infrequent, rare diseases are, taken together, a significant public health problem. According to the Office of Rare Diseases in the United States, more than 6 000 rare diseases affect around 25 million Americans. In the Europe Union, despite the low incidence of a single disease, patients affected by rare diseases are about 35 million. These diseases are often chronic and disabling and are a cause of premature mortality.

A critical point in the management and treatment of people with rare diseases is proper diagnosis, as knowledge of these diseases is limited among health-care professionals. This may often cause delays in diagnosis, appropriate treatment and care.

For many uncommon conditions, diagnostic services for rare diseases are often established in association with a research programme. When the research programme terminates (or its funding ends) the related service components also often disappear abruptly unless the research team is able to transfer its know-how to a service laboratory, usually in the same institution. The financial and legal implications of running a clinical service are, however, significantly greater than those of a research project. Few researchers are aware of this. As a result, many rare conditions present a problem of access. Only one or a few laboratories in the world may offer and/or accurately perform tests on a specific rare disorder and a patient specimen may have to be sent to another country to be tested.

A survey carried out in 1998-99 by an expert working group to the UK National Health Service (NHS) Executive and the Human Genetics Commission (Laboratory Services for Genetics) indicated that approximately 27% of the UK workload for the rarer disorders was managed by sending samples from the receiving laboratory for analysis elsewhere. It also indicated that 34 disorders for which it would be possible to offer clinically valid and useful tests were not available on a diagnostic basis to clinical users in the United Kingdom.

The OECD survey confirms these results on a larger scale and shows that access to testing for rare disorders is a shared problem across member countries. 64% of respondents (529 laboratories), including laboratories in every country participating in the survey, indicated that their laboratory received specimens from outside the country (overall mean, 2.5% of all specimens received). Furthermore, laboratories in all settings were receiving transborder specimens. In all, over 18 000 specimens crossed borders in 2002. Of the laboratories receiving transborder specimens, 73% reported that these were for rare diseases, and 25% for testing offered only as part of a research study.

There are significant policy issues associated with the transborder flow of samples. At present, the issue of greatest concern is the lack of internationally agreed good practices for quality assurance in molecular genetic testing (MGT). A related issue is the need for an internationally accepted mechanism to assist with and evaluate test referrals across countries.

A first challenge, however, is to better understand the key features of the transborder flow phenomenon through an in-depth analysis of survey data and a review of the available literature. This chapter is an attempt to do so.

Background information

Referral of samples across borders does not occur in any organised or regulated way. Health-care centres may rely on a variety of informal or formal networks to secure genetic testing for rare diseases. These networks include professional associations, rare disease networks, a tradition of collaboration between countries or between institutions, patients' associations, etc.

In the United States, GeneTests and the University of California at San Diego's UCSDW3BG Biochemical Genetics database are two major US resources that list US and non-US diagnostic laboratories (the latter when the test in not available in a US laboratory). Participation in these databases is voluntary. In May 2004, GeneTests listed 605 labs. Of these, more than half, 343, were only research laboratories.

In Europe, there are two similar databases, EDDNAL and Orphanet, which provide information on tests in European laboratories. In addition, several countries have national lists of molecular laboratories. Some disease-specific networks also maintain lists of specialised health-care centres and testing facilities (for example, ESDN for skeletal dysplasia, NEPHIRD for epidemiological data collection on specific rare disorders). Most of these networks are sponsored by the European Commission.

Commercial enterprises are now attempting to fill the gap in rare disease testing by offering services on an international scale. In general, they act as referral nodes to a network of private and public laboratories. It is however too early to report on the outcome of this type of initiative.

A study on movement of samples for ten rare diseases in European countries was carried out in 2003 by D. Taruscio and collaborators at the Istituto Superiore di Sanità (Italy). The study was commissioned by the EC-Joint Research Centre Institute for Prospective Technological Studies Project[3] The human genetics societies of the 25 EU countries were contacted. The study confirmed the heterogeneity of approaches and of networking initiatives. There are however, privileged corridors for referrals, often based on personal contact and professional co-operation. For example, Sweden (the Swedish Department of Clinical Genetics in Lund) sends samples for Marfan syndrome testing to Germany and samples for Rett syndrome testing to Denmark. Ireland has arrangements for Marfan syndrome testing with Salisbury (United Kingdom) and for Rett syndrome testing with Leiden (Netherlands). Estonia sends samples for Marfan syndrome testing to Lithuania.

3. *www.jrc.es/home/publications/publication.cfm?pub=1124*

To determine the actual requirements regulating transfer of samples in each country, a separate survey of experts and government representatives was carried out by the OECD in 2003 (Table 2.1). In a number of countries, transport of samples has to be authorised only if the declared purpose is research. For clinical samples, there is usually no specific provision. On the other hand, when data accompany the samples, various requirements for data protection may apply and these often differ significantly across countries.

Table 2.1. National guidelines/requirements for the international transfer or receipt of clinical samples*

Country	Transfer/receipt
Austria	No specific guidelines
Belgium	There is no specific legislation- Arreté Royal 15/04/88 Relatif aux Banques de Tissues et du Prelevement which addresses conservation, handling, transportation and distribution of human tissues may apply.
Canada	The CCMG issued a policy statement concerning DNA banking in 1991. The guidelines stipulate that records and samples should be maintained indefinitely. The guidelines are restricted to DNA banking in relation to medical genetic diagnostic services and stipulate that a DNA bank is "a facility that is entrusted to store DNA so that it will be preserved for future analysis, for the purpose of promoting the health and well-being of the depositor and his/her relatives and descendants".
Czech Republic	There is no specific legislation (laboratories follow standards according to ISO 17025).
Finland	There is no specific legislation. However, new rules were introduced in the Act on Use of Human Organs and Tissues for Medical Purposes, 1 September 2001.
France	Guidelines are available. The storage time of tests results should be 30 years. Importation and exportation of samples for research purposes has to be authorised. The authorisations are delivered by the Ministry of research (code de la Santé Publique art R 1245.12, 1235/6, 1235/10). If the reason for import/export is medical, there is no specific regulation except for the transporter who requires an authorisation from the Ministry of Transport.
Germany	There is no uniform legislation.
Ireland	No specific guidelines.
Italy	Conditions are specified in the 1999 National Bioethics Committee Guidelines on Genetic Testing.
Japan	Requirements are specified the in the Guidelines of Japan's Bioethics Committee.
Norway	Requirements are based on Act 21 of 21st February 2003 on Biobanks. The Act regulates the collection, storage and use of human material. Diagnostic and Treatment Biobanks are defined as "collection of human biological material delivered for medical examination, diagnostics and treatment."
Portugal	There is no specific provisionl (new legislation is in preparation).
Spain	Requirements are included in the privacy law and the national Royal Decree 411/96 on the use of human tissue. The latter includes the definition and functions of tissue banks.
Sweden	Swedish Parliament Law on Biobanks in Health Care 2002; 297-Swedish Research Council-May 2003. The act regulates how human biological material is to be collected, stored and used for certain purposes with respect for the personal integrity of the individual. Biobanks are defined *as " biological material from one or more human beings that is collected and preserved for an indefinite or limited period and whose origin is traceable to an individual or individuals*".
Switzerland	There is no specific provision.
Turkey	Laboratories follow the principles of the UNESCO declaration on human genetic data.
United Kingdom	Requirements are based on the guidelines developed by the Royal College of Pathologistsl The Human Tissue Authority is drafting codes of practice relating to the removal and storage of material following the Human Tissue Act (2004).
United States	Guidelines mostly relate to the retention and storage of newborn screening blood-spot samples. Requirements vary by State. The Clinical Laboratory Improvement Amendments (CLIA) does not have specific language for genetic testing, at this time, and therefore such samples are subjected to the general requirements which specify samples must be retained during the testing process.

Note: Based on responses to the questions: "Are there any specific guidelines/requirements in your country for the international transfer or receipt of human samples for research purposes? Do any specific guidelines/requirements apply to the clinical diagnostic sector?"

* Included in Annex B.

Summary of survey results

Dimension of transborder flow

A significant proportion (64%, n=529), although highly variable (range 20-90%), of laboratories in every country indicated they receive specimens from other countries (Table 2.2). Among those that do, 73% (n=386) indicated that the specimens were for rare disease testing, although there was broad range of responses among countries (range 28-100%) (Table 2.3). Among the laboratories that receive specimens from other countries, 23% (n=121) indicated the tests are usually offered as part of a research study (range 0-100%) (Table 2.3)

Table 2.2. Percentage and number of laboratories that receive transborder specimens, by country

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
%	41	50	69	33	90	66	30	54	43	59	46	58	78	69	67	42	64	20
n	14	4	20	2	93	84	3	65	3	16	35	18	56	97	6	5	7	1

Table 2.3. Percentage and number of laboratories that receive transborder specimens for rare disease or research testing, by country

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Total n	14	4	20	2	93	84	3	65	3	16	35	18	56	97	6	5	7	1
Rare disease																		
%	78	100	80	50	81	78	33	64	33	68	52	100	66	78	67	100	28	100
n	11	4	16	1	75	66	1	42	1	11	18	18	37	76	4	3	2	1
Research																		
%	57	0	20	0	43	25	33	38	33	31	31	0	16	5	17	40	57	100
n	8	0	4	0	31	20	1	21	1	5	9	0	9	5	1	1	4	1

Countries receiving samples

The percentage of samples received from outside the country borders ranged from <1% of total laboratory volume to 100% of volume in one laboratory (located in the United Kingdom) (Figure 2.1). Table 2.4 shows the geographical spread of countries involved in the transborder referrals of samples. Although the data represent a snapshot of the current situation, they show that transborder flow of samples is common and that a number of countries have set up fairly large referral networks (*e.g.* US labs referred to laboratories in 14 countries, UK to 13, Belgian to 10, French to 12, Italian to 11, German to 10, Spanish to 12).

These countries share some common features: a highly developed MGT sector, highly developed national rare disorder networks and clinical research, significant ethnic mix in the population.

Laboratories in these countries may, however, also act as "dispatchers" or "relay centres", *i.e.* they might send samples to appropriate testing centres on behalf of laboratories in third countries that lack the networks or expertise. This would need confirmation through further investigation.

Barriers to transborder exchange of specimens were indicated by 27% of directors. They included: difficulties with reimbursement for services (66%), liability issues (22%), regulatory requirements of other countries (21%) and complexity of required forms and documents (27%). Less frequently cited as barriers were local regulations prohibiting such referral (1%) and customs regulations (1%).

In many countries, insurance or social security does not pay for services furnished outside the country except under special circumstances. The interpretation of exceptional conditions is often decided on a case-by-case basis. Thus, out-of-pocket payments for patients may be an important issue for international referral of samples.

Figure 2.1. Distribution of specimens received across borders among all participating laboratories

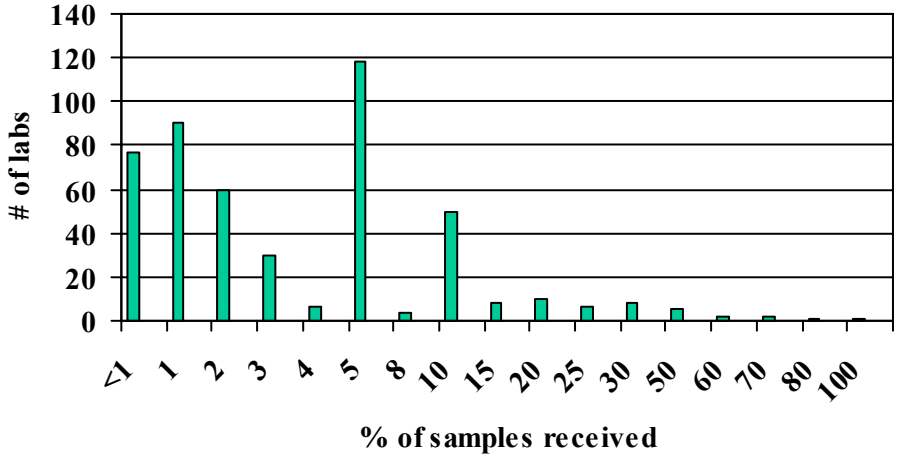


Table 2.4. Countries from which samples are received

Country	% of labs receiving specimens from country/(n)	Countries receiving specimens
Australia	18/89	Canada, Finland, France, Germany, Ireland, Italy, Sweden, Switzerland, UK, USA
Austria	17/84	France, Germany, Italy, Spain, Switzerland, UK, USA
Belgium	25/123	Austria, Canada, France, Germany Ireland, Italy, Spain, Switzerland, UK, USA
Canada	17/84	Austria, Finland, France, Germany, Italy, Switzerland, UK, USA
Czech Republic	9/44	Austria, France, Germany, Italy, Portugal, Spain, Switzerland, UK, Sweden
Denmark	12/59	Austria, Canada, Finland, France, Germany, Italy, Sweden, Switzerland, UK, USA
Finland	9/44	Austria, Canada, France, Germany, Italy, Sweden, Switzerland, UK, USA
France	24/118	Austria, Canada, Finland, Germany, Italy, Norway, Portugal, Spain, Sweden, Switzerland, UK, USA
Germany	30/148	Austria, Canada, Finland, France, Italy, Spain, Sweden, Switzerland, UK, USA
Greece	19/94	Austria, France, Germany, Italy, Sweden, Switzerland, UK, USA
Hungary	12/59	Austria, Finland, France, Germany, Ireland, Italy, Spain, Sweden, UK, USA
Iceland	2/10	Germany, Norway, Sweden, Switzerland, UK, USA
Ireland	15/74	Austria, Canada, Finland, France, Germany, Sweden, Switzerland, UK, USA
Italy	27/133	Austria, Belgium, Canada, Finland, France, Germany, Portugal, Spain, Sweden, UK, USA
Japan	7/34	Austria, Canada, France, Italy, UK, USA
Korea	1/5	Germany, Switzerland, UK, USA
Luxembourg	2/10	Canada, France, Germany, Switzerland, UK
Mexico	7/34	Canada, France, Germany, Spain, Switzerland, USA
Netherlands	18/89	Austria, Belgium, Canada, Finland, France, Germany, Italy, Portugal, Spain, Sweden, UK, USA
New Zealand	9/44	Canada, France, Germany, Switzerland, UK, USA
Norway	10/50	Finland, France, Germany, Ireland, Italy, Sweden, Switzerland, UK, USA
Poland	11/54	Austria, Canada, France, Germany, Italy, Sweden, Switzerland, UK, USA
Portugal	18/89	Austria, France, Germany, Italy, Spain, Sweden, Switzerland, UK, USA
Slovak Republic	7/34	Austria, France, Germany, Italy, Spain, Switzerland, UK, USA
Spain	25/123	Austria, Canada, Finland, France, Germany, Italy, Portugal, Sweden, Switzerland, Turkey, UK, USA
Sweden	13/64	Austria, Canada, Finland, France, Germany, Italy, Norway, Switzerland, UK, USA
Switzerland	16/79	Austria, Canada, France, Germany, Italy, UK, USA
Turkey	21/103	Austria, Canada, France, Germany, Italy, Portugal, Spain, Sweden, UK, USA
United Kingdom	31/153	Austria, Belgium, Canada, Finland, France, Germany, Ireland, Italy, Portugal, Spain, Sweden, Switzerland, USA
United States	34/168	Austria, Belgium, Canada, Finland, France, Germany, Ireland, Italy, Norway, Portugal, Spain, Sweden, Switzerland, UK

Current practice

Bivariate analysis of the transborder flow

Laboratories receiving transborder specimens were analysed against laboratories that do not. There was no significant difference between laboratories that did and did not receive transborder specimens in terms of the type of testing offered, indication of a requirement to have a copy of the informed consent, result reporting, whether or not the laboratory director signs the report, whether or not the laboratory has SOPs, the type of professionals employed, whether or not the laboratory indicated licensing as a requirement in their country.

There was also no significant difference between labs that did and did not receive transborder specimens and the primary setting of the laboratory where the analysis was carried out. The five setting groups were examined to see if there was a statistically significant difference in transborder flow. The analysis did not reveal any statistical difference between any of the pairings made. When, however, each individual type of setting was compared to the other four, there was a statistically significant difference ($p=0.011$) between independent and all other settings, with independent laboratories less likely to receive transborder specimens compared to all other sites (Table 2.5).

There was no significant difference between laboratories that did and did not receive transborder specimens and storage when the four options provided in the question were examined. The analysis did not reveal any statistical difference between any of the pairings made. When each possible response was compared to the other three, there was a statistically significant difference ($p=0.001$) between those that stored indefinitely and all other storage times. Laboratories that store indefinitely are more likely to receive transborder specimens (Table 2.5).

There were some consistent differences between laboratories that received transborder specimens and those that did not. Laboratories that received transborder specimens were more likely to include a statement on the limitations of the test result, suggestions for further testing when appropriate, and especially the implications of a positive result for other family members.

There was a significant difference between laboratories that did and did not receive transborder specimens and whether or not a physician employed by the lab provided genetic counselling. Laboratories that received transborder specimens were more likely to provide genetic counselling.

Multivariate analysis of the transborder flow

Exploratory analyses of transborder flow were carried out for the variables listed in Table 2.5.

Table 2.5. Results of multivariate analysis of variables related to transborder flow

Variable	p value	Significant
Country	p=0.290	No
Setting (independent vs. all others)	p=0.011 (less likely)	Yes
Formal training	p=0.273	No
Affiliated or associated with a clinical or medical genetics unit	p=0.003 (more likely)	Yes
Technicians employed (<4, >4)	p=0.038 (more likely to have a small number of technicians)	Yes
MD vs. other types of director	p=0.241	No
Ever refer specimens to another testing laboratory located outside of your country	p=0.344	No
<1 000 vs. >1 000 specimens	p=0.77	No
Commercial test kits vs. in-house only and both	p=0.339	No
SOPS (yes for all or some vs. no)	p=0.167	No
Statement of limitations on the report	p=0.026 (more likely)	Yes
Suggestions for further testing	p=0.031 (more likely)	Yes
Report signed	p=0.258	No
Require informed consent	p=0.464	No
Confidentiality policy	p=0.389	No
Storage (indefinitely vs. others)	p=0.006 (more likely to store indefinitely)	Yes
Participate in PT	p=0.217	No
Do prenatal testing	p=0.285	No
Offer tests covered by patents	p=0.344	No

Multivariate analysis (linear regression) identified two factors that account for most of the difference between laboratories that did and did not receive transborder specimens: affiliation or association with a clinical or medical genetics unit and indefinite storage of samples. The laboratories associated with a clinical unit and that stored samples indefinitely were likely to be located in major public hospital or research centres.

Although there was no significant difference between laboratories that did and did not receive transborder specimens and their requirement to have a copy of the informed consent, there was a statistically significant difference in this requirement when the setting of the laboratory was considered. Specifically (of laboratories that received transborder specimens), public hospital, private hospital and public non-hospital laboratories had a requirement for informed consent in 50%, 51% and 52%, respectively. In contrast, of the laboratories in the independent and research settings that accept transborder specimens, 72% and 63%, respectively, require informed consent.

Discussion

Dimension of transborder flow

Analysis of survey data discloses that 64% of laboratories received specimens from other countries. Among these, 73% indicated that the specimens were for rare disease testing. Therefore, 47% of the 827 laboratories involved in the survey performed genetic tests for rare diseases on biological samples from outside their country, and 16% received specimens from abroad for non-rare diseases. Although a stated motive was that they received these specimens as part of a research study, possible other reasons need to be further explored.

The impact of well-established rare disease or other clinical networks should be assessed to understand whether they have any role in the observed international referral patterns.

Regulatory environment

Analysis of background information reveals that different countries may have quite diverse regulatory approaches and requirements (see Chapter 4; Table 2.1). It is worth noting that bodies issuing guidelines varied (from government agencies to national medical associations). In most instances, regulations on transfer only concern samples for research purposes.

Among countries that did not have official requirements, a few reported that regulations are being prepared; therefore, the situation for these countries may change in the short to medium term. In other instances, responsibility is given to local authorities.

Current practice

Cross-analysis was performed in order to identify what factors may differentiate laboratories that received transborder specimens from those that did not.

Multivariate analysis (linear regression) identified two factors that account for most of the difference between laboratories that did and did not receive transborder specimens: affiliation or association with a clinical or medical genetics unit and indefinite storage of samples. Additional statistical analysis shows that laboratories that received transborder specimens were more likely to include: a statement on the limitations of the test result, suggestions for further testing when appropriate, and especially, the implications of a positive result for other family members.

There were also some consistent differences concerning result reporting and availability of genetic counselling. Laboratories that received transborder specimens were also more likely to provide genetic counselling; however, this question might have raised some ambiguity concerning how this relates to samples referred from other countries.

These results are consistent with what is to be expected if transborder referral occurs primarily for rare disorders and as part of a research or experimental protocol. Nonetheless, this raises questions regarding the documented differences in quality control practices across countries, particularly in relation to confidentiality, storage and consent.

In this respect, interesting, and related, information is provided by responses to the question on setting and requirement of informed consent among laboratories that receive transborder specimens. Responses show that independent and research laboratories were

significantly more likely to require informed consent than public hospital, private hospital and public laboratories. Also, the rate of public hospital, private hospital and public laboratories requiring informed consent was lower than expected, *i.e.* equal to or slightly higher than 50% (for further details, see Chapter 4).

Even though there are no differences in the type of testing offered , it may be of value to identify the types of tests that are most requested in transborder referrals. Other specific questions that the survey raises and on which further information may be needed concern the requirements for certification/accreditation and the sources and options for reimbursement in out-of-country referrals.

Conclusions

The survey provided valuable comparative information on transborder flow of samples across countries. Proper exploitation of these data could represent a powerful tool for defining ways to improve the quality of genetic testing internationally. In conclusion, it was expected that rare disorder specimens often have to be sent to another country to be tested (see Introduction). The survey not only confirmed this hypothesis but revealed that transborder flow actually involves the majority of laboratories, and that it is particularly significant in some countries (Belgium, France, Italy, Spain, United Kingdom, Germany, United States). All these results point to the significance of transborder flow at international level and, therefore, to the need to enable it through clear and internationally agreed codes of conduct or procedural guidelines.

The survey identified many important aspects of current laboratory practices and genetic services. Transborder flow clearly attempts to fill a serious gap in the availability of tests for rare disorders in many countries.

In dealing with patients with rare genetic conditions for whom there might be no appropriate treatment, it seems essential that they would not in any way be disadvantaged by a failure even to diagnose their condition. A number of recommendations can thus be drawn.

Improving availability of rare-disease testing

There is a need to improve the availability of gene testing for rare diseases and to translate research findings into validated clinical testing, as many tests are provided only in research settings. This will require the development of mechanisms and guidelines for determining the clinical readiness of potential tests. Issues to be further explored include how analytic validity, clinical validity and clinical utility of genetic tests are currently assessed across the different jurisdictions, particularly for newly developed rare-disease tests.

Promoting quality testing

It is also necessary to promote quality testing. There is a lack of a recognised and internationally agreed set of basic indicators for quality. In several instances, quality might be inferred by comparing practice with national guidelines and regulatory requirements; however, their implementation may vary markedly across countries. Concerning quality, an important, as well as difficult, issue is to determine those practices that can affect patient outcomes and should be considered as priority issues to be addressed internationally. Guidance and quality indicators need to be developed for all testing phases and have to be available also for genetic tests for rare diseases.

Thus, priority issues for international action may include:

- Bridging regulatory differences among countries in terms of confidentiality practices, reimbursement, sample transport and storage, accreditation/certification.
- Addressing factors relevant to the analytical quality of laboratories, such as participation in proficiency testing and training.
- Addressing factors relevant to the availability and quality of result reporting and genetic counselling.

Possible areas for international co-operation in drawing mutually accepted guidelines may include (but may not be limited to):

- General areas (*e.g.* reporting practices) in which certain practices differ and international co-operation can provide significant benefits.
- Critical issues (*e.g.* indicators for laboratory quality, confidentiality) for which there is still a need to develop approaches and criteria; therefore, an international effort may be recommended.

Improving access to rare-disease testing

International co-operation will benefit from integration and exploitation of existing resources at regional, national and international levels, with special attention to: national reference centres for diseases and associated networks, networks for genetic testing and nationally and internationally funded projects on rare diseases and genetic testing.

Finally there is currently no strategic international overview for the designation of rare-disease testing services and no mechanism to assist in referrals or to ensure the availability of effective tests and/or to avoid unnecessary duplication of provision (*e.g.* allocation of particular tests).

There is also no uniformly adopted funding basis for the interchange of diagnostic samples. Barriers to access should be addressed internationally. Efforts need to be considered to improve coverage and reimbursement for all tests with an established clinical utility, including “niche” tests.

Chapter 3

REPORT WRITING

Introduction

The usefulness of any medical test requires results to be reported, understood and used appropriately for patient management. While genetic testing cannot be considered unique among medical tests, particular issues must be emphasised when molecular genetic test results are reported. The traditional medical model aims to treat disease, whereas results from genetic tests are often used to educate patients and providers about disease susceptibility or in family planning decisions and to prevent complications from disease. DNA-based testing is ordered to determine if a genotype that is associated with a risk for a medical condition is present. However, the genotype, in itself, can be uninformative or misinterpreted if certain test-, patient- and family-specific information is not used in developing an interpretation. Molecular genetic test results often have implications for other family members, and health-care professionals need to understand this as well. For carrier, pre-symptomatic and susceptibility testing, the patient is often asymptomatic and the test result may be the sole indicator of increased risk. As such, it is essential for the test result to be understood, and the certainty or uncertainty of the analytic test result, its limitations and what it potentially means for the patient tested and the family must be communicated. For diagnostic testing, similar principles apply. A result report that is clear and complete is a vital step towards ensuring understanding of the test result by health-care providers and subsequent communication to the patient.

Genetic testing is a rapidly evolving area, and studies show physicians have a relatively poor knowledge of genetics (Capelli *et al*., 1998; Erickson *et al*., 2000). Nonetheless, in some countries, referral for genetic testing has increased (Benach *et al*., 1999). In some cases, this has occurred as a consequence of guidelines from professional organisations recommending DNA-based screening, as in the case of cystic fibrosis prenatal screening in the United States (American College of Obstetricians and Gynecologists and American College of Medical Genetics, 2001; Vastag, 2003). Genetic tests play a major role in providing information relevant to risk assessment for susceptibility to disease or in informing couples of the risk of having a child with a medical condition. In 2001, published results of a survey of physicians showed that many were not prepared to interpret genetic risk information when presented with results from a hypothetical report for BRCA1/2 gene analysis (Dawson *et al*., 2001). The same study revealed that many test reports do not provide a complete set of informative elements for those who may use the report for patient management decisions. Other studies have reported significant variability in how laboratories report genetic test results (Bakker *et al.*, 1999; Andersson *et al.*, 2002).

A follow-up study in 2003 assessed the physician-perceived usefulness of and satisfaction with medical reports on genetic tests for cystic fibrosis and factor V Leiden and identified several elements that physicians desire in a report (Andersson *et al.*, 2003). Physicians wanted genetic test reports that are comprehensive and include information

useful for clinical decision making, genetic counselling information and information on implications for family members. These findings argue for a strong interpretive component in reports on genetic test results.

Questions are sometimes raised as to where to draw the line in the interpretation of results between the role of the laboratory and that of the physician. An argument can be made that laboratories possess expertise on the technologies employed to test for sequence variations, knowledge of the clinical validity of tests offered and of the limitations of those tests. For certain results, laboratories can suggest follow-up testing to clarify the meaning of an analytic result. Given the speed at which genetic tests are evolving, it is not reasonable to expect the majority of physicians, especially generalists, to be familiar with the most recent aspects of tests available and their benefits and limitations as they apply to their patients.

A number of guidelines, recommendations and best practices have been developed to guide laboratories in preparing useful test reports. Tables 3.1-3.3 compare some of these. From these recommendations, a core set of elements are commonly proposed for inclusion in the report. They include:

- Clear identification of the patient for whom the test was ordered.
- The reason the test was ordered, including relevant clinical and family-specific information.
- The analytic result (genotype).
- An interpretation of the test result, including its relevance to the reason the test was ordered.
- Limitations of the test and its reported result.
- Implications for other family members.
- Recommendations for follow-up testing, if appropriate.
- Recommendations for genetic counselling.

Table 3.1. Comparison of recommended information elements

Administrative and patient information

	American College of Medical Genetics[1]	College of American Pathologists[2]	NCCLS MM1A[3]	UK Clinical Molecular Genetics Society[4]	Swiss Society of Medical Genetics[5]
Information recommended:					
Name of individual	√	√	√	√	√
Date of birth	√		√	√	√
Laboratory identification number	√	√	√	√	√
Ethnicity, where appropriate	√			√	√
Reference to other family members, if appropriate	√		√	√	√
Signature of laboratory director or other authorised individual	√	√	√		√

Notes:

1. American College of Medical Genetics (2003), Standards and Guidelines for Clinical Genetics Laboratories, *www.acmg.net/Pages/ACMG_Activities/stds-2002/stdsmenu-n.htm*.

2. College of American Pathologists, Laboratory General Checklist; Molecular Pathology Checklist (2003), *www.cap.org/apps/docs/laboratory_accreditation/checklists/checklistftp.html*.

3. NCCLS (2000), Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline, NCCLS document MM1-A (ISBN 1-56238-395-7). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, USA.

4. UK Clinical Genetics Society (2003), Report Writing, *www.cmgs.org/BPG/Guidelines/2nd_ed/report-writing.htm*.

5. SSMG (Swiss Society of Medical Genetics) (2003), Reporting guidelines: clinical molecular genetic testing, *www.sgmg.ch/sections/Documents/Statements/publications.htm*.

Table 3.2. Comparison of recommended information elements

Information about the specimen and test ordered

	American College of Medical Genetics[1]	College of American Pathologists[2]	NCCLS MM1A[3]	UK Molecular Genetics Society[4]	Swiss Society of Medical Genetics[5]
Information recommended:					
Specimen type tested		√	√		√
Differentiate foetal samples from those of their mother					√
Specimen collection time/date	√	√			
Time of receipt of specimen in laboratory	√				
Indication for testing	√		√		√
Test performed	√		√	√	√
Methodology	√	√	√	√	√
Mutations tested	√	√	√	√	√

See notes under Table 3.1.

Table 3.3. Comparison of recommended information elements

Test results, interpretation and follow-up

	American College of Medical Genetics[1]	College of American Pathologists[2]	NCCLS MM1A[3]	UK Molecular Genetics Society[4]	Swiss Society of Medical Genetics[5]
Information recommended:					
Test result	√	√	√	√	√
Interpretation of test result	√	√	√	√	√
Limitations of the test and result	√	√		√	√
Recommendations for follow-up testing, when appropriate	√			√	√
Recommendations for genetic counselling	√	√	√	√	√
Date of report	√	√	√		
Reference to a preliminary report, if issued	√			√	√
Means to contact the laboratory	√	√			√
Clearly indicate when results come from a different laboratory than the one issuing the report				√	√

See notes under Table 3.1.

The interpretation of a molecular genetic test depends on the context in which the test is ordered, the clinical question asked, limitations of the technology employed and family implications. Guidelines have generally recognised these needs and include recommendations to ensure that appropriate information is provided. Guidelines often recognise that the test report may be used by health-care professionals other than the ordering physician and include recommendations that reports should be sufficiently comprehensive to allow the result to be understood in the context of why the test was ordered. Another aspect that guidelines uniformly recognise is the need for standardised nomenclature, particularly with regard to the description of mutation variations. To address this, guidelines emphasise that reports need to be clear, concise, accurate, complete and credible.

The reporting quality score

A reporting quality score was developed to simplify the analysis of the factors that influence reporting practices. Report items covered by questions that allowed only "Yes" or "No" answers – 11(c), 11(d), 11(f), 11(e) and the seven sub-sections of 11(b) – were graded as "basic", "specific" or "also useful" and assigned values of 3, 2 or 1, respectively, to make up the total reporting quality score for each respondent (Table 3.4). "Basic" items were considered essential to any report, "specific" items contribute to the interpretation of the report and are often context-specific, while "also useful" items would not invalidate the report if absent, but are useful for audit and interpretation. Because most laboratory standards and guidelines mandate the inclusion of two patient identifiers on all patient materials, the responses were combined to include patient name, date of birth and unique laboratory identifier in a single "basic" item. Respondents were awarded 3 points if they indicated that any two of these three items were included on each report. Date of birth was also included separately as a "specific" item because of its importance

in the interpretation of genetic test results. The grading of items was agreed by debate among the Steering Group members.

Table 3.4. The reporting quality score

Question	Report items	Value	Responses (%)
	Basic		
11(b)	Two unique identifiers	3	100
11(b)	Genotype and/or haplotype identified for the individual	3	95
	Specific		
11(b)	Date of birth of patient	2	88
11(b)	Reason for testing or disease locus tested	2	89
11(c)	Statement on the limitations of the test	2	78
11(d)	Signed by the laboratory director	2	84
11(f)	Implications of the result for other family members	2	61
	Also useful		
11(b)	Date of report	1	99
11(b)	Sample collection date	1	86
11(e)	Suggestions for further testing	1	82

It must be recognised that this scoring system does not take into account the differences in reporting practices in different countries. For example, some countries do not allow laboratories to suggest further tests. Neither does the score reflect the wide variation in the format and presentation of reports. While an excellent presentation can never make an inadequate report adequate, poor presentation can turn a report that contains all the required information into an inadequate report, as key data may be overlooked by the recipient. Finally, the reporting quality score indicates self-reported laboratory compliance to practices accepted as important. The score does not measure actual utility or effectiveness of the reports to health-care providers and their patients. The reporting quality score may be appropriately viewed as a quality indicator, not a quality measure.

Survey results: analysis and discussion

Respondents not issuing reports

Reports were issued by 95% of responding laboratories. The only variable that correlated strongly with the 5% of laboratories that did not issue a report was being in a research setting ($R^2 = 0.6532$).

Range of scores

The highest possible reporting quality score was 19 (Table 3.5). Overall, the mean reporting score was 16.4 (SD 2.6) with a range of 14 to 19. The median score was 18. The high mean and median scores suggest high quality of reporting in the participating laboratories. The higher median score suggests that the distribution of scores is negatively skewed, with most laboratories having scores above the mean. Many standards used by accrediting organisations (NCCLS, 2000; and Table 3.1) dictate that all patient materials

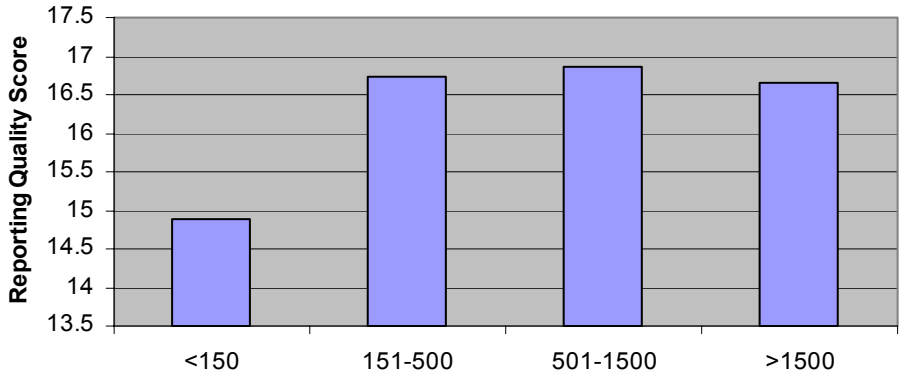
should be identified by two separate identifiers such as name, date of birth or laboratory number. Analysis showed that all laboratories in fact included at least two of these items on their reports, and 86% included all three.

Factors influencing reporting quality score

Number of samples received

The reporting quality score was analysed with respect to the number of samples accessioned in 2001. Laboratories that accessioned fewer than 150 samples had significantly lower scores (p=0.004) than all others (Figure 3.1). Laboratories receiving lower numbers of samples are more likely to be in a research setting and have less opportunity to participate in proficiency testing (PT) schemes than laboratories receiving larger numbers of samples.

Figure 3.1. Samples accessioned in 2001



Pair-wise analysis

Pair-wise exploratory analyses were performed to compare the report quality assurance (QA) score with a number of other factors (*e.g.* setting, director qualification, etc.). The results of these analyses (Table 3.5) identified a number of factors that were associated with a report score, including the setting of the laboratory, a director with formal training in genetics, affiliation with a clinical or medical genetics unit, the availability of standard operating procedures (SOPs), the licensing and accreditation status of the laboratory, participation in PT and maintenance of turnaround time data.

Table 3.5. Pair-wise analysis of factors influencing reporting quality score

Question	Variable	p value	Significant	Direction
2(a)	Setting (research vs. all others)	0.006	Yes	Research setting has lower scores
3(b)	Consulting relationship or affiliation with a clinical or medical geneticist	0.009	Yes	Laboratories affiliated with a geneticist have higher scores
4(a)	MD (including MD/PhD) vs. all other types of directors	0.442	No	
4(c)	Director certified	0.389	No	
4(d)	Director with formal training in genetics	0.002	Yes	Directors with formal training had higher scores
5(a)	Laboratory affiliated or associated with a clinical or medical genetics unit	0.003	Yes	Non-affiliated respondents have lower scores
5(b)	Physicians employed or associated with your laboratory provide genetic counselling services	0.206	No	
5(c)	Laboratory employs any non-physician professionals who provide genetic counselling	0.353	No	
7(a)	Some/all samples are collected off-site of vs. on-site only	0.126	No	
7(c)	Laboratory receives specimens for testing from outside the country	0.453	No	
7(j)	Laboratory refers specimens to another testing laboratory	0.135	No	
10(a)	Standard operating procedures are in place (yes for all or some vs. no)	0.001	Yes	Respondents without any SOPs have lower scores
12(a)	Laboratory requires a copy of the informed consent	0.142	No	
12(e)	A written policy about confidentiality is in place	0.442	No	
12(f)	Laboratory retains specimens after analysis (indefinitely vs. all others)	0.531	No	
13(a)	Are molecular genetic testing laboratories required to be licensed in your country?	0.233	No	
13(b)	Laboratory is licensed	0.048	Yes	Unlicensed laboratories have lower scores
13(c)	Laboratory is accredited/certified	0.039	Yes	Laboratories not accredited/certified have lower scores
13(e)	Laboratory participates in any proficiency testing programmes	0.013	Yes	Laboratories not participating in PT have lower scores
14(a)	Laboratory maintains data on turnaround times	0.007	Yes	Laboratories not maintaining data on turnaround time have lower scores
14(b)	Laboratory carries out prenatal or pre-implantation testing	0.001	Yes	Laboratories not offering prenatal/pre-implantation diagnosis have lower scores
15(a)	Laboratory offers genetic tests which are covered by patents	0.198	No	

Laboratory setting

The analysis of laboratory setting (Question 2a) with respect to the reporting quality score was carried out in two ways. First, the five setting groups were analysed to see if there were statistically significant differences in report scores between the settings. The analysis, which was done using both Scheffe and Turkey B functions using pairings of different settings or a maximum of three-way analysis, did not reveal any statistical difference between any of the pairings made. However, there was a trend for respondents in the research setting to have lower scores than the others. When the data were analysed

and the research setting was compared to all other settings, there was a statistically significant difference (p=0.006), with respondents from research settings having lower reporting quality scores. These differences in mean report scores from the different settings are provided in Table 3.6.

Table 3.6. Mean reporting quality score by laboratory setting

Laboratory setting	Mean reporting score
Public hospital	16.52
Private hospital	16.47
Public non-hospital-based laboratory	17.21
Private non-hospital-based or independent	16.81
Research	15.39

Most of the other factors identified by pair-wise comparison (*e.g.* affiliated or associated with a clinical or medical genetics unit; accredited, certified and licensed; participate in PT) have in common access to guidance and/or oversight of laboratory operations. In addition, these factors may also provide the laboratory with educational opportunities that may assist them in report development. Specifically, accredited, certified and/or licensed laboratories presumably have a quality system in place or under development. This is likely reflected in their attention to the content of their reports. Similarly, participation in PT/EQA (external quality assessment) provides the laboratory with regular expert review of their report content and format which can contribute to having higher quality reports. As PT assessors use reporting guidelines to guide them in their assessments, laboratories participating in PT are more likely to be aware of and to be compliant with such guidelines. Affiliation with a genetics unit may give laboratories access to more direct feedback on report structure and content than is available to laboratories without such an affiliation. Correlation of the existence of SOPs with improved reporting scores may reflect specific attention given to the mechanism for reporting results.

Finally, maintenance of turnaround time data as a factor associated with higher report score is of interest. Laboratories that maintain data on turnaround time may be more focused on the needs of their service users that those that do not: service users see turnaround time as more important by than service providers. The observation that these laboratories are more likely to produce high-quality reports may reflect their focus on the needs of the service user and the patient.

Multivariate analysis

In order to determine which of the factors contributed most to the report score, multivariate analysis was performed with report score used as a continuous variable. The analysis identified existence of SOPs, provision of prenatal testing services, affiliation with a genetics unit, any setting other than research and collection of data on turnaround times as the most important factors in the report score, and the existence of SOPs was the most important factor (Table 3.7).

Table 3.7. Variables associated with higher reporting quality scores on multivariate analysis

In order of contribution

Question	Variable	Cumulative R^2
10(a)	SOPs exist for some or all procedures	.287
14(b)	Offer prenatal/pre-implantation testing	.432
5(a)	Affiliated with genetics unit	.522
2(a)	Any other setting vs. research	.576
14(a)	Maintain data on turnaround time	.632

Conclusions

It is encouraging that the majority of laboratories are issuing reports of high quality, as indicated by the high mean scores in all settings. The finding that there is a tendency for laboratories in research settings to issue poorer reports is of concern. It must be recognised that such laboratories perform an important role in providing "esoteric" tests that would otherwise not be available. PT schemes are unlikely to be available for such tests, so these laboratories are less likely to benefit from the exposure to this type of peer review. A balance must be struck between ensuring the highest quality of service, which may require regulations too burdensome for such laboratories, and ensuring that a wide range of tests for rare disorders is maintained. Research laboratories should be encouraged to improve their reports. The Human Genetics Societies, which include both researchers and medical geneticists among their members, could have an important role in this respect. In some cases, research results could be confirmed and reported by a local diagnostic laboratory.

The report is the interface between the testing laboratory and the patient via the referring clinician. Laboratories that demonstrate a commitment to a system for ensuring and improving quality by becoming accredited, participating in PT schemes and maintaining records on turnaround times are also more likely to issue high-quality reports. Guidelines on report content and format are useful in encouraging best practice. Participation in PT/EQA schemes that assess interpretation provides useful feedback on report style and content.

The overview and comparison of existing guidelines presented here indicate that there is an opportunity for shared international action to consolidate a number of recommendations and best-practices in a set of principles generally acceptable to the international community. These consolidated recommendations should encourage a uniformly high standard of reporting of genetic test results worldwide.

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Chapter 4

CONSENT, STORAGE AND CONFIDENTIALITY

Introduction: critical issues

Storage

In clinical settings, large numbers of tissues are collected for diagnostic or therapeutic reasons. These tissues are usually sent to a clinical, diagnostic or pathology laboratory for examination. Genetic testing laboratories also receive a wide range of specimens (Table 4.1). These laboratories are, in general, under obligation to keep these specimens for a minimum amount of time. For example, in the United States, to be accredited, laboratories must keep cytology slides for a minimum of five years, histopathology slides for a minimum of ten years, and paraffin blocks for a minimum of two years (CLIA, 2004). Similar guidelines apply in other OECD countries. Once the regulated length of time for storage is met, institutions may continue to store pathology specimens.

There are a number of reasons for the storage of clinical specimens. Short-term storage is necessary to allow re-analysis of a specific sample in case the result is questionable or not plausible. The reasons for long-term (indefinite) storage may vary, particularly in the case of DNA testing. DNA analysis for clinical purposes differs from many other clinical genetic tests in several ways. First, the long-term stability of DNA may permit later analysis if questions arise that were not envisioned at the time of procurement. Second, rapid advances in DNA diagnostic capabilities place special responsibilities on the providers of these services to keep samples in case new scientific developments, such as the discovery of new genes and mutations, require re-testing (although it should be possible to obtain a new sample). A more important reason for long-term storage can arise in the context of family analysis. For example, genetic analysis of a patient may yield a mutation whose significance for the pathogenesis of the disease is unclear. Analysis of family members can give valuable information concerning the linkage of a given mutation to the specific trait. Equally important may be information that no mutation is found in a particular family member. Thus long-term storage of specimens and of related health and genetic data may be in the interest of patients as well as families. This allows for review and verification should this become necessary.

Table 4.1. Specimen types received by laboratories

Specimen type	% of respondents	n
Whole blood	95	786
Post-mortem (tissues or fluids)	44	364
Mouthwash or buccal smear samples	34	281
Dried blood spots	28	231
Organ tissue	51	422
Cultured fibroblasts	47	389
Foetal blood	36	298
Direct amniotic fluid	38	314
Cultured amniocytes	50	413
Chorionic villus cells	49	405
Guthrie cards	26	215
Other response written in:		
Paraffin blocks	3	25
Extracted DNA	3	25
Bone marrow	2	17
Hair bulbs	1	8

In a 1994 survey of GeneTests, an online national directory of DNA diagnostic laboratories in the United States, 63% of the labs stated that they archived DNA (McEwen and Reilly, 1995). DNA archives ranged in size from fewer than 100 to more than 1 000 samples in storage. Most laboratories archived DNA as a service to referring physicians or for individuals and families at risk for a particular genetic disorder, for such purposes as gene mapping, and as a service to clinical, forensic or research laboratories, and 72% (n=595) of the laboratories surveyed indicate that they store samples indefinitely.

Concerns arising from long-term storage centre primarily on confidentiality, privacy and consent issues. The World Health Organisation's (WHO) 1998 "Proposed International Guidelines", which specifies that "potentially valuable specimens that could be useful to concerned families in the future should be saved and should be available" (WHO, 1998, p. 22) also states that "genetic samples from individuals must be handled with respect, should be taken only after the consent is obtained, and, should be used only as stated in the consent document". Yet only 53% of laboratories participating in the OECD survey required providing a copy of the informed consent document (*e.g.* a document describing the test and its benefits and limitations) to the lab prior to testing for at least one analysis offered, while 62% had a specific written policy about confidentiality of genetic testing results.

It is to be noted that guidelines or procedures for the retention, storage and retrieval of human samples are in place only in half of the countries taking part in this survey (see Annex A), and are often incomplete where they do exist. Furthermore, in most of these countries the main legal reference is the rules related to biobanks, for which there is currently no agreed international definition or shared understanding of how they might appropriately apply to the medical care context (as opposed to the medical research

context). Most existing international statements as well do not address the specific issue of long-term storage or of archived samples originating from medical care, the context of medical care being largely left to individual countries.

Another problematic factor is the legal status of DNA samples and of the related genetic information. For example, in the event that DNA is deemed genetic information, the rules related to privacy and confidentiality of personal data usually apply. If, however, DNA is deemed biological material, then the rules related to biobanks or the use of biological material may apply.

Confidentiality

In most OECD countries, protection of health data relies on the combined application of privacy and confidentiality and personal data protection laws. Most countries also provide for recourse to overarching constitutional protection or, in the absence of such, to human rights legislation. Also in most OECD countries, there are no specific laws distinguishing the processing of health data or genetic data from other personal or sensitive data, so that genetic data are not treated differently from other medical or private data. Only seven out of the 18 participating countries reported having specific regulations in place addressing the confidentiality of genetic data (see Annex B). However, there is a general trend across OECD countries to try and discourage genetic discrimination by introducing both civil and criminal legislative actions. Furthermore, principles relating to the need to ensure confidentiality of genetic data have been enunciated in a number of international forums.

On 16 October 2003, the General Conference of UNESCO adopted the International Declaration on Human Genetic Data. Article 13 of the declaration states that the confidentiality of human genetic data linked to an identifiable person, family, or group shall be guaranteed in accordance with national legislation or regulations and in conformity with international human rights law.

In 2004, the Steering Committee on Bioethics of the Council of Europe (CDBI) released, for public comment, a draft version of a Protocol to the Convention on Human Rights and Biomedicine, which covers genetic data. The Protocol does not offer any specific guidance on the processing, communication and storage of personal genetic data. It does, however, include provisions relating to the collection of personal genetic data, particularly on informed consent. The provisions are extensively based on the Convention.

Additional instruments may apply to the protection of health/medical data and data arising from genetic testing. These are:

- The 1980 OECD Guidelines for the Protection of Privacy and Transborder Data Flows (Privacy Guidelines).
- The 1981 Council of Europe Convention for the Protection of Individuals with regard to automatic processing of personal data (Convention 108).
- The Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the Protection of individuals with regard to the processing of personal data and on the free movement of such data.

Common to these international instruments are a core set of principles. These include:

- Collection limitation and data quality principles.
- Purpose specification and use limitation principles.
- Right of access of the data subject.
- Appropriate security measures.
- Openness and accountability.
- Specific written consent for sensitive data.

While all OECD countries share the goals of enhancing privacy protection for their citizens, legislation often takes different approaches. This is clear from the survey results, which show that 62% of the labs had written guidelines on confidentiality. It would appear essential, however, that in the case of transfer of human biological samples, data sets and related information to another country, an at least equivalent level of security and protection of privacy is ensured and that comparable quality assurance standards should apply.

The growing use of digital technology within the health-care sector, combined with the increased globalisation and commercialisation of genetic testing services, is leading to the need for and development of some form of international agreement on storage and confidentiality guidelines. This, as discussed further in the following sections, might constitute an important area for international collaboration.

Informed consent

The indispensable initial step in preparation for genetic testing is the process of "informed consent". A written statement describing the risks and benefits of genetic testing is presented to the patient to read and sign before the evaluation and/or test is performed. It is intended as a safeguard to ensure the patient's autonomy and to provide an opportunity to learn and understand information with respect to both the positive and negative consequences of genetic testing. Informed consent is meant as a process, not simply a contractual agreement. However, the practice varies considerably across and within countries.

One of the critical issues is the extent of information given or the degree of disclosure for valid consent. Informed consent for genetic testing may contain some of the following items:

- Procedures of the test and communication of the results.
- Procedures adopted to ensure confidentiality.
- Implications of all possible results, such as:
  - Inconclusive results.
  - Psychological stress created by the knowledge of a possible future illness or the possibility of bearing children affected by a serious disease.
  - The need to decide whether or not to undergo treatment that may prevent the disease or reduce its harmful effects.
  - That no treatment may available.

- The possibility that the results may provide unwanted information (e.g. non-paternity, etc.).
- The need to decide whether to communicate this information to other persons involved.
- Risks regarding employment and/or insurance.
- In prenatal diagnoses, the use of invasive techniques for the collection of foetal samples and the option to interrupt the pregnancy if the foetus is found to be affected.
- Storage and possible secondary uses of samples.

The extent of the information provided in the consent process is often determined by the magnitude of the risks, discomfort and inconvenience involved in the procedure. However, individuals should have the prerogative of controlling information about themselves even when there is no major risk involved. An ideal written informed consent should specify all information provided, the problems discussed and the choices resulting from the discussions. It is deemed important to provide information in language that is comprehensible to potential subjects. Subjects should not be influenced to reach a specific decision regarding a genetic test.

The genetic test originally performed for a specific disease may have a narrow scope. This may change with time, advances in knowledge and technologies. These considerations should be included in the information provided prior to testing, especially in situations in which samples might be retested. Furthermore, for additional scientific use of the samples, a blanket (broad) or narrow consent at the time of collection of biological samples may have important implications for possible future use. It is generally thought that patients should be informed as much as possible about the type of test(s) to be conducted and, in particular in the case of long-term storage, about possible secondary use(s), risks and benefits, potential third-party access to samples, procedures to protect confidentiality (coding/de-identification).

Guidelines or procedures on informed consent are in effect in all but one of the countries surveyed (Annex B) even though they are specific to genetic testing only in 50% of the countries.

Survey results, analysis and discussion

Retention of specimens

The majority of laboratories surveyed stored samples indefinitely (72%, n=595) (Figure 4.1). In 13 out of the 18 countries, at least 50% of the labs retained samples indefinitely. However, there is considerable variability. In one country, 100% of the labs stored samples over the long term, in another, 50% of the labs kept samples for less than 30 days.

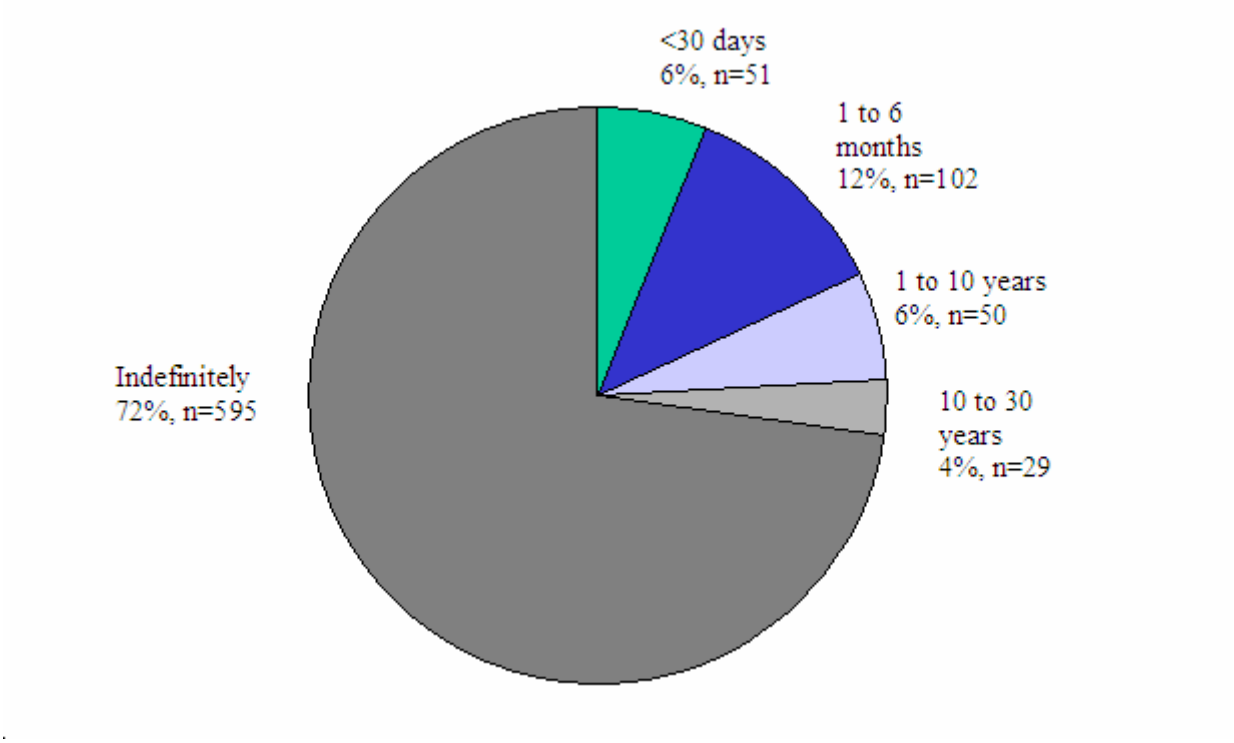
Impact of guidelines

In countries with specific guidelines concerning the retention of specimens, more laboratories keep specimens for an indefinite period than in countries without guidelines. Currently, national guidelines applicable to the retention of clinical specimens (Chapter 2, Table 2.1) concern:

- Legislation on biobanks.
- Legislation on newborn screening.
- Legislation on the use of biological materials.

The main legal reference appears to be the rules related to biobanks.

Figure 4.1. Length of storage of specimens



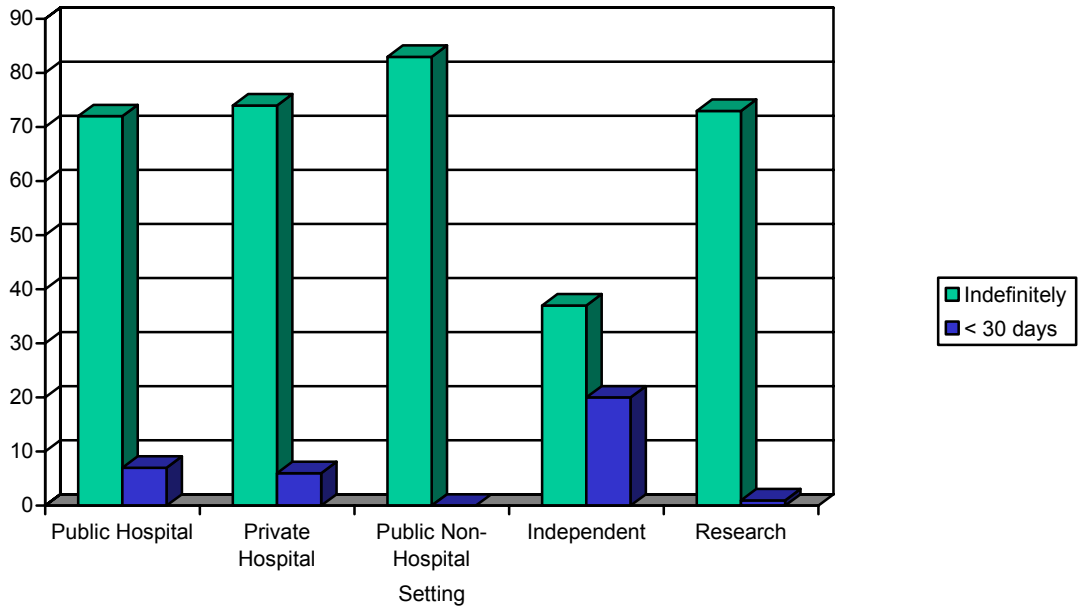
Laboratory setting

Cross-analysis shows that practices may vary according to laboratory setting (Figure 4.2). Independent labs were less likely to retain specimens indefinitely than all other settings, and were more likely to retain specimens less than 30 days. In contrast, research labs were more likely than independent labs to retain specimens indefinitely. Length of storage did not depend on whether testing was carried out as part of a research project or not ($p=0.012$). Furthermore, there was no difference in how long labs retained specimens with respect to whether or not they required informed consent ($p=0.014$). Interestingly, there was also no significant correlation between laboratories reporting having standard operating procedures (SOPs) and the length of time they retained specimens ($p=0.212$). It is thus conceivable that SOPs do not address retention of specimens in a uniform way.

The reason for the lower percentages of indefinite retention of samples by independent labs is most likely due to cost considerations in relation to storage. In addition, independent laboratories are also more likely to have a shorter lifespan than public diagnostic laboratories and may in general be less inclined to take on long-term storage commitments. It is conceivable that liability concerns also play a role. In this

respect, it is noteworthy that independent labs have the highest rate of positive responses to the question regarding presence of written confidentiality policy.

Figure 4.2. Storage of samples by setting



Informed consent

The overall rate of labs requiring a copy of the written informed consent before any genetic testing is performed was surprisingly low (57%, n=474). There is also considerable variation among the participating countries, with a range of 0% to 100% of labs reporting that they required informed consent (Table 4.2). For example, in two countries, 100% of the labs required proof of informed consent, whereas in five less than 20% did so. A possible explanation for this low rate is that 56% of the labs included in the survey are in a public hospital setting (Table 4.4). These laboratories may receive specimens from physicians practicing at or closely linked to the hospital. In this case, laboratories may not document informed consent but consider that it is the referring doctor's role to discuss the significance of tests and to record the discussion and consent in the patient's notes. However this does not hold true in all countries.

Referring physicians were the persons who most often obtained informed consent (24%), followed by genetic counsellors affiliated with the laboratory (16%) and genetic counsellors from a referring institution (14%), while doctoral-level genetics professionals accounted for a total of 13%.

Interestingly, labs that required informed consent were not found to have a higher results reporting index (p=0.412, see Chapter 3) or quality assurance index (see Chapter 1, p=0.558) when compared to labs that did not have such a requirement. Although the need for informed consent has been identified as an important clinical issue associated with genetic testing, labs that had this policy in place did not have significantly better reporting and quality assurance (QA) indices than those that did not. Therefore, the practices of

labs with regard to clinical and patient management issues do not necessarily correlate with their reporting and QA practices.

Table 4.2. Percentage and number of labs requiring informed consent by country

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
%	82	37	41	17	94	54	10	66	100	59	63	29	10	51	11	100	54	0
n	28	3	12	1	104	69	1	80	7	16	46	9	7	72	1	12	6	0

Impact of guidelines

In countries with specific guidelines or procedures on informed consent for MGT the percentage of laboratories requiring copy of the informed consent form prior to any genetic testing is higher than in countries without guidelines**.** The great majority of labs (69%) accessioned the specimens and contacted the referring physician if no informed consent was provided. This is in clear compliance with existing guidelines. Guidelines appear therefore effective in driving good practice on informed consent and might constitute an area of international co-operation in relation to transborder flow of samples. However, if informed consent is lacking, some labs rejected the specimen (13%) and some analysed it and reported results (8%). Both situations have the potential for creating problems. For example, if the rejected specimen is a prenatal specimen or post-mortem tissue, rejection may interfere with the specimen's integrity. In the latter case, if the specimen is analysed and the results reported, the lab has no real policy on the need for informed consent. Interestingly, labs that collected specimens on site with the assistance of a geneticist were more likely to require informed consent, a difference that is statistically significant when compared to labs collecting exclusively off site ($p=0.043$) (Table 4.3). This observation presumably reflects the availability of personnel to obtain consent at the time of specimen collection.

Table 4.3. Percentage of labs requiring informed consent according to site of specimen collection

Site of collection of specimens	Both on and off site	On-site by geneticist	On-site by non-geneticist	Off-site only
Require informed consent	54%	63%	57%	42%

Laboratory setting

Non-hospital public laboratories, independent laboratories and research laboratories were more likely than private and public hospital laboratories to require informed consent (Table 4.4). Of all laboratory settings, research labs had the highest rate of acquisition of informed consent while public-hospital-based laboratories had the lowest. The former finding may be related to possible use of the samples for research purposes, which is usually accompanied by obtaining informed consent from the research subject. As previously mentioned, a possible explanation for the lower rate of requirement of consent in hospital settings might be that consent is presumed to be acquired by the referring hospital physician.

Table 4.4. Percentage of labs in different settings that require informed consent

	Public	Private	Non-hospital public	Independent	Research
Require informed consent	48%	57%	61%	66%	77%

Confidentiality

Overall, 63% of the labs (n=523) had a written confidentiality policy, with a broad range among countries of 47% to 100%. In only one country did less than 50% of the laboratories report having a confidentiality policy. In two countries all responding laboratories appeared to have a confidentiality policy (Table 4.5).

Table 4.5. Written policy about confidentiality/country

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
%	65	50	59	100	61	60	60	47	100	74	53	71	64	78	78	83	73	80
n	22	4	17	6	63	77	6	57	7	20	37	22	46	110	7	10	8	4

Impact of guidelines

Existing guidelines appear to have minimal or no correlation with lab policies about confidentiality of genetic testing results. This is not surprising considering the fact that in almost all of the countries surveyed health data protection relies on the combined application of a number of legal instruments which are in general not specific to genetic testing.

Of note, 66% and 69% of labs that offered pre-symptomatic and predisposition testing had a confidentiality policy, 34% and 31% did not (Table 4.6). Non-hospital-based public labs and independent laboratories were nonetheless more likely than research, public-hospital and private-hospital labs to have a confidentiality policy while research labs had the lowest rate for a privacy policy (Table 4.7).

Table 4.6. Percentage of laboratories with a confidentiality policy in relation to type of tests offered

	Diagnostic	Pre-symptomatic	Predisposition	Pharmacogenomics
Have a confidentiality policy	62%	66%	69%	69%

Table 4.7. Percentage of laboratories in each type of setting that have a confidentiality policy

	Public	Private	Non-hospital public	Independent	Research
Have a confidentiality policy	61%	69%	83%	85%	51%

The generally low positive response rate for written policies on confidentiality of genetic testing results is surprising and troubling, in particular since there appears to be no difference in the confidentiality practices of laboratories performing pre-symptomatic and predisposition testing in countries that have clear confidentiality requirements for data arising from such testing. The fact that research labs had the lowest positive response rate for written policies on confidentiality raises a number of issues, particularly in the

context of the significant transborder flow of samples for rare genetic disease testing (see below) as well as long-term storage of samples.

Transborder flow

Multivariate analysis (linear regression) indicated that there was no significant difference between labs that did and did not receive transborder specimens and their requirement to have a copy of the informed consent (p=0.464; see chapter 2 on transborder flow). Similarly, there was no significant difference in relation to written policies on confidentiality (p=0.389). According to these data, the need for informed consent or confidentiality policies is clearly not a barrier to transborder flow. As transborder referrals are often based on personal contact and professional co-operation, the latter results may not be surprising. They raise certain issues nonetheless since multivariate analysis also shows that laboratories that store indefinitely are more likely to receive transborder specimens (p=0.006).

Conclusions

A number of concerns arise from long-term storage of patient samples primarily in relation to confidentiality, privacy and consent issues. The survey included questions addressing laboratory practices on these issues.

Guidelines or procedures on informed consent in the medical care context are well established in most OECD countries and, based on this study, are applied in about 60% of the laboratories. In countries with specific guidelines or procedures on informed consent for MGT, the proportion of laboratories requiring a copy of the informed consent form prior to any genetic testing is higher than in countries without guidelines**.** Of significance, the majority of laboratories (69%) appear to behave according to guidelines, i.e. in the absence of informed consent they process the specimens and contact the referring physician.

There was no significant difference between laboratories that do and do not receive transborder specimens and their requirements for written policies on confidentiality and/or for documentation of informed consent. This suggests that the need for documented informed consent or confidentiality policies or otherwise is not currently acting as a specific barrier to transborder flow. Problems may arise when specimens are referred between countries that may have significantly different provisions.

One might expect written confidentiality policies to be an essential requirement for a molecular genetic testing (MGT) laboratory. This, however, does not seem to be the case, since about 33% of the laboratories surveyed reported not having a written confidentiality policy. The generally low positive response rate for written policies on confidentiality of genetic testing results is surprising. In particular, there appears to be no difference in the confidentiality practices of laboratories performing pre-symptomatic and predisposition testing including in those countries where there are clear and specific confidentiality requirements concerning such testing. The fact that research laboratories have the lowest positive response rate for written policies on confidentiality also raises a number of issues (in particular related to data protection and privacy) given that these laboratories are significant providers of rare genetic disease testing which may generate sensitive information and are bound to store samples long-term.

The transfer of human biological samples or data sets and related information to another country should require ensuring at least a comparable level of security and protection of privacy and of quality assurance standards. This area constitutes an opportunity for international co-operation.

It is therefore suggested that countries should consider ways to implement more effectively the existing consent and confidentiality guidelines in the context of transborder exchange of samples and long-term storage. There may also be a need to give patients the right to delete specific items of information that they do not wish to have disclosed, possibly depending on the specific circumstances.

Security of the stored samples and data can, however, only be achieved by a clear-sighted recognition of what needs to be secured and which information needs to be restricted and by appropriate risk analysis. There is little evidence of clear guidance on these issues for laboratories. As stated in a review (Rosen, 1999), existing provisions implicate greater responsibility for health-care and clerical staff in making distinctions between what should be considered sensitive "genetic information" and what should not, but this is extremely difficult in the absence of commonly accepted guidelines and definitions.

A first approach might be to afford protection for data arising from genetic testing (or any sub-category) on a varying scale depending on the nature of the information or of its use, according to the principle of proportionality stated in the 1992 OECD Security Guidelines. The objective should be to seek to match the risks with cost-effective security measures.

This approach depends on being able to identify and locate the genetic data in such a way as to allow the introduction of specific and additional security measures. This is technically and legally easier if data and samples are stored at locations different from those of patients' medical records.

In summary international action appears necessary to achieve a shared understanding of requirements concerning:

- The long term retention of specimens in the medical care context.
- Privacy and consent, particularly in the context of transborder flow of clinical samples.

A balance must nonetheless be struck between ensuring appropriate privacy protection and the need to avoid unintended restrictions on the broader availability of genetic testing, the use of residual samples for public health activities, and the exchange of vital information.

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Chapter 5

LICENSING, ACCREDITATION, CERTIFICATION AND PROFICIENCY TESTING/EXTERNAL QUALITY ASSESSMENT

Introduction

A number of instruments can be applied to regulate quality assurance (QA) in molecular genetic testing (MGT) laboratory practice. They include laboratory accreditation, licensing and certification, external quality assessment (EQA) or proficiency testing (PT), internal quality control, and use of standard operating procedures (SOPs).

Both licensing and accreditation/certification are well established in some countries as methods of regulation and oversight and to promote the quality of clinical laboratories. However, they are not equivalent (see Table 5.1). Licensing is *permission* from a governmental agency to operate a laboratory. It may involve documenting the existence, institutional accountability and, in general terms, the activities of the facility, such as the menu of services provided. In return, the laboratory is officially registered and may be publicly listed. The granting of a licence may not require a formal audit of policies, procedures or practice. Licensing places a relatively small overhead cost on the laboratory.

Accreditation is formal recognition of a laboratory's *competence*. It is only granted after a formal on-site audit by inspectors of the management, environment, policies and procedures of the laboratory plus specific scientific/technical competences measured against external standards. For example, the ISO 17025 standard is designed for the accreditation of testing and calibration laboratories of all types. The ISO 15189 standard is related to ISO 17025 which is relevant to general medical laboratories but not *specific* to MGT laboratories. These standards are not themselves accreditation systems but may be referred to by the authoritative national agencies that award accreditation (for example, UK Clinical Pathology Accreditation Ltd and SWEDAC).

Modern accreditation standards related to clinical laboratories place emphasis on having an effective quality management system in place; on a commitment to meeting the needs of patients and their doctors as users of laboratory services; and maintaining a continuous cycle of quality improvement at the heart of all policy making and operations.

Achieving and maintaining compliance with accreditation standards is a major test of management and adds significantly to the costs of the laboratory process. Consequently, many laboratories complain of lacking the resources to apply a quality management system. The institution of a quality management system usually requires a dedicated quality manager and incurs costs in staff time to maintain traceable documentation for the entire laboratory workflow to comply with accreditation standards. Harder to quantify are the savings in terms of improved efficiency through a more robust testing process, such as fewer repeated tests, control of clinical incidents, improved risk management and reduced medico-legal costs.

The accreditation process includes an audit of the laboratory infrastructures and all other quality control and quality assessment measures. To achieve accreditation a laboratory must be adequately staffed by personnel with appropriate qualifications and training. It must have adequate documentation, such as SOPs for analytical tests. In addition it must demonstrate external assessment of its test results, preferably through participation in a recognised laboratory PT/EQA scheme (see below). It may also be obliged to demonstrate satisfactory performance and show that it is responsive to performance shortcomings demonstrated through PT/EQA.

The challenges of meeting accreditation requirements for a molecular genetics laboratory are often those involved in making a transition from a research environment to the norms required of established clinical laboratories. In many cases, externally validated technologies are not in place. For example, few reagent kits that have been approved by the US Federal Drug Administration or carry the CE mark of the European Union are available for molecular genetic tests. Most molecular genetic tests require in-house produced reagents (oligonucleotide primers) that impose a considerable burden of validation on the laboratory. Moreover, some countries' accreditation agencies may lack an inspectorate with the specific expertise to audit molecular genetic laboratories.

Certification is a well-recognised indicator of the quality management of an organisation but it is less stringent than accreditation. It involves an audit of an internally defined quality management system but does not require examination of specific competences against external standards. ISO9001:2000 is an example of a certification standard that can be applied to any manufacturing process or service.

The licensing and accreditation section of the survey

The licensing and accreditation section of the survey focused on the status of MGT centres with regard to external permission (licensing), external audit (accreditation/ certification) and PT/EQA schemes designed to compare laboratory analytical performance.

PT/EQA are means by which a laboratory can compare its performance for an individual test or technique against that of other laboratories. Typically a PT/EQA scheme agency such as the European Molecular Genetics Quality (EMQM) Network (www.emqn.org) or the College of American Pathologists (CAP) provides a number of biological samples of known and validated genotype to participating laboratories. Laboratories are asked to genotype the samples (for mutations in a gene associated with a particular genetic condition, for example Huntington disease) and return their reports to the PT/EQA agency. Genotype accuracy and interpretation of data are assessed by a panel of experts and individual comments on the performance are returned to participating laboratories. Laboratories are asked to act on shortcomings to improve their performance.

The steering group thought that licensing, accreditation, certification and participation in PT/EQA are generally considered important markers of performance and quality.

Definitions

Table 5.1 reproduces definitions for licensing, accreditation, certification and proficiency testing (where possible those agreed as ISO norms). It also gives definitions from the glossary included in the survey as an aid to responders.

Table 5.1. Definitions

Term	Survey/formal	Definitions
Licensed	Survey glossary	"Granted permission from a governmental agency to operate a laboratory"
	Formal definition	"Leave, permission, permit from government etc. to…carry on some trade, etc."*
Accredited	Survey glossary	"Formal recognition of the competence of a laboratory by an authoritative organisation (for example CAP)."
	Formal definition	"Procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks." **
Certification	Survey glossary	Not given
	Formal definition	"Procedure by which a third party gives written assurance that a product, process or service conforms to specific requirements."**
Proficiency testing/external quality assessment	Survey glossary	"Proficiency testing may also be called External Quality Assessment (EQA). This usually involves the distribution of samples to participating laboratories by an external agency. The results of tests on these samples are checked and form a measure of laboratory performance."
	Formal definition	"Determination of laboratory testing performance by means of inter-laboratory comparisons."** "External Quality Assessment refers to a system of objectively checking laboratory results by means of an external agency. The checking is necessarily retrospective, and comparisons of a given laboratory's performance on a certain day with that of other laboratories cannot be notified to the laboratory until some time later. This comparison will not therefore have any influence on the tested laboratory's output on the day of the test. The main object of EQA is not to bring about day to day consistency but to establish between-laboratory comparability."***

* *Concise Oxford Dictionary*, Fowler and Fowler (eds.), fifth edition, Oxford: Clarendon Press, 1974.

** ISO/IEC Guide 2, "General terms and their definitions concerning standardization and related activity", 1996.

*** World Health Organisation, *External Assessment of Health Laboratories* (1981).

Survey results, analysis and discussion

To enhance the value of the analysis of this part of the survey the steering group agreed that countries would be identified.

Licensing

To determine the actual requirements in each country, a separate survey of experts and government representatives was carried out (see Table 5.3 and Annex A). Representatives from six countries (the Czech Republic, Finland, Ireland, Sweden, Turkey and the United Kingdom) indicated that licensing was not currently required and 13 (Austria, Belgium, Canada, France, Germany, Italy, Japan, Norway, Portugal, Spain, Switzerland, and the United States) indicated that a licence was required. In some countries, diagnostic centres require a licence for any clinical testing; others require a specific licence for genetic testing. In Austria and France, a licence is required for laboratories offering genetic tests of a highly predictive nature (for example prenatal diagnosis) but not for centres offering less predictive testing (for example for thrombotic risk factors).

Overall 55% (n=455) of laboratory directors indicated that licensing was required in their country. Centres in five countries (Austria, Finland, France, Ireland and the United States) responded to the question about the requirement for licensing that were 90% to 100% consistent with the actual licensing situation in force in their country (Table 5.2). In 13 countries (Belgium, Canada, the Czech Republic, Germany, Italy, Japan, Norway, Portugal, Spain, Sweden, Switzerland, Turkey and the United Kingdom), responses were in general inconsistent with the actual licensing norms.

Table 5.2. Percentage and number of laboratories in each country that indicated that a licence is required

	AUS	BEL	CAN	CZE	FIN	FRA	GER	IRE	ITA	JAP	NOR	POR	SPA	SWE	SWI	TUR	UK	USA
Yes	82 (28)	50 (4)	41 (12)	83 (10)	0 (0)	92 (95)	34 (43)	10 (1)	49 (59)	72 (5)	40 (2)	33 (9)	25 (18)	22 (2)	29 (9)	27 (3)	22 (16)	98 (138)
No	18 (6)	50 (4)	59 (17)	17 (2)	100 (6)	8 (8)	66 (85)	90 (9)	51 (62)	18 (2)	60 (3)	67 (18)	75 (55)	78 (7)	71 (22)	73 (8)	78 (56)	2 (3)
Yes	55 (455)																	
No	45 (372)																	

Table 5.2 reports data from each country. There is significant variability in responses from individual centres within countries. This may be explained by laboratory directors' lack of awareness of regulations. An example is the response from UK laboratories, which have no formal requirement of a licence to operate. However, the establishment of the UK Genetic Testing Network (UKGTN), which is supported by the government (www.dh.gov.uk\genetics), has made laboratory directors aware of increasing oversight. Laboratories may be granted full membership of UKGTN if they meet certain minimum quality requirements, including accreditation. The answers from the UK laboratories (yes 22%, no 78%) probably reflect uncertainty about the term "licensing" in this context. The correct answer is "no".

On the other hand, the responses of Austrian laboratories may be consistent with the requirement of a licence to operate if the laboratory offers highly predictive genetic testing (see above).

A clear conclusion from the responses to question about the licensing requirement is that information about laboratories' obligation to be licensed has not been successfully disseminated to molecular genetic testing laboratories in most OECD countries.

Table 5.3. National requirements for licensing and accreditation

Country	Is a license for genetic testing labs required? (from Table 5.2) (The situation regarding licensing, accreditation and certification as reported by country representatives).	Percentage of responses to question 13a consistent with reported licensing requirements	Compliance with licensing regime (based on rates of correct responses to question 13b)
Austria	Yes (for predictive tests). The lab director but not the laboratory is licensed.	Yes (n.a.)	>94%
Belgium	Yes. Licensing is required to receive re-imbursement. Accreditation is required for some clinical laboratories but there is no legal requirement for accreditation of molecular genetic testing laboratories	No (50%)	100%
Canada	Yes. All laboratories that perform laboratory testing for diagnosis, prophylaxis and treatment of patients must be licensed by the Ministry of Health and Long-term Care. Only the Ontario Province has a licensing requirement for MGT laboratories. The Ontario Medical Association (OMA) is designated in Ontario Regulation 682, made under the Laboratory and Specimen Collection Centre Licensing Act, as the agency to carry out examinations and evaluations of proficiency in the performance of tests in medical laboratories. The OMA's Quality Management Program – Laboratory Services (QMP-LS) is in the fifth year of development of a five-year peer review accreditation system for medical laboratories in Ontario. All laboratories will be accredited by the QMP-LS.	No (n.a.)	100%
Czech Republic	No. No licensing system is available.	No (17%)	Not applicable

Table 5.3. National requirements for licensing and accreditation *(continued)*

Country	Is a license for genetic testing labs required? (from Table 5.2) (The situation regarding licensing, accreditation and certification as reported by country representatives).	Percentage of responses to question 13a consistent with reported licensing requirements	Compliance with licensing regime (based on rates of correct responses to question 13b)
Finland	No. In Finland molecular genetic laboratories do not need a specific licence, but all private clinical diagnostic laboratories must have an easily obtainable working permit. Public laboratories belong to the health-care system and do not require any additional licensing. One competent authority (FINAS) accredits clinical laboratories. FINAS is a member of European Accreditation, and the standard used for accreditation of clinical laboratories is ISO 17025. In future ISO 15189 will be used. In some cases certification under ISO 9001 is awarded.	Yes (100%)	Not applicable
France	Yes. A license is required for predictive tests. Two categories of tests are regulated by the Ministry of Health: prenatal tests and pre-symptomatic or predictive genetic tests. For prenatal tests, only authorised labs can deliver services (legislation 1994). The authorisation is delivered to a specific practitioner in a specific location. If an authorised practitioner moves to another institution, he/she is required to re-apply, and if an authorised laboratory hires a new practitioner, it is also is required to re-apply. In addition, all private laboratories performing clinical tests have to be authorised (legislation 1975). Public laboratories do not fall within this system, but must be located in a hospital to be authorised. Public university laboratories are not allowed to deliver test results to patients. However, if they are the only service provider for a genetic condition, they have to have an unofficial agreement with an authorised laboratory to approve results.	Yes (92%)	100%
Germany	Yes. In general, a licence ("Approbation") is required to operate any laboratory providing medical tests. There is no specific licence required for genetic testing. The German accrediting agencies work according to DIN-EN-ISO standards 15189 or 17025 for accreditation and 9001 for certification. However, existing criteria and check-lists for accreditation are oriented to the requirements of routine clinical chemistry laboratories. Special criteria for accreditation of molecular genetic testing laboratories are in preparation.	No (66%)	92%
Ireland	No. Specific licensing is not required for MGT laboratories. Formal accrediting organisations/agencies exist but do not currently accredit medical laboratories.	Yes (90%)	100%
Italy	Yes. All clinical laboratories are required to have general approval equivalent to a license from a regional authority. However, there is no specific requirement for genetic laboratories. A specific regional law (ex art.25, Regional Regulation 833, 25 February 1984) describes the requirement for laboratory accreditation and devolves the responsibility to regional authorities. In Italy, ISO standards and the UNI-EN accreditation system and D.lgs 626/94 are recognised. There are no specific accreditation standards for genetic laboratories.	No (51%)	91%
Japan	Yes. Japan has a licensing scheme for clinical laboratories. Genetic testing practice is regulated under the scheme. The relevant law concerns clinical laboratory technicians, public health laboratory technicians and other related personnel. Under this legislation, all clinical and public health laboratories are required to be inspected and accredited by the local authority.	No (72%)	100%
Norway	Yes. All clinical laboratories are required to have approval from the government. A licence is required to become head of a genetic laboratory. Accreditation is not required.	No (40%)	100%

Table 5.3. National requirements for licensing and accreditation *(continued)*

Country	Is a license for genetic testing labs required? (from Table 5.2) (The situation regarding licensing, accreditation and certification as reported by country representatives).	Percentage of responses to question 13a consistent with reported licensing requirements	Compliance with licensing regime (based on rates of correct responses to question 13b)
Portugal	Yes. All clinical laboratories are required to have general approval from the government. There are no specific requirements for molecular genetic testing laboratories. The Portuguese Quality Institute (IPQ), a member of the European Co-operation for Accreditation, has charged the Portuguese Agency for Certification (APCER) with the certification of diagnostic laboratories. IPQ, through APCER, may evaluate the practices of laboratories according to European Directive 88/320. No accreditation is however required.	No (67%)	100%
Spain	Yes. Clinical laboratories require a licence issued by the Regional Health Authorities. There are no specific requirements for molecular genetic testing laboratories. AENOR is recognised as an agency in Spain competent to accredit clinical analysis laboratories. There is no specific legislation for genetic testing laboratories, but they are considered clinical analysis laboratories.	No (75%)	100%
Sweden	No. There are no licensing requirements in Sweden. SWEDAC is the agency competent to accredit diagnostic laboratories in Sweden.	No (78%)	Not applicable
Switzerland	Yes. Switzerland is in the process of moving to a new regulatory system. A condition for receiving a licence is accreditation through the Swiss Accreditation Service (SAS), a signatory member of EA/ILAC multilateral agreements and part of a federal agency. Many private/Independent laboratories and public laboratories have been or are currently being accredited by SAS according to ISO/IEC 17025: 1999 requirements.	Yes (n.a.)	100%
Turkey	No. A licensing system is in preparation under the Ministry of Health. There is currently no accreditation system relevant to clinical laboratories.	No (73%)	Not applicable
United Kingdom	No. There is no formal licensing system for molecular genetic testing laboratories. However, laboratories may register with the officially supported UK Genetic Testing Network if they meet certain criteria, including accreditation. The UKGTN approved test list is linked to the National Health Service reimbursement system. Laboratories considering offering genetic tests directly to the public are required to consult with the Human Genetics Commission.	No (78%)	Not applicable
United States	Yes. All clinical laboratories are required to be certified under the Clinical Laboratory Improvement Amendments (CLIA) regulations or by a mechanism in states having their own programme that is deemed equivalent or more stringent than CLIA. CLIA regulations recognise certain accrediting organisations (such as the American College of American Pathology, CAP). CAP is a private, not a government-owned or operated organisation.	Yes (98%)	94%

n.a. Not available.

Laboratory directors were asked whether molecular genetic testing laboratories are required to be licensed by a government agency in their country. It was therefore possible to identify a set of countries in which laboratory directors were clear about the requirement for a licence for genetic testing or the lack thereof. Laboratory directors also were asked if their laboratory was actually licensed; this allowed indirect assessment of the rate of compliance with licensing regimes for diagnostic service (Table 5.4).

Table 5.4. Percentage and number of licensed laboratories by country

	AUS	BEL	CAN	CZE	FIN	FRA	GER	IRE	ITA	JAP	NOR	POR	SPA	SWE	SWI	TUR	UK	USA
Yes	94 (32)	100 (8)	100 (29)	75 (8)	0 (0)	100 (103)	92 (118)	0 (0)	91 (110)	100 (7)	100 (5)	100 (27)	100 (73)	44 (4)	100 (31)	18 (2)	92 (66)	94 (132)
No	6 (2)	0 (0)	0 (0)	25 (4)	100 (6)	0 (0)	8 (10)	100 (10)	9 (11)	0 (0)	0 (0)	0 (0)	0 (0)	56 (5)	0 (0)	82 (9)	8 (6)	6 (9)
Yes	91 (755)																	
No	9 (72)																	

In those countries where laboratory directors were aware of the requirement for licensing, there was a correspondingly high rate of compliance (94% in the United States). In Austria, 6% of laboratories reported that they did not hold a licence, but this may be consistent with the regulatory system, as only centres carrying out highly predictive genetic tests are required to be licensed (see above).

Among laboratory directors in countries where there was uncertainty as to the licensing arrangements or the terminology used, the response to this question was mixed (Czech Republic, Sweden, Turkey, United Kingdom).

In Canada, all clinical laboratories are required to be licensed and all the responding molecular genetic testing laboratories reported that they comply. However, a majority (59%) of centres answered "no" when asked if licensing is required. This may reflect the varying requirements regarding MGT across Canadian provinces. For example, only the Ontario Province has established specific requirements for MGT laboratories.

Cross-analysis of the responses of laboratories about their licensing status and the laboratory setting indicated that independent laboratories were more likely to be licensed (likelihood ratio: 4.143). This may be because of more stringent regulation for commercial providers. In addition licensed laboratories had a larger mean number of tests accessioned (1 470) than non-licensed centres (616).

In conclusion, responses to the survey indicate that where a national licence system is in place and there is high level of awareness of requirements, there is a correspondingly high rate of compliance by genetic testing laboratories.

Accreditation

In contrast to responses on licensing, when laboratory directors were asked if their laboratory was accredited or certified, the responses seem to indicate that many directors of laboratories differentiate between the terms "licensing" and "accreditation/certification", since responses better reflected national requirements. The range of positive responses to the accreditation/certification query (Table 5.5; 0-100%) nonetheless reflects the great diversity among countries with regard to accreditation/certification of their managerial and scientific competence. Some countries may put governmental, professional or commercial pressure on laboratories to achieve accreditation, whereas others may exert little pressure. Some countries do not possess a system to achieve accreditation from a national agency.

A substantial minority (44%, n=362) of molecular genetic testing laboratories in OECD countries are not accredited. Only ten out of 18 countries reported accreditation/ certification rates equal or above 50% and only five out of 18 had rates over 70%.

The overall message from the responses to this item is that accreditation/certification has not penetrated diagnostic molecular genetic testing laboratories to a high degree and with any consistency across OECD countries.

Table 5.5. Percentage and number of laboratories accredited/certified by country

	AUS	BEL	CAN	CZE	FIN	FRA	GER	IRE	ITA	JAP	NOR	POR	SPA	SWE	SWI	TUR	UK	USA
Yes	53 (18)	100 (8)	59 (17)	50 (6)	33 (2)	69 (71)	34 (43)	10 (1)	44 (53)	86 (6)	0 (0)	15 (4)	38 (28)	56 (5)	87 (27)	9 (1)	79 (57)	84 (118)
No	47 (16)	0 (0)	41 (12)	50 (6)	67 (4)	31 (32)	66 (85)	90 (9)	56 (68)	14 (1)	100 (5)	85 (23)	62 (45)	44 (4)	13 (4)	91 (10)	21 (15)	16 (23)
Yes	56 (465)																	
No	44 (362)																	

Laboratory directors also were asked to indicate which accreditation agency had accredited their laboratory. The responses were reasonably consistent with expectations (Table 5.6). For example Clinical Pathology Accreditation (CPA) is awarded mostly to UK laboratories, while the College of American Pathologists accreditation serves mostly the United States and Canada. Responses, however, also indicate that CAP accreditation also serves a significant number of Japanese laboratories. Japanese laboratories participate in CAP accreditation to demonstrate to their users compliance with an internationally recognised quality management system. Other Japanese centres use national agencies for this purpose (Medical Service Promotion Society, Iryo-Kanren-Sabisu Shinkokai).

Some inconsistencies in the data (for example in responses from Belgium and Sweden) may be explained by responses from laboratories citing either the accreditation/ certification authorities active in their country or accreditation/certification of general diagnostic activities within their institution. These responses may, however, not be directly relevant to the MGT activities of the laboratory.

In addition to the responses listed in Table 5.6, 22% of laboratories also indicated "other" as a choice. On examination of these responses (not shown), 14 centres cited the Clinical Laboratory Improvement Amendment (CLIA), the US federal legislation that sets standards against which CAP accredits laboratories. Seven centres cited other unspecified agencies and two cited the Ontario Laboratory Association. A further five responses cited recognised national accreditation agencies and the 13 remaining responses represented agencies or systems that are not relevant to formal accreditation.

Table 5.6. Percentage and number of laboratories accredited by specific systems by country

	AUS	BEL	CAN	CZE	FIN	FRA	GER	IRE	ITA	JAP	NOR	POR	SPA	SWE	SWI	TUR	UK	USA
n	18	8	17	6	2	71	43	1	53	6	0	4	28	5	27	1	57	118
A	0	0	29 (5)	0	0	8 (6)	0	0	0	83 (5)	-	0	0	0	0	0	3 (2)	85 (100)
B	0	0	0	0	0	8 (6)	0	0	2 (1)	0	-	0	0	0	0	0	93 (53)	2 (2)
C	0	100 (8)	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0
D	0	0	0	0	50 (1)	4 (3)	32 (14)	0	2 (1)	0	-	0	4 (1)	100 (5)	100 (27)	0	3 (2)	0
E	50 (9)	0	0	33 (2)	50 (1)	4 (3)	32 (14)	0	34 (18)	33 (2)	-	0	32 (9)	0	18 (5)	0	3 (2)	2 (2)
F	100 (18)	75 (6)	41 (7)	67 (4)	0	76 (54)	0	0	55 (29)	33 (2)	-	50 (2)	39 (11)	0	0	100 (1)	0	7 (8)
G	5 (1)	0	53 (9)	0	0	20 (14)	67 (29)	100 (1)	20 (11)	0	-	50 (2)	36 (10)	40 (2)	0	0	3 (2)	19 (22)

		%	n
A	CAP	25	118
B	CPA	13	62
C	Belttest	2	8
D	ISO17025	12	54
E	ISO9001	14	67
F	System sponsored by country's government	31	142
G	Other	22	103

Proficiency testing/external quality assessment programmes

Accreditation and certification address quality assurance at a managerial and systems level. PT or EQA are systems of oversight that allow inter-laboratory comparison of analytical performance relevant to a specific genetic test (such as for cystic fibrosis) or technology (such as DNA sequencing).

Overall, 74% (n=616) of laboratories indicated they participate in PT/EQA, and 13 out of 18 countries recorded rates of participation in PT/EQA above 70% (Table 5.7). This result may overstate the levels of participation in PT/EQA schemes specific to molecular genetic testing as the question was general and allowed a legitimate positive response if a centre was active in any PT/EQA scheme relevant to the laboratory (for example a cytogenetic or biochemistry scheme).

Cross-analysis indicates that research laboratories were less likely to participate in PT/EQA. Furthermore, laboratories that participated in PT/EQA had a significantly higher test accessioning volume (mean of 1 362 for centres participating in PT/EQA compared to a mean of 271 for those that were not). These results may reflect the lack of availability of PT/EQA schemes for more specialised diagnostic tests and a less developed quality assurance culture in the research sector.

Table 5.7. Percentage and number of laboratories participating in specified PT/EQA programmes

	AUS	BEL	CAN	CZE	FIN	FRA	GER	IRE	ITA	JAP	NOR	POR	SPA	SWE	SWI	TUR	UK	USA
Yes	76	100	83	50	100	67	80	80	63	100	80	67	45	89	87	91	88	86
n	26	8	24	6	6	69	102	8	76	7	4	18	33	8	27	10	63	121
No	24	0	17	50	0	33	20	20	37	0	20	33	55	11	13	9	12	14

	%	n
Yes	74	616
No	26	211

The responses to a question about the schemes used (Table 5.8) reflected the regional influence of PT/EQA schemes. CAP and CORN schemes were mainly used in North American countries and the German scheme was concentrated in German-speaking countries (Austria, Germany and Switzerland). EMQN and other schemes centred on Europe have not penetrated North America. More than 70% of laboratories participated in one or more PT/EQA schemes.

There were 16 different responses under the "other" category, of which seven are well-established PT/EQA schemes (Lab Quality, OQUASTA, ISFG, ISS, QMPLS, DGKC and Instand).

Table 5.8. Percentage and number of laboratories participating in PT programmes by country

	AUS	BEL	CAN	CZE	FIN	FRA	GER	IRE	ITA	JAP	NOR	POR	SPA	SWE	SWI	TUR	UK	USA
Tot n	26	8	24	6	6	69	102	8	76	7	4	18	33	8	27	10	63	121
A	0	0	75 (18)	0	0	4 (3)	0	0	5 (4)	100 (7)	0	22 (4)	0	0	0	0	2 (1)	83 (100)
B	0	0	0	0	0	4 (3)	0	0	0	0	0	0	0	0	0	0	0	7 (8)
C	0	0	0	0	0	4 (3)	0	0	78 (59)	0	0	0	0	0	0	0	0	2 (2)
D	61 (16)	0	0	0	0	0	89 (91)	0	3 (2)	0	0	0	6 (2)	0	67	0	0	0
E	15 (4)	88 (7)	0	67 (4)	0	19 (13)	20 (20)	0	18 (14)	0	75 (3)	22 (4)	9 (3)	25 (2)	33	20 (2)	17 (11)	0
F	18 (5)	12 (1)	25 (6)	0	0	25 (17)	5 (5)	50 (4)	18 (14)	0	100 (4)	72 (13)	45 (15)	25 (2)	37 (10)	10 (1)	38 (24)	2 (2)
G	8 (2)	0	0	0	0	0	0	90 (7)	0	0	0	22 (4)	6 (2)	50 (4)	15	0	95 (60)	2 (2)
H	8 (2)	0	0	0	0	17 (12)	5 (5)	0	5 (4)	0	25 (1)	22 (4)	0	0	33	0	3 (2)	0
I	0	0	58 (14)	67 (4)	50 (3)	56 (39)	15 (15)	0	22 (17)	43 (5)	0	22 (4)	15 (5)	50 (4)	15	50 (5)	14 (9)	48 (58)
J	46 (12)	0	46 (11)	0	100 (6)	9 (6)	15 (15)	0	13 (10)	0	0	22 (4)	39 (13)	100 (8)	15	0	6 (4)	19 (23)

		%	n
A	CAP	22	137
B	CORN	1	11
C	Italian Scheme	10	64
D	German Scheme	18	111
E	CF Thematic Network	14	87
F	EMQN	20	123
G	UKNEQAS	13	81
H	EAA/EMQN	5	30
I	Inter-laboratory exchange of specimens	30	182
J	Other	18	112

Table 5.9. Number of laboratories participating in the CF Network, EMQN and molecular cytogenetics UKNEQAS schemes, 2002 and 2003

	AUS	BEL	CAN	CZE	FIN	FRA	GER	IRE	ITA	JAP	NOR	POR	SPA	SWE	SWI	TUR	UK	US	Total
E	6/5	8/8	0/1	2/2	1/1	34/34	39/44	3/4	29/31	0/0	2/1	1/2	16/16	0/4	7/11	1/2	16/16	2/27	168/ 225
F	2/4	8/10	2/3	2/4	2/3	19/22	7/6	2/4	6/10	0/0	2/5	5/5	6/19	2/5	7/9	0/1	15/12	2/2	74/ 124
G		-/2						-/2				-/3	-/1		-/1		-/29		-/38

Source: Rob Elles; E = CF Thematic Network; F = EMQN; G = UKNEQAS).

To validate the survey data, independent confirmation was sought from PT/EQA scheme organisers. Table 5.9 shows the number of laboratories participating in the EMQN, CF Network and UKNEQAS schemes for molecular genetics and cytogenetics in 2002/03 as reported by scheme organisers. The reported numbers of participations in EMQN schemes and the CF Thematic network scheme correlate approximately with the numbers reported in the OECD survey (Table 5.8). The apparent discrepancy in the reported numbers for participants in UKNEQAS can be explained by the fact that laboratories in the OECD survey could report participation in all UKNEQAS schemes including that offered for cytogenetic testing.

Barriers to participation in PT schemes

Barriers to participation in EQA/PT were also explored (Table 5.10). Among the 26% of laboratories (n=211) that did not participate in any PT/EQA scheme, 65% (n=137) found no PT/EQA scheme available. This reflects the limited range or availability of test-specific PT/EQA schemes compared to the great diversity of services offered. As an example, in the United Kingdom over 300 genetic tests are formally recognised by the UK Genetic Testing Network[4] but less than 20 EQA schemes specific to disease service, representing the most frequently offered tests, are available through UKNEQAS[5].

4. *www.dh.gov.uk/genetics*

5. *www.ukneqas.org.uk*

Table 5.10. Percentage and number of laboratories reporting barriers to participation in PT/EQA schemes

Includes only countries having laboratories that do not participate in PT/EQA

	AUS	BEL	CAN	CZE	FIN	FRA	GER	IRE	ITA	JAP	NOR	POR	SPA	SWE	SWI	TUR	UK	USA
n	8	0	5	6	0	34	26	2	45	0	1	9	40	1	4	1	9	20
A	0	-	40 (2)	67 (4)	-	9 (3)	0	0	4 (2)	-	0	0	12 (5)	0	0	100 (1)	0	15 (3)
B	100 (8)	-	80 (4)	33 (2)	-	79 (27)	69 (18)	0	60 (27)	-	100 (1)	67 (6)	45 (18)	100 (1)	100 (4)	100 (1)	100 (9)	55 (11)
C	0	-	40 (2)	67 (4)	-	29 (10)	15 (4)	0	35 (16)	-	0	67 (6)	35 (14)	0	0	0	0	45 (9)
D	0	-	0	33 (2)	-	9 (3)	15 (4)	100 (2)	18 (8)	-	0	0	20 (8)	0	0	0	0	15 (3)

A	Cost of participation is too high	10
B	No proficiency testing programme is available for the tests we offer	65
C	There is insufficient staffing in the laboratory to complete proficiency tests	31
D	Other	14

Many molecular genetic testing PT/EQA schemes have only one or two distributions of three to five samples relevant to a testing service for a particular genetic condition a year (EMQN, UKNEQAS, ISS, CF Thematic network). In contrast, EQA schemes for clinical chemistry laboratories have significantly more regular and frequent distributions (monthly or bi-monthly for example).

Staff time was seen as a barrier to participation in PT schemes by 31% of MGT laboratory directors. This may be explained by the lack of automation for most molecular genetic tests and the relatively small size of many MGT laboratories. The current practice of concentrating PT/EQA schemes and sample distribution in a single time period each year may be particularly onerous for small laboratories. However, the cost of participation was not generally a barrier (10% of respondents).

Responses to this question confirmed that there are significant unmet needs for PT/EQA schemes for molecular genetic testing laboratories.

Barriers to certification/accreditation

Of the 46% of centres (n=362) that reported that they were not accredited/certified, only 8% (n=28) were working towards it (Table 5.11). These laboratories are concentrated in seven of the 18 participating countries. In nine countries, no laboratories reported that they were seeking accreditation. In only two countries more than 60% of the responding laboratories were doing so.

Table 5.11. Percentage and number of laboratories reporting barriers to certification/accreditation

Includes only countries that had laboratories that are not certified/accredited

	AUS	BEL	CAN	CZE	FIN	FRA	GER	IRE	ITA	JAP	NOR	POR	SPA	SWE	SWI	TUR	UK	USA
n	16	0	12	6	4	32	85	9	68	1	5	23	45	4	4	10	15	23
A	0	-	33 (4)	75 (4)	0	9 (3)	0	0	4 (3)	-	0	0	11 (5)	0	0	60 (6)	0	14 (3)
B	100 (16)	-	67 (8)	25 (2)	100 (4)	81 (26)	70 (59)	0	62 (42)	-	0	65 (15)	44 (20)	100 (4)	100 (4)	30 (3)	100 (15)	54 (12)
C	0	-	33 (4)	0	75 (3)	31 (10)	15 (13)	0	35 (24)	-	100 (5)	65 (15)	36 (16)	0	0	30 (3)	0	45 (10)
D	0	-		0	0	0	15 (13)	100 (9)	18 (12)	-	40 (2)	0	20 (9)	0	0	0	0	14 (3)

A	Laboratory is in the process of seeking certification/accreditation	8
B	Cost is too high	64
C	Accreditation is not mandatory	46
D	Other	28

A total of 64% (n=232) and over 60% of laboratories in ten out of 18 countries reported that cost was a barrier to accreditation. This is likely to reflect awareness of the cost of achieving accreditation/certification standards and the significant and constant overhead cost of maintaining compliance.

In nine countries, over 30% of laboratory directors reported that accreditation was not mandatory and that this was a reason for not seeking it. Overall, 46% of the laboratories cited this as a reason for not seeking accreditation.

Cross-analysis was carried out for those countries for which the majority of directors said licensing was required (Austria, France and the United States). Laboratories in these countries were also more likely to be accredited/certified (74% accredited/certified versus 43% of other countries' laboratories). This may simply reflect differences in the availability of an accreditation/certification system. However, the laboratories in these countries were not more likely to participate in PT/EQA, having participation rates similar to those of other respondents (p=0.324). Since 94% of all labs have SOPs for at least some procedures, no differences could be detected between laboratories in these countries than in the others. On the other hand, laboratories with SOPs are more likely to participate in PT/EQA. This probably reflects the order in which quality assurance targets are met, as it often puts the establishment of SOPs and participation in PT/EQA first and accreditation/certification (a much more challenging and costly target) second.

The overall results indicate that almost half of all molecular genetic testing centres in the countries surveyed are both accredited/certified and not actively seeking accreditation/certification. A majority of laboratories cite cost and lack of national requirements as factors. This suggests that regulation and the implementation of appropriate incentives can act as major drivers towards laboratory accreditation.

Conclusions and recommendations for international action

The survey results indicate that QA requirements have not penetrated diagnostic MGT laboratories across OECD countries to a significant degree or with any consistency. It also reveals that a number of the terms used in the survey (for example, the difference between licensing and accreditation) are largely unfamiliar to laboratories. In particular, directors from almost every country provided erroneous responses when asked if licensing was required in their country. Yet, licensing is required by half of the countries participating in the survey, although the conditions that apply to the requirement may vary significantly. While this complicated the analysis of the data, it did not prevent drawing some general conclusions. Lack of clarity in the meaning and use of terms in the molecular genetic testing sector is an important finding. It highlights the urgent need to establish international agreement and a broader understanding of terms at all levels as an aid to harmonisation, mutual recognition and adoption of common quality systems.

Independent laboratories and high-volume laboratories were more likely to be licensed and accredited/certified. This may be because of the more established culture of quality assurance among industrial/commercial service providers and the ability of larger and more mature centres to absorb the costs associated with accreditation/certification. High-volume laboratories are probably more mature centres, perhaps within larger departments that are more likely to seek licensing, accreditation or certification.

In addition, independent service providers outside the public infrastructure may feel a greater need to secure the confidence of their users through accreditation/certification. By contrast, laboratories in the public sector may feel that the confidence of users is gained through their association with the accountable frameworks provided by social health systems.

Licensing of MGT laboratories does not contribute directly to the quality of their output. However, it is a valuable tool which is used by local or national governments to monitor service providers, and it may indicate a particular concern for oversight, particularly where highly predictive tests are offered (France, Austria).

By contrast, accreditation is a powerful tool to improve quality assurance. It requires having the laboratory assessed against external standards by independent audit. This helps to achieve consistency among laboratories that are accredited by the same accreditation agency. Furthermore, international standards such as ISO 17025 and ISO 15189 relate clinical laboratories to laboratories such as chemical analysis and food standards laboratories. Where national accreditation agencies base their systems on the same or compatible standards, there is the potential for achieving similar levels of competence internationally.

A second and more detailed level of external performance oversight is offered by PT/EQA. In molecular genetic testing, these systems are relatively undeveloped and evidence linking participation in PT/EQA to high standards is sparse. However, it is generally recognised that PT/EQA allows monitoring of performance at individual

laboratory and at collective levels. Recently, PT/EQA schemes for MGT have benefited from an international approach and fresh thinking (an emphasis on interpretation of data and a relationship to the evolution of best practice).

Certification is a system to ensure that a laboratory is compliant with a quality management system that is defined internally. It is a useful step, but it is not equivalent to accreditation.

Accreditation/certification of diagnostic MGT laboratories is the most effective way to improve quality assurance, but it is not widespread among participating countries. The overall results indicate that almost half of all MGT centres in the countries surveyed are not accredited/certified and not actively seeking accreditation/certification. Cost was cited as the most significant barrier.

Achieving and maintaining compliance with accreditation standards is a major test of management and adds significantly to the costs of the laboratory process. Many laboratories may not have sufficient resources to apply a quality management system. The institution of a quality management system usually requires a dedicated quality manager and staff time to maintain traceable documentation for the entire laboratory work-flow to comply with accreditation standards. Harder to quantify are the savings in terms of improved efficiency through a more robust testing process, for example fewer repeated tests, control of clinical incidents, improved risk management and reduced medico-legal costs. The accreditation process includes an audit of the laboratory infrastructures and all other quality control and quality assessment measures. To achieve accreditation, a laboratory must be adequately staffed by personnel with appropriate qualifications and training. It must have adequate documentation, such as standard operating procedures for analytical tests. In addition it must demonstrate an external assessment of its test results, preferably through participation in a recognised laboratory proficiency testing or external quality assessment scheme. It may also be required to demonstrate satisfactory performance and show that it is responsive to performance shortcomings demonstrated through PT or EQA. In most institutions, maintaining a quality management system may impose a noticeable overhead on the laboratory's total budget.

Laboratories in all of the countries surveyed participated in PT/EQA. However, a significant proportion of molecular genetic testing laboratories in each country did not. The survey revealed that lack of availability of suitable PT/EQA schemes was the main barrier to participation.

The reward for a growing and quality-assured sector for molecular genetic testing is public confidence in a new and powerful application of genetic technology. International collaboration is a strong feature at the professional level and in terms of the transborder flow of genetic test referrals and should be encouraged to ensure more complete service provision to meet the needs of patients and families, especially those at risk of very rare genetic conditions. However, patients should feel assured of the quality of service provision when their samples are sent abroad. In addition service providers need a "level playing field" to prevent unfair competition and avoid development of inappropriate balances in transborder flows.

An international and mutually recognised badge of quality assurance is the key to securing public confidence and ensuring comprehensive availability of services through international collaboration. This can only be achieved through international recognition of minimum acceptable standards for quality assurance systems.

In conclusion, almost half of all MGT laboratories are not accredited or certified and are not actively seeking accreditation or certification. Responses strongly suggest that regulation and the implementation of appropriate incentives can act as major drivers towards laboratory accreditation. Public policy has thus a role to play.

Although more fundamental policy changes may be required in the long run, since MGT laboratories should aim towards accreditation as the internationally recognised mark of laboratory competence, immediate improvements can and should be pursued.

The analysis of survey results and the discussion of existing national requirements indicates an opportunity for shared international action to:

- Recognise and disseminate existing international terminology relevant to this area.
- Clarify national requirements with regard to licensing and accreditation/certification.
- Facilitate international recognition of minimum acceptable standards for quality assurance systems.
- Develop internationally acceptable standards for transborder test referrals.
- Identify measures to make relevant PT/EQA schemes available across all OECD countries.

Such actions may provide an opportunity for both providers and consumers to recognise quality differences in genetic testing and make their decisions accordingly. In particular, patients need to have good information on quality and the ability to use that information as they see fit to meet their needs.

Chapter 6

EDUCATION AND TRAINING

Introduction

The levels of competence of the laboratory personnel who provide and interpret clinical molecular genetic tests are a crucial factor in ensuring quality of service. In particular, laboratory directors should possess expertise in the technologies employed (to test for sequence variations), knowledge of the potential limitations of the tests used, and understanding of what the test result may mean for the clinical condition referred. This chapter explores the status of training and education in molecular genetic laboratories that are providing results for health-care in 18 member countries of the OECD.

A comprehensive multinational assessment of competence presents challenges, owing to differences in requirements among countries. In some countries there is a legal requirement for a licensed physician to be responsible for a clinical molecular genetics laboratory, regardless of the nature of that individual's specialised training. Other jurisdictions require an MD or PhD with formal training and certification in clinical molecular genetics, while still others have no legal requirements in this respect. There is also some variability in the requirements at national or regional levels for the training of laboratory technologists. Furthermore, diagnostic cytogenetic and biochemical genetic laboratory services were established more than 30 years ago, clinical molecular genetics has developed recently from a basic research environment and is perceived as an evolving medical subspecialty in a number of OECD countries.

Clinical molecular genetic testing is unique among specialised medical laboratory services in that it is almost entirely cause-and disorder-specific rather than outcome-specific, it has familial implications, and it can be used for pre-symptomatic and/or predictive purposes as well as for confirmation of a clinical diagnosis. These unique aspects, together with the sector's rapid technological developments, complicate the implementation of molecular genetic laboratory tests and the interpretation and delivery of their results. Currently more than 10,000 genetic disorders have been catalogued by Online Mendelian Inheritance in Man (OMIM), and about 1 700 of these have been ascribed to specific mutations in the human genome. The number of genetic conditions with a known cause continues to increase, and the research laboratories that carry out these studies are often the first test sites for these disorders. For this reason, laboratories that provide molecular genetic results for health-care purposes can be either research or non-research (diagnostic) facilities, they are widely distributed among OECD member countries, and each provides a distinct repertoire of tests. Rapid technological developments and transfer of tests from research into clinical practice requires the laboratory director to be well aware of limitations of tests and methodologies and of using research-based results rather than clinical results in clinical practice.

Summary of survey results

Education and training of director

To explore the question of director training in diagnostic and research molecular genetic laboratories and how this relates to other aspects of genetic services, a series of cross-analyses were performed on the questions regarding these issues.

Academic degree

In 99% (n=824) of the laboratories participating in the survey, the director had an MD and/or a PhD degree; 51% had an MD or equivalent degree and 58% had a PhD (42% MD, n=347; 9% MD/PhD, n=72; 48% PhD, n=405). The remaining laboratories were directed by an individual with an MSc (<1%, n=3). The majority of directors that had a PhD, with or without an MD, had a degrees in genetics (45%), molecular biology (29%), biology (25%), biochemistry (23%) and/or other disciplines. The directors often had more than one area of specialisation, since the combined total for individual academic disciplines exceeded 100%.

Certification, training and experience

Approximately 74% (n=612) of the laboratories stated that the director was certified or registered to practice clinical laboratory medicine by an officially recognised body. However, only 67% (n=554) of laboratory directors had formal training in molecular genetics. This may result, in part, from those jurisdictions in which the laboratory director is legally required to be an MD but there is no requirement of specialisation in molecular genetics.

The mean number of years of experience for molecular genetic laboratory directors was 10.5 +/- 5.6 years (range 1-31 years). This reflects the emergence of clinical molecular genetics as a recognised discipline within the last ten to 15 years. On this basis, most of the directors participating in the survey were likely to have been part of the founding generation of clinical molecular geneticists.

Supervision

In the vast majority of laboratories (93%, n=769), the director was available to provide on-site supervision. This presumably indicates that the director is present in the laboratory on a regular basis and may reflect the high degree of complexity involved in the implementation and interpretation of clinical molecular genetic tests. However, the proportion of certified and formally trained directors who were available to provide on-site supervision was much lower (74% and 67%, respectively). This, combined with a range of up to 31 years of experience for some laboratory directors, may indicate that a significant proportion of these directors have positions that evolved from a basic education in technology development and molecular biological research into clinical molecular genetics.

Education and training of laboratory technical personnel

Employment

Six percent (n=50) of the responding laboratories did not employ individuals who performed the actual patient testing. When the laboratory settings are examined (Table 6.1), it is apparent that less than half (44%) of the sites that did not employ individuals who performed the actual patient testing were research laboratories. The remaining 56% were in a diagnostic setting, most of these in a public hospital. The diagnostic laboratories that did not employ technical personnel represented only about 3.5% of laboratories overall (29/827), and although this is a clear minority, the basis of this employment structure in these laboratories requires additional investigation.

Table 6.1. Laboratory setting and employment of individuals who perform the actual patient testing

Setting	Employ technicians		Do not employ technicians	
	n	%	n	%
Public hospital	441	95	22	5
Private hospital	64	97	2	3
Public non-hospital	29	89	4	11
Independent	99	100	0	0
Research	143	87	22	13
Total	776		50	

The remaining 94% of laboratories that did employ individuals who performed the actual patient testing, had a mean of 5.5 +/- 4 employees, with a range between 1 and 56. Only a minority of labs employed more than ten persons.

Education

A minimum degree for all molecular testing personnel was required by 91% (n=706) of the laboratories. The required degree was relatively equally distributed between a bachelor's degree (41%, n=318) and specific qualifications for medical technologists (43%, n=334), while 9% (n=70) required a masters degree and 10% required some other type of unspecified qualification.

Training

Most labs (91%, n=706) required molecular-based training of personnel before they are considered qualified to perform tests. Most labs, therefore, required both a formal degree and molecular-based training before a new molecular testing staff member is permitted to perform any patient testing that will be reported for health-care purposes. The molecular-based training was typically performed in house (92%, n=649). In-house training (n=649) consisted of bench training in 93% of the laboratories requiring in-house training (n=604) and reading of standard operating procedures (SOPs) in 87% (n=565). A small number of laboratories (23%, n=162) had a formal in-house training course that was required for new personnel. Many labs also required previous experience from another molecular genetic testing facility (42%, n=297), research experience (31%, n=219), or formal training by a professional organisation (19%, n=134).

Genetic counselling: affiliation, education and training

Affiliation

Most (72%, n=595) of surveyed laboratories had an affiliation or association with a unit offering genetic counselling services. There was substantial variation among laboratories in each country (range 10% to 100%) that had this infrastructure in place.

Provision of counselling

In 75% (n=620) of the laboratories, an affiliated physician provided genetic counselling, and only a minority (21%, n=173) employed non-physicians who provided genetic counselling. A minimum degree was required for counsellors affiliated with 90% of laboratories. In 56% of these laboratories, a bachelor's or a master's degree was required for counsellors, and in 30% the counsellor was required to have an MD or a PhD.

Cross-analyses of survey results

Qualifications of director

An initial analysis of whether or not the presence of a laboratory director with an MD is associated with any other survey responses was carried out.

Table 6.2. Analysis of factors associated with the presence of laboratory director with an MD

Variable	p value	Significant
Country	<0.001	Yes
Setting (independent vs. all others)	0.861	No
Formal training	0.164	No
Affiliated or associated with a clinical or medical genetics unit	0.811	No
Technicians employed (<4, >4)	0.160	No
Receive specimens for testing from outside of the country	<0.05 (more likely)	Yes
Ever refer specimens to another testing laboratory located outside of your country	0.875	No
<1 000 specimens vs. >1 000	0.231	No
Commercial test kits vs. in-house only and both	<0.001 (less likely)	Yes
SOPS (yes for all or some vs. no)	0.476	No
Statement of limitations on the report	0.155	No
Suggestions for further testing	0.067	No
Implications for family members	0.201	No
Require informed consent	0.819	No
Confidentiality policy	<0.003 (more likely)	Yes
Storage (indefinitely vs. others)	0.083	No
Participate in PT	0.897	No
Do prenatal testing	0.004 (more likely)	Yes
Offer tests covered by patents	0.717	No

Factors associated with the presence of an MD laboratory director are primarily the country in which the laboratory is located and the source of laboratory reagents. The former finding is probably due to legal requirements for this qualification in some jurisdictions. Other factors associated with the presence of an MD laboratory director include a greater likelihood that these laboratories receive specimens from outside the country, have a written confidentiality policy in place and carry out prenatal testing.

These analyses provide no clear associations with indicators of laboratory performance based simply on the minimum degree of the laboratory director (MD vs. all others). A more meaningful interpretation of associations between education, training and laboratory quality indicators requires an analysis of all laboratory personnel at each site.

Comparison of recommendations and requirements for competence of laboratory staff

Competence of the laboratory personnel who provide and interpret clinical molecular genetic tests is clearly importance. A comprehensive multinational assessment of competence presents challenges, owing to differences in requirements among countries. This is of concern, given the relatively high rate of transborder flow of specimens for genetic testing. However, an approximate measurement of competence – generally defined as an adequate combination of academic achievement, training and experience – can be made. A number of guidelines, recommendations and best practices have been developed by certifying agencies to promote the establishment of standards for the education and training of laboratory personnel. From these recommendations/requirements a core set of the most common elements was compiled. Table 6.3 provides a comparison of these core recommendations or requirements: laboratory director has an MD or PhD, laboratory director has formal clinical molecular genetics training, laboratory director is certified in clinical molecular genetics, laboratory technologists have a university degree, and laboratory technologists have relevant training prior to testing patient material.

Table 6.3. Comparison of recommendations and requirements for clinical laboratory personnel

Recommendation or requirement	ACMG[a]	CCMG[b]	CLIA[c]	CAP[d]	CPSA[e]	EMQN[f]	ESHG[g]	HGSA[h]	ISO[i]
Lab director has MD or PhD	√	√	√	√	√		√	√	
Lab director is certified	√	√	√		√			√	
Lab director has formal training	√	√	√	√		√	√	√	√
Lab technicians have a degree	√	√	√	√	√				
Lab technicians have training		√	√	√	√		√		√

Note: Five out of these nine organisations are North American. In addition, this table provides an overview of common recommendations or requirements established by various national and international groups. While there appears to be significant overlap, it should be noted that most were developed to be used in particular settings and the recommendations or requirements identified are not necessarily worded exactly as stated.

a. American College of Medical Genetics (2003), Standards and Guidelines for Clinical Genetics Laboratories, *www.acmg.net/Pages/ACMG_Activities/stds-2002/stdsmenu-n.htm*

b. Canadian College of Medical Geneticists (2002), CCMG Molecular Genetics Guidelines, *http://ccmg.medical.org/policy.html*

c. Clinical Laboratory Improvement Amendments of 1988 (2003), 42 CFR Part 493, Subpart M--Personnel for Non-waived Testing, *www.phppo.cdc.gov/clia/regs/subpart_m.aspx#493.1351*

d. College of American Pathologists (2003), Molecular Pathology Checklist, *www.cap.org:80/apps/docs/laboratory_accreditation/checklists/checklistftp.html*

e. College of Physicians and Surgeons of Alberta (2003), Major Laboratory Questionnaire for Accreditation – Molecular Genetics, *www.cpsa.ab.ca/facilitiesaccreditation/lab_standards.asp#Questionnaires*

f. European Molecular Genetics Quality Network (2002), Draft Best Practice Guidelines for Laboratory Internal Quality Control, *www.emqn.org*

g. European Society of Human Genetics (2001) Provision of Genetic Services in Europe – Current Practices and Issues, *www.eshg.org/PPPC.htm*

h. Human Genetics Society of Australasia (2004), HGSA Accreditation in Molecular Genetics, *www.hgsa.com.au/*

i. International Organization for Standardization (2003), Medical Laboratories – Particular Requirements for Quality and Competence, ISO 15189, *www.iso.org*

On the basis of these recommendations and/or requirements, adherence to best practices can be approximated for each laboratory, since several of the survey questions about laboratory personnel addressed these core elements. This measurement of education and training (the education and training index– ETI) assigns equal value to five criteria. The maximum possible ETI for each laboratory is 5. Any laboratory that does not employ individuals who perform the actual patient testing is not included since this would result in a maximum ETI of 3. Each component of the ETI is given equal value, since certification or registration of the laboratory director may not be available in all OECD countries (80% of labs were non-research [diagnostic], but only 69% of respondents said they were certified). It is unlikely that certification can be achieved without achieving the other two ETI requirements for a laboratory director (MD or PhD with formal training). Therefore, certification should result in a score of 3 out of 3, whereas an uncertified director would result in a score of 2 or less out of 3. This would essentially lead to a more weighted value to certification alone. Any director who is not certified, and does not have the credentials for certification in any setting, would presumably not meet the first two requirements and therefore the lab would have a total ETI of 3 or less even with competent technologists.

The mean ETI for all laboratories that employ individuals who perform the actual patient testing is 4.16.

Table 6.4. Education and training index (ETI) for diagnostic laboratories

Question	Education items: requirements	Value	Responses (%)
4(a)	Highest degree of laboratory director is MD or PhD	1	99
4(c)	Director registered or certified to practice	1	74
4(d)	Director has formal training in molecular genetics	1	67
6(c)	Laboratory requires technicians to have a minimum degree	1	91
6(e)	Laboratory technicians are trained before they perform tests	1	91

Two ETI requirements with the lowest percentage of "yes" responses are formal training (4d) and registration or certification (4c) of the director. The lower rate of formal training-as argued previously- may result from those jurisdictions in which the laboratory director is legally required to be an MD but there is no requirement of specialisation in molecular genetics. A total of 66% of laboratory directors had formal training in molecular genetics, but this summary statistic is based on a combined response from research and non-research (diagnostic) laboratories. Separating responses from these two types of laboratories shows a significant difference in the extent of formal training (Table 6.5a).

Table 6.5. Summary of responses to the question:
"Has [the director] received any formal training in molecular genetics
(*e.g.* graduate or postgraduate level study?)"

a. Based on laboratory setting

	Research	Diagnostic	p value
Yes	41	73	<.001
No	59	27	<.001

b. All laboratories, sorted by country

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Yes	59	0	72	83	75	61	10	67	57	59	68	58	55	80	67	87	64	40
No	41	100	28	17	25	39	90	33	43	41	32	42	45	20	33	13	36	60

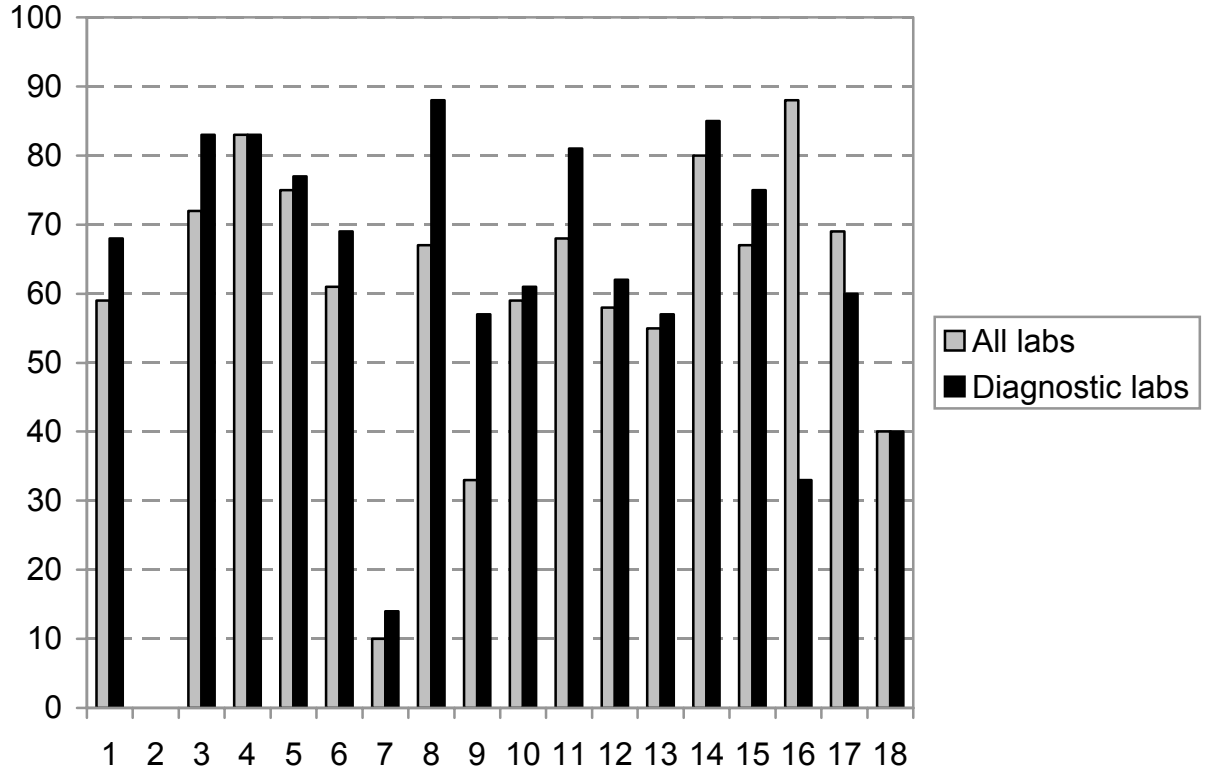
c. Diagnostic laboratories only, sorted by country

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Yes	68	0	83	83	77	69	14	88	57	61	81	62	57	85	75	33	60	40
No	32	100	17	17	23	31	86	12	43	39	19	38	43	15	25	67	40	60

Levels of formal training also vary by country. Table 6.5b and Figure 6.1 show the relative percentage of laboratories with laboratory directors with formal training in each country. These percentages are based on responses from all molecular genetics laboratories. All countries, other than country 2, had a certain percentage of directors with formal training.

When responses from research laboratories are removed from the data set, country-specific differences in levels of formal training for non-research (diagnostic) laboratory directors is apparent (Table 6.5c and Figure 6.1). Overall, there is a trend towards higher levels of formal training for diagnostic laboratory directors in all countries, although there are some exceptions. Country 2 had no directors with formal training, less than 15% of country 7's diagnostic directors had formal training, and countries 16 and 17 both had higher levels of formal training among research laboratory directors than among diagnostic directors. This indicates a limitation of access to formal training programmes in these countries.

Figure 6.1. Percentage of all laboratories and non-research (diagnostic) laboratories in each country whose laboratory directors have received formal training in molecular genetics



The low overall level of laboratory director certification is primarily due to the fact that responses from research and diagnostic laboratories are combined in Table 6.5. Table 6.6a shows, as would be expected, that there are significantly fewer research laboratories with certified directors, since certification of a research laboratory director is not a typical requirement. When responses from all laboratories are sorted by country, considerable

variation is observed, possibly owing to the inclusion of data from research laboratories (Table 6.6b and Figure 6.2). However, when the responses from research laboratories are removed from the dataset, there is some indication of a lack of availability of certification in some OECD countries, particularly in countries 2, 4, 9, 10, 11 and 16 (Table 6.6c and Figure 6.2). All countries, except country 9, have a greater percentage of certified diagnostic laboratory directors than research directors (Figure 6.2). Survey question 4c did not specifically ask whether or not the director was certified in clinical molecular genetics, and therefore any clinical laboratory medical certification would suffice. In addition, in none of the countries surveyed did 100% of respondents indicate that certification or registration was not available (Tables 6.6b and 6.6c). It is therefore difficult to assess definitively whether or not the availability of certification is the limiting factor. Representatives of each participating country were contacted and asked whether or not certification or registration is available in their country. These data were compared to the responses from diagnostic laboratories (Table 6.6c). Certification or registration is not available in countries 2, 7 or 11. The data in Figure 6.2 support these findings, except for country 7. Most of this country's diagnostic directors have obtained certification from an external national organisation.

Table 6.6. Summary of responses to the question "Is [the director] certified or registered to practice clinical laboratory medicine by any officially recognised body?"

a. Based on laboratory setting of respondents

	Research	Diagnostic	p value
Yes	38	83	<.001
No	24	14	0.006
Not available	38	3	<.001

b. From all laboratories, sorted by country

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Yes	70	50	72	67	87	67	70	64	28	52	60	87	85	86	89	42	64	40
No	24	50	24	0	2	20	20	23	28	33	20	13	11	14	0	14	27	60
n.a.	6	0	3	33	11	13	10	13	44	18	20	0	4	0	11	42	9	0

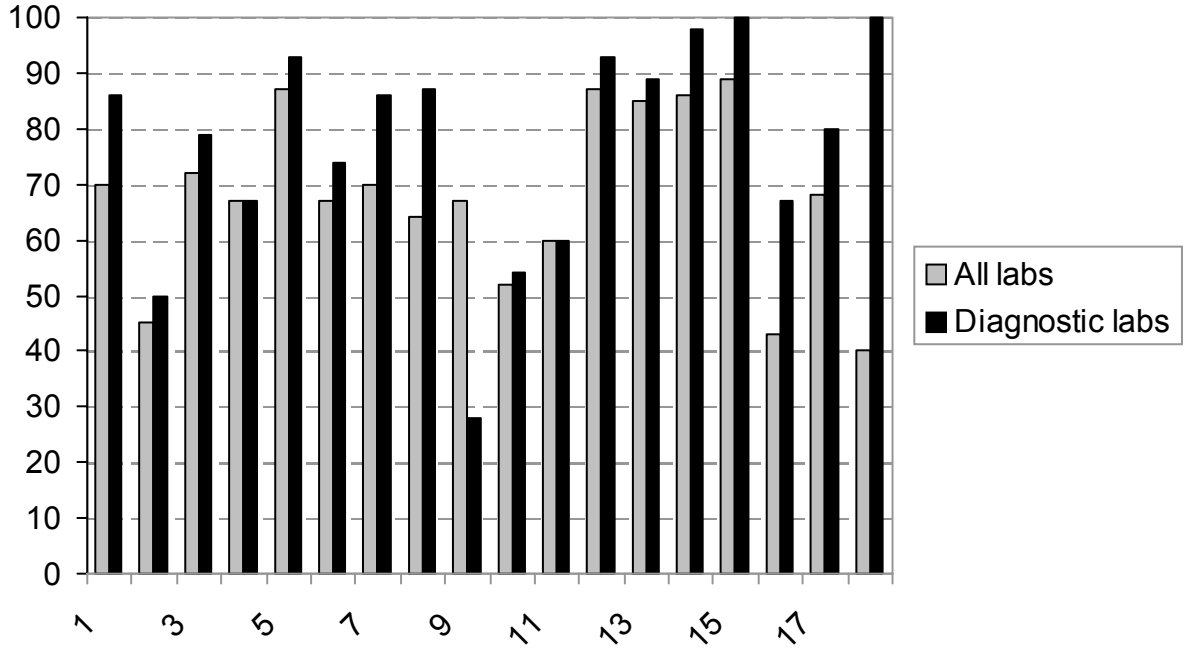
c. Diagnostic laboratories only, sorted by country

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Yes	86	50	79	67	93	74	86	87	28	54	60	93	89	98	100	67	80	40
No	14	50	21	0	0	20	14	11	28	42	38	7	11	2	0	33	20	60
n.a.	0	0	0	33	7	6	0	1	44	4	2	0	0	0	0	0	0	0
A*	Y	N	Y	Y	Y**	Y	N	Y			N		Y	Y	Y	Y		

*The availability (A) of certification within each country (Y=yes, N=no) was determined by OECD steering group representatives from that country.

** Available and/or required for private laboratories only, not for public laboratories.

Figure 6.2. Percentage of all laboratories and non-research (diagnostic) laboratories in each country that have laboratory directors who are certified or registered to practice clinical laboratory medicine by any officially recognised body.



The ETI is simply a measure of several quality indicators for laboratory personnel. It is not intended to be used as a score for comparing countries. The applicability of this summary statistic is dependent upon whether or not ETI criteria (primarily laboratory director formal training and certification) can be met within each country that participated in this survey.

In addition to the ETI criteria identified in Table 6.4, affiliation with a counselling unit could be considered. However, specific counselling recommendations or requirements are listed by only three (CCMG, ESHG, and HGSA) of the nine organisations that address personnel requirements. Two of the three (CCMG and HGSA) only make specific mention of this recommendation in regard to pre-symptomatic or predisposition testing. Similarly, very few of these organisations recommend or require the laboratory director to be available to provide on-site supervision. Another criterion that could be included in the ETI would be based on the response to question 6h which asks for specification of the minimum experience required before technicians perform any testing. However, it may be difficult to convert these data into a quantitative score and very few of the organisations listed in Table 6.3 have recommendations or requirements for minimum laboratory technician experience.

Analysis

The first, and most obvious application of the education and training index is a comparison between non-research (diagnostic) laboratories and research laboratories

(question 2a). Research laboratories are not expected to meet the same standards as diagnostic laboratories and, therefore, are expected to have a significantly lower ETI. This is found to be the case (Table 6.7).

Table 6.7. Mean ETI based on primary laboratory classification

Primary lab classification (2a)	Mean ETI	p value	Significant
Diagnostic	4.31	<0.001	Yes
Research	3.51		

Other factors that may have a significant association with the ETI were investigated. Responses to a number of "yes" or "no" survey questions were compared to the laboratory ETI. An initial assessment of all laboratories (Table 6.8) reveals significant associations between a higher ETI and a diagnostic laboratory designation (as per Table 6.7), a consulting relationship with a clinical or medical geneticist, an affiliation with a clinical genetics unit, the presence of standard operating procedures, the review of SOPs, a written policy about confidentiality, licensing of the laboratory, accreditation of the laboratory, participation in proficiency testing programmes, and maintenance of data on turnaround times.

Table 6.8. Pair-wise analysis of factors associated with the education and training index in all laboratories

		Mean ETI		
Question	Variable	Yes	No	p value
1	Testing services (pre-symptomatic and/or predisposition vs. all others)	4.17	4.09	0.143
2(a)	**Setting (all others vs. research)**	**4.31**	**3.51**	**<0.001**
3(b)	**Consulting relationship or affiliation with a clinical or medical geneticist**	**4.29**	**3.88**	**<0.001**
4(f)	Director available to provide on-site supervision	4.16	3.96	0.265
5(a)	**Laboratory affiliated or associated with a clinical or medical genetics unit**	**4.24**	**3.93**	**0.002**
5(d)	Minimum qualification required for genetic counsellors	4.39	4.08	0.233
7(c)	Laboratory receives samples for testing from outside the country	4.21	4.09	0.189
7(j)	Laboratory refers specimens to another testing laboratory	4.16	4.26	0.412
10(a)	**Standard operating procedures are in place**	**4.33**	**3.39**	**<0.001**
10(c)	**All standard operating procedures are reviewed by laboratory director**	**4.26**	**3.94**	**0.005**
11(a)	The laboratory issues a report	4.17	4.11	0.816
12(a)	Laboratory requires a copy of the informed consent	4.23	4.10	0.145
12(e)	**A written policy about confidentiality is in place**	**4.46**	**3.92**	**<0.001**
12(f)	Laboratory retains specimens (indefinitely vs. all others)	4.16	4.15	0.876
13(b)	**Laboratory is licensed**	**4.41**	**3.82**	**0.020**
13(c)	**Laboratory is accredited/certified**	**4.41**	**3.87**	**<0.001**
13(e)	**Laboratory participates in any proficiency testing programmes**	**4.28**	**3.85**	**<0.001**
14(a)	**Laboratory maintains data on turnaround times**	**4.27**	**3.76**	**<0.001**
14(b)	Laboratory carries out prenatal or pre-implantation testing	4.23	4.09	0.116
15(a)	Laboratory offers genetic tests that are covered by patents	4.13	4.04	0.232

The significant association of laboratory setting (question 2a) with ETI may bias the results when responses from all laboratories are grouped together. Therefore, a second analysis was carried out in which responses from research laboratories were removed from the dataset. The results in Table 6.9 indicate that a number of the significant associations between survey responses and ETI were found among diagnostic (non-research) laboratories. Specifically, a consulting relationship with a clinical or medical geneticist, an affiliation with a clinical genetics unit, a written policy about confidentiality, accreditation of the laboratory, and participation in proficiency testing programmes were all significantly associated with a higher ETI.

Table 6.9. Pair-wise analysis of factors associated with the education and training index in diagnostic laboratories

		Mean ETI		
Question	**Variable**	**Yes**	**No**	**p value**
1	Testing services (pre-symptomatic and/or predisposition vs. all others)	4.33	4.29	0.237
3(b)	**Consulting relationship or affiliation with a clinical or medical geneticist**	**4.53**	**3.81**	**<0.001**
5(a)	**Laboratory affiliated or associated with a clinical or medical genetics unit**	**4.41**	**3.89**	**<0.001**
7(c)	Laboratory receives samples for testing from outside the country	4.42	4.11	0.197
7(j)	Laboratory refers specimens to another testing laboratory	4.39	4.13	0.349
12(a)	Laboratory requires a copy of the informed consent	4.29	4.32	0.609
12(e)	**A written policy about confidentiality is in place**	**4.54**	**3.80**	**<0.001**
12(f)	Laboratory retains specimens (indefinitely vs. all others)	4.39	4.15	0.646
13(c)	**Laboratory is accredited/certified**	**4.41**	**3.94**	**<0.001**
13(e)	**Laboratory participates in any proficiency testing programmes**	**4.42**	**3.91**	**<0.001**
14(a)	Laboratory maintains data on turnaround times	4.32	4.20	0.701
14(b)	Laboratory carries out prenatal or pre-implantation testing	4.34	4.28	0.329
15(a)	Laboratory offers genetic tests that are covered by patents	4.36	4.21	0.267

Note: Setting is removed since the analysis in Table 6.7 compared diagnostic with research labs and research labs were removed from the analysis for this table. Laboratory is licensed has been removed since with research labs removed, nearly all labs were licensed. Director available to provide on-site supervision, minimum qualification required for genetic counsellors, standard operating procedures are in place, and the lab issues a report were removed from analysis as the vast majority of diagnostic labs replied "yes" to these items.

Multivariate analysis

Multivariate analysis was used with ETI analysed as a continuous variable to identify the factors that contribute most to the ETI. Setting (research vs. all others), report quality index, confidentiality policy, accreditation and maintenance of turnaround time data were the factors that provided the greatest prediction of variance (Table 6.10). Accreditation accounted for 8% of the variance, and these factors together accounted for 19% of the variance. The correlation of the reporting index (see Chapter 3) and the quality assurance index (see Chapter 1) revealed that each of these indices correlated highly with the ETI with R^2 values of 0.680 ($p<0.001$) and 0.712 respectively ($p<.001$).

Table 6.10. Variables associated with higher education and training index on multivariate analysis

In order of contribution

Question	Variable	Cumulative R^2	P value
13(c)	Laboratory is accredited/certified	0.089	0.001
14(a)	Laboratory maintains data on turnaround times	0.130	0.001
12(e)	A written policy about confidentiality is in place	0.159	0.012
2(a)	Setting	0.190	0.011

Conclusions

There are relatively few molecular genetic laboratory directors with formal training in molecular genetics and/or certification in several of the participating countries. These two elements are the most significant contributors to the variability in the education and training index (ETI) observed in the survey data. The low overall level of laboratory director certification and molecular genetics training is probably due to differences in national requirements and a lack of availability of certification in some OECD countries. Furthermore, in some countries there is a legal requirement that the person responsible for the direction of clinical molecular genetics laboratory is a licensed MD, regardless of that person's formal specialised training. The majority of directors responding to the survey are also likely to be among the founding generation of clinical molecular geneticists.

A higher ETI is associated with several important quality indicators for the operation of a clinical molecular genetic laboratory. This association can be found in all responding laboratories and is not diminished when research laboratories are excluded from the analysis.

The ETI may be the most significant contributor to the report quality index (Chapter 3). Multivariate analysis indicates that a higher ETI results in higher-quality laboratory reports.

Other factors having a significant association with a high education and training index are a consulting relationship or affiliation with a clinical or medical geneticist, laboratory affiliation or association with a clinical or medical genetics unit, availability of standard operating procedures (SOPs), review of all SOPs by laboratory director, availability of a written policy about confidentiality, licensing of laboratory, accreditation or certification of laboratory, laboratory participation in any PT programmes, laboratory maintenance of data on turnaround times, and a high report quality index.

A comparison between non-research (*i.e.* clinical) laboratories and research laboratories also reveals that research laboratory personnel who have not been trained in clinical service standards, perhaps not surprisingly, do not meet these standards to the extent that clinical laboratory personnel do and therefore have a lower ETI.

In addition to the requirements listed in the ETI, the survey also explored affiliation of laboratories with a counselling unit. An overview of available recommendations on personnel requirements issued by nine national and international groups reveals that specific counselling recommendations or requirements are listed by only three of the nine organisations. Two organisations make specific recommendations in regard to pre-symptomatic or predisposition testing. In 75% (n = 620) of the laboratories, an affiliated physician provides genetic counselling; only 21% of laboratories (n = 173) employ non-

physicians to provide genetic counselling. A number of research laboratories also had an affiliation with a unit that provides genetic counselling services. This may present an opportunity, in some countries, to work through the genetic counselling profession to address laboratory quality assurance and improvement issues.

These data may be useful in establishing guidelines on education and training requirements for OECD member countries. They should be used to encourage the development of formal training and certification programmes in jurisdictions where these opportunities are currently limited or unavailable.

Chapter 7

CONCLUSIONS AND RECOMMENDATIONS

In 2000, OECD Member countries agreed that preventive medicine based on the knowledge and techniques of the new genetics could make a profound contribution to human health in the new millennium, provided governments implement the appropriate regulatory and legal frameworks to retain the confidence of the public.

This view was subsequently endorsed both by science and technology, as well as the health, Ministers meeting together at the OECD level in 2004. Issues of quality will substantially influence how patients and providers will adopt and utilise new genetic tests and may have significant implications for the future of genomic technologies in the delivery of health care. Governments have a responsibility to ensure that quality assurance is central to the development of genetic testing and their successful integration in clinical practice.

This OECD study was developed in response to these issues. The results provide the first detailed information about quality management practices in molecular genetic testing laboratories on an international scale. They confirm the steady growth of molecular genetic testing and its widespread availability. The total number of specimens processed by laboratories increased from 874 608 in 2000 to 1 401 536 in 2002.

Molecular genetic testing is offered in both public and private settings, the majority within or in close proximity to the location of clinical genetics services. For the most part, genetic tests are provided as services by laboratories that develop, assemble and perform their own tests, with few laboratories indicating they rely entirely on commercial test kit systems. This creates a potential for variability.

The most important referral source to MGT laboratories are clinical geneticists and physicians, who act as the main gate-keepers mediating access to genetic tests in most countries. There are however, a variety of arrangements and layers of control. In only three of the participating countries can patients request genetic testing directly. This too creates a potential for variability.

Measures have been taken to control the costs of genetic testing services in all OECD countries. There is considerable convergence in the policies adopted, although the methods may differ according to the way in which a country's health care system is organised and financed. Currently cost containment measures for genetic testing operate, as in all other sectors of health care, by acting on supply or on consumer demand. Public and private health insurers play a significant role in defining patient and provider use and access to genetic tests. However discussions on criteria to establish validity and utility of genetic testing and their uptake are at an early stage in many OECD countries. As a result there is considerable geographical disparity in the availability of genetic tests across OECD countries. Disease prevalence does not appear as a main factor in determining test availability.

The study shows that laboratories in all countries use referral networks that exist either within or outside one's country to send samples across borders Although the data represent a snap-shot of the current situation, they do show that the practice is relatively common and that a number of countries have set up fairly large networks both for referral and to provide laboratory services.

The majority of laboratories surveyed store samples indefinitely. Reasons cited for this practice include needing samples available to verify test results. Appropriate guidelines on informed consent and protection of privacy are in place in most OECD countries. However, the low positive response rates for both documented informed consent and written policies on confidentiality appear to indicate that laboratories are offered little practical guidance in this regard and that governments need to assure that national arrangements on consent and confidentiality are robust.

A number of mechanisms are in place in all OECD countries to reduce risk from inappropriate and inaccurate testing and to assure the quality of MGT procedures. In general, the tool-kit in place for ensuring quality in molecular genetic testing laboratories is not very different from that for general diagnostic laboratories. Both licensing and accreditation/certification are well established in some countries as methods of regulation and oversight and are intended to promote the quality of clinical laboratories. However, survey results indicate that implementation of these instruments in the context of molecular genetic testing present challenges. Specific requirements for licensing and accreditation/ certification have not penetrated diagnostic molecular genetic testing laboratories across OECD countries to a high degree and with any consistency. Considerable variations were found in mechanisms of licensing, certification, and accreditation which includes standards by which tests are performed, results are reported, and in the qualifications held by laboratory personnel.

A variety of financial and organisational barriers appear to prevent laboratories from pursuing quality improvements. Regulation and the implementation of appropriate incentives and access to financial resources could act as major drivers in improving quality.

The majority of laboratories are issuing reports of generally high quality. A number of key factors are associated with higher reporting quality. These factors correlated strongly with a commitment to a quality management system.

The survey found that in many countries few laboratory directors have had specific training in molecular genetics or are formally certified. This result reflects the different requirements across jurisdictions as well as the fact that such qualifications and certification systems were not available until recently in many countries. Analysis suggests that a core set of qualifications may have a significant overall impact on performance.

Comparison between diagnostic MGT laboratories and laboratories in the research setting reveals that research laboratories are not always operating to the same standard as "service laboratories". However, it is essential to recognise that research laboratories perform a vital role in providing tests for rare disorders, which would not otherwise be available. One of the difficult challenges in the use of genetic tests is a constantly changing knowledge base and research laboratories are key to maintaining progress in genetic testing. The right balance must be struck between ensuring that a wide range of tests for rare disorders is available and ensuring high quality of service.

Key conclusions from the study

1. **Accreditation to a defined quality standard is the single most important measure to ensure quality. Regulation and the implementation of appropriate incentives can act as major drivers towards laboratory accreditation.**

   Recommendations are:

   - That consistent use of existing international terminologies in the area of accreditation/certification and proficiency testing/external quality assessment (PT/EQA) should be encouraged.
   - That the national/regional requirements for licensing and accreditation/certification of molecular genetic testing laboratories should be clarified.
   - That international mutual recognition of PT/EQA systems should be facilitated.
   - That measures to make PT/EQA or other appropriate systems of quality assessment available to molecular genetic testing laboratories in all settings, including research laboratories should be identified.
   - That the barriers to accreditation/certification and the need for molecular genetic testing laboratories in diagnostic settings to reach these standards should be addressed.

2. **The "internationalisation" of genetic testing for medical and research purposes and the establishment of genetic testing networks has become inevitable and necessary.**

   Recommendations are:

   - Those national and international barriers to accessing genetic testing for rare diseases should be examined and addressed and that the role of co-operation between national and international networks for improving access to genetic testing for rare diseases should be explored.
   - That the ways in which analytic and clinical validity and clinical utility of genetic tests are currently assessed across the different jurisdictions should be explored, particularly for newly developed genetic tests and tests for rare disease which may require cross-border referral.

3. **Appropriate professional qualifications and standards are important to assure laboratory competence in providing genetic testing services.**

   Recommendations are:

   - That existing recommendations and requirements for technical and professional qualifications for personnel involved in molecular genetic testing should be reviewed, and those opportunities for the development of a minimum set of common values and criteria for professional competence should be identified.

- That the development of formal training leading to professional qualification should be encouraged where opportunities for such training are currently limited or unavailable.

4. All laboratories should issue a report when test results are provided for clinical decision-making or counselling the patient or family. Systems that recognise the competence of the laboratory (*e.g.* accreditation, PT/EQA schemes) should include the evaluation of laboratory reporting practices.

Recommendations are:

- That existing recommendations and best-practice guidelines on result reporting should be consolidated into a set of principles generally acceptable to the international community. In doing so, differences in country-specific practices should be taken into account.
- That the special issues facing research laboratories in providing quality clinical services when tests results are returned for patient management or counselling should be examined.

5. A balance must be achieved between ensuring appropriate privacy protection, and the need to avoid unnecessary restrictions on equity of access to genetic testing, the use of samples for public health activities and the exchange of information vital to medical care. A shared understanding should be achieved and policy for international guidelines developed:

Recommendations are:

- That such guidelines should address the long-term retention and storage of specimens in the context of medical care (as opposed to research).
- The guidelines should also address current privacy and security issues, particularly in the context of trans-border flow of clinical samples.

Annex A

LICENSING AND ACCREDITATION IN 18 OECD COUNTRIES

Country	Licensing	Accreditation/certification
Austria	Licensing is mandatory for laboratories performing predictive/presymptomatic testing. The laboratory director has to make an application for a permit at the Federal Ministry of Health and Women. The laboratory but not the laboratory director is licensed (the requirements are defined in general by the Austrian Gene Technology Act (BGBl. No. 510/1994) and are explained in detail in the Austrian Book of Biotechnology, Chapter 1.	Some laboratories are certified according to ISO 9001.
Belgium	Licensing is necessary for test reimbursement.	There is no specific accreditation requirement for molecular genetic diagnostic laboratories. Reference laboratories that perform HIV testing and forensic DNA testing laboratories must be accredited by Beltest and according to ISO 17025.
Canada	All laboratories that perform testing for diagnosis, prophylaxis and treatment of patients must be licensed by the Ministry of Health and Long-Term Care. Only the Ontario Province has a licensing requirement for MGT laboratories.	The Ontario Medical Association (OMA) is the agency designated in Ontario Regulation 682, made under the *Laboratory and Specimen Collection Centre Licensing Act,* as the agency to carry out examinations and evaluations of proficiency in the performance of tests in medical laboratories. The OMA's Quality Management Program – Laboratory Services is in the fifth year of development of a five-year peer review accreditation system for medical laboratories in Ontario.
Czech Republic	No licensing system is available.	In the Czech Republic there is one competent authority that accredits clinical laboratories, the Czech Accreditation Institute.
Finland	In Finland molecular genetic laboratories do not need any specific license, but all private clinical diagnostic laboratories need an easily obtainable working permit.	In Finland there is one competent authority (FINAS) that accredits clinical laboratories. FINAS is a member of European Accreditation and the standard currently used for accreditation of clinical laboratories is ISO 17025, soon to be replaced by ISO 15189. In some cases certification under ISO 9001 is awarded.
France	Two categories of tests are regulated by the Ministry of Health: prenatal tests and presymptomatic or predictive genetic tests. A license is required for predictive tests. For prenatal tests, only authorized labs can deliver services (legislation 1994). The authorization is delivered to a specific practitioner in a specific location. If an authorized practitioner moves to another institution, he/she has to re-apply. Conversely, if an authorized laboratory hires a new practitioner, it is also required to re-apply.	There is no accreditation requirement for molecular genetic diagnostic laboratories. However, all private laboratories performing clinical tests have to receive an authorization (legislation 1975) and are required to follow the procedures of the Guide de Bonne Execution des Analyses de Biologie Medicale. Public laboratories do not fall within this system, but must be located in a hospital. Public university/research laboratories are not allowed to report back to patients. However, if they are the only service provider for a genetic condition, they may have an unofficial agreement with an authorized laboratory to approve results.
Germany	In general a license (or approbation) is required to operate any laboratory providing medical tests. There is no specific license required for genetic testing.	Special criteria for accreditation of molecular genetic testing laboratories are in preparation. The German accrediting agencies work according to DIN-EN-ISO standards 15189 or 17025 for accreditation and 9001 for certification. However, existing criteria and check-lists for accreditation are oriented to the requirements of routine clinical laboratories.
Ireland	No specific licensing is required for MGT laboratories.	No formal accreditation is required for medical laboratories. Formal accrediting organizations/agencies exist but they do not accredit medical laboratories.

Country	Licensing	Accreditation/certification
Italy	All clinical laboratories are required to have a general approval from a regional authority. However, there is no specific requirement for genetic laboratories.	Accreditation requirements are set by regional authorities. (ex art.25 regional regulation 833, 25th February 1984) . ISO standards and UNI-EN accreditation systems and D.lgs 626/94 are recognized. There are currently no specific accreditation requirements for MGT laboratories.
Japan	Japan has a licensing scheme for medical laboratories in general. Genetic testing is regulated according to the "law concerning clinical laboratory technicians, public health laboratory technicians and other related personnel".	All clinical and public health laboratories have to be accredited and inspected by the local authority.
Norway	A license is needed to become director of genetic laboratory.	Accreditation is not required. However, all clinical laboratories have to receive formal approval by the competent authorities.
Portugal	There are no specific licensing requirements for MGT laboratories.	No specific accreditation is required for MGT laboratories. However, all clinical laboratories have to receive formal approval by the competent authorities. The Portuguese Quality Institute (IPQ), which is a member of the European Co-operation for Accreditation, has charged the Portuguese Agency for Certification (APCER) with the certification of diagnostic laboratories. IPQ, through APCER may evaluate the practices of laboratories according to European Directive 88/320.
Spain	Clinical laboratories require a license issued by the regional health authorities. There are no specific requirements for MGT laboratories.	There are no specific requirements for MGT laboratories as they are considered clinical diagnostic laboratories. AENOR is the agency competent to accredit clinical diagnostic laboratories in Spain. Accreditation is not mandatory.
Sweden	There are no licensing requirements in Sweden.	SWEDAC is the agency competent to accredit diagnostic laboratories in Sweden. There are no special requirements for MGT laboratories.
Switzerland	Clinical laboratories require a license issued by the competent federal authorities. Switzerland is in the process of converting to a new regulatory system. A condition for receiving a license will be accreditation through the Swiss Accreditation Office (SAS).	Switzerland is in the process of converting to a new regulatory system. Laboratories will have to be accredited according to international standard ISO/IEC 17025 : 1999 and in the near future according to ISO 15189 : 2003. Some private/independent and public GT labs are already accredited according to these requirements.The Swiss Accreditation Service (SAS), signatory member of EA/ILAC, is the agency competent to accredit diagnostic laboratories in Switzerland.
Turkey	A licensing system is in preparation under the Ministry of Health.	There is no accreditation system relevant to clinical laboratories in Turkey There is however an accreditation service, "TURKAK" (not specific for genetic testing)-which in the near future may certify or accredit according to ISO9001, ISO17025.
United Kingdom	There is no formal licensing system for molecular genetic testing laboratories in the UK. However laboratories may register with the officially supported UK Genetic Testing Network if they meet certain criteria including accreditation.	In the UK accreditation is mandatory and accreditation systems are overseen by the UK Accreditation Service. Clinical Pathology Accreditation UK Ltd (CPA) is the formally recognised competent agency. CPA works according to standards based on ISO 17025 (testing and calibration laboratories) and ISO15189 (Clinical Laboratories).
United States	All clinical laboratories are required to be certified under the Clinical Laboratory Improvement Amendments (CLIA) regulations or by a mechanism in states having their own programme that is determined to be equivalent to or more stringent than CLIA. Some states have additional licensing requirements. There are four separate sets of CLIA rules: *(a)* standards, *(b)* application and fees, *(c)* enforcement, and *(d)* approval of accreditation programs. The rule on standards comprises most of the regulations with which laboratories must comply (Code of Federal Regulations, Section 176, Part 493, Title 42). The CLIA requirements to ensure quality testing include proficiency testing (PT), patient test management, quality control (QC), and quality assurance (QA).	The CLIA regulations recognize certain accrediting organizations (such as the College of American Pathology (CAP)). CAP is a private, not a government owned or operated organization. CAP develops its own standards and evaluates laboratories for compliance with these standards.

Annex B

NATIONAL GUIDELINES ON INFORMED CONSENT, CONFIDENTIALITY AND STORAGE OF SAMPLES

Country	Consent	Confidentiality	Retention/storage/retrieval
Austria	Patient has to provide written informed consent prior to any predictive/ presymptomatic analysis. (Austrian Gene Technology Law) Gentechnikgesetz, BGBl No. 510/1994, updated BGBl No. 73/1998) entered into force in January 1995, amended in 1998. The law considers conditions required when patients are to undergo genetic testing. Includes handling, qualification and protection of data and genetic counselling.	The Gentechnikgesetz, Gene Technology Law includes requirements on the protection of data.	No specific legislation.
Belgium	The patient has the right to informed consent prior to any medical act. There is no specific provision for genetic testing (Patients' Rights Act 2002).	The 2001 law on privacy protection extends to the individual's personal and health data. There is no specific provision for genetic testing. The general Patients' Rights Act of 2002 also applies.	There is no specific legislation, but the *Arrêté Royal du 15/04/88 relatif aux banques de tissus et du prélèvement*, ,which addresses conservation, handling, transportation and distribution of human tissues may apply.
Canada	Informed consent requirements are addressed by the guidelines developed by the Canadian College of Medical Geneticists-(CCMG).	There is no specific legislation. Confidentiality is addressed in the guidelines on "Retention and Maintenance of Clinical Genetics Records" developed by the CCMG and by the Ethics and Public Committee.	The CCMG issued a policy statement concerning DNA banking in 1991. The guidelines stipulate that records and samples should be maintained indefinitely. The guidelines are restricted to DNA banking in relation to medical genetic diagnostic services and stipulate that a DNA bank is "a facility that is entrusted to store DNA so that it will be preserved for future analysis, for the purpose of promoting the health and wellbeing of the depositor and his/her relatives and descendants".
Czech Republic	Professional Guidelines exist.	There is no specific legislation.	There is no specific legislation (laboratories follow standards according to ISO 17025).
Finland	The patient has the right to informed consent prior to any medical act. There is no specific provision for genetic testing (Law on Patients' Rights).	There is no specific provision. Protection relies on the Personal data Information Act of 1999 and on the Patients' Rights Law.	There is no specific legislation. However, new rules were introduced in the Act on Use of Human Organs and Tissues for Medical Purpose, September 1, 2001.
France	An informed formal consent is required for all genetic tests (Loi de 1994, Art R 11 31.5 et Art 15 Laws established in 1994 on the Respect of the Human Body, and Patient's Rights) Law.	Protection relies on the Patients' Rights Law and on the 1995 Code of Medical Ethics. Law No 94-548 of July 1994 on the handling of private data in biomedical research also applies. All computerized data have to be stored in a safe environment, and should not be accessible to third parties. All data sets have to be declared to the National Commission of Informatics and Liberty (CNIL).	Guidelines are available. The storage time of tests results should be 30 years. Importation and exportation of samples for research purposes has to be authorised. The authorisations are delivered by the Ministry of research (code de la Santé Publique art R 1245.12, 1235/6, 1235/10). If the reason for import/export is medical, there is no specific regulation except for the transporter who requires an authorisation from the Ministry of Transport.
Germany	The German Society of Human Genetics and the German Medical Association have both issued guidelines.	There is no specific provision. Protection relies on the application of a number of legal instruments. The collecting, storage and use of genetic information has to be done according to the regulations of the Federal Data Protection Law (BDSG). The principle of medical confidentiality is recognized by constitutional right.	There is no uniform legislation.

Country	Consent	Confidentiality	Retention/storage/retrieval
Ireland	There is no provision.	There is no specific provision. Protection relies on the application of the Data Protection Acts.	There no specific provision.
Italy	Requirements for informed consent are specified in the 1999 National Bioethics Committee Guidelines on Genetic Testing	The treatment of genetic data, regardless of who processes them, is permitted only when specifically authorized by the Guarantor. The Guarantor is an authority set up under law no. 675 of 31 December 1996: "Protection of persons and other subjects in the case of the treatment of personal data". This law, according to the broad notion of personal data treatment provided by art. 1, para. 2, sub-section b, is applicable also to genetic tests.	Conditions are specified in the 1999 National Bioethics Committee Guidelines on Genetic Testing.
Japan	Requirements for informed consent are specified in the Guidelines of Japan's Bioethics Committee and in the guidelines of the Council for Science and Technology.	Requirements are specified the in the Guidelines of Japan's Bioethics Committee.	Requirements are specified the in the Guidelines of Japan's Bioethics Committee.
Norway	Requirements for informed consent are specified by Act No. 56 of 5th August 1994 on the medical use of biotechnology.	Requirements are based on Personal Data Registers Act of 2000, which entered into effect on January 2001 replacing the Personal Data Registers Act of 1978. (The 2000 Act was designed to update Norwegian law to comply with the European Union Directive). Available at: *www.datatilsynet.no*.	Requirements are based on Act 21 of 21st February 2003 on Biobanks. The Act regulates the collection, storage and use of human material. Diagnostic and Treatment Biobanks are defined as "collection of human biological material delivered for medical examination, diagnostics and treatment."
Portugal	There is no specific legislation. Regulation is embedded in the Penal Code. Decree 9108/97 includes non-binding provisions regarding genetic testing and screening.	There is no specific provision. Protection relies on the application of the 1988 Personal Data Protection Act.	There is no specific provision. (New legislation is in preparation).
Spain	There is no specific legislation. Requirements are based on the General Health Law.	There is no specific provision. Protection relies on the General Health Law and other legal instruments, including the 2001 law on the Protection of Personal Data.	Requirements are included in the privacy law and the national Royal Decree 411/96 on the use of human tissue. The latter includes the definition and functions of tissue banks.
Sweden	Requirements are set by the Act No. 114 of 14th March 1991 concerning the use of genetic technology in medical screening and by the Swedish Parliament Law on Biobanks in Health Care of 2002.	Protection relies on the 1980 Secrecy Act and the Supervision Act. In March 2004, the Committee on Genetic Integrity proposed a new act on genetic integrity, which extends protection by prohibiting genetic examination as a condition for obtaining insurance or employment.	Swedish Parliament Law on Biobanks in Health Care 2002; 297-Swedish Research Council-May 2003. The act regulates how human biological material is to be collected, stored and used for certain purposes with respect for the personal integrity of the individual. Biobanks are defined *as " biological material from one or more human beings that is collected and preserved for an indefinite or limited period and whose origin is traceable to an individual or individuals*".
Switzerland	Requirements are set by the 1993 *Guidelines for Genetic Investigations in Humans*. Of the Swiss Academy of Medical Science. Furthermore, according to Article 24 paragraph 2 of the Swiss Constitution the genetic make-up of a person may only be investigated, registered or revealed with the person's consent or on account of a legal basis. The Confederation is in charge of the legislation. A federal law is in preparation.	There are no specific provisions. Since January 2000, under article 13, medical confidentiality is recognized by constitutional right.	There is no specific provision.
Turkey	Requirements are stated in the 1998 regulations of Genetic Diagnostic Center by the Ministry of Health and Civil Code Art. 23/24).	Requirements are stated in the 1998 regulations of Genetic Diagnostic Centers by the Ministry of Health and Civil Code (Art. 23/24).	Laboratories follow the principles of the UNESCO declaration on human genetic data.

Country	Consent	Confidentiality	Retention/storage/retrieval
United Kingdom	Informed consent In the National Health Service is based on guidance issued by the Departmetn of Health for example "Good practice in consent" HSC2001/023".	Confidentiality requirements are based on the report of the Human Genetics Commission "inside Information 2002" *www.publications.doh.gov.ipu/confiden.*	Requirements are based on the guidelines developed by the Royal College of Pathologists. The Human Tissue Authority is drafting codes of practice relating to the removal and storage of material following the Human Tissue Act (2004).
United States	There are no federal requirements for informed consent specific for genetic tests. There are some state-specific requirements for informed consent, the format of which is not specified (*e.g.* New York: *www.wadsworth.org/labcert/clep/Survey/standards.pdf.* Informed consent is also addressed in the Standards and Guidelines for Clinical Genetics Laboratories document from the American College of Medical Genetics (*/www.acmg.net/Pages/ACMG_Activities/stds-2002/c.htm*).	The Administrative Simplification provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA, Title II) require the Department of Health and Human Services to establish national standards for electronic health care transactions and national identifiers for providers, health plans, and employers. It also addresses the security and privacy of health data. These protections apply to clinical data and when data is required for treatment of the patient for disease. There are some state-specific requirements for informed consent (*e.g.* New York: *www.wadsworth.org/labcert/regaffairs/clinical79-l_1_2002.pdf*). Provisions exist also as part of the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics (*www.acmg.net/Pages/ACMG_Activities/stds-2002/c.htm*).	Guidelines mostly relate to the retention and storage of newborn screening blood-spot samples. Requirements vary by state. The Clinical Laboratory Improvement Amendments (CLIA) does not have specific language for genetic testing, at this time, and therefore such samples are subjected to the general requirements which specify samples must be retained during the testing process.

Annex C

MEMBERS OF THE EXPERT STEERING GROUP AND NATIONAL CONTACT POINTS

Austria	**Mr. Gerald HÖFLER** University of Graz
	Mr. Dietmar VYBIRAL Federal Ministry for Health and Women Biotechnology and Genetic Engineering Vienna
Belgium	**Ms. Elisabeth DEQUEKER** University of Leuven Center for Human Genetics
Canada	**Ms. Nancy CARSON** Head of the Molecular Genetics Diagnostics Laboratory Children's Hospital of Eastern Ontario (CHEO) Ottawa
	Ms. Lynn MAINLAND Acting Manager, Human Genetics Health Sciences Policy Division & Communications Branch Health Canada Ottawa
	Mr. Martin SOMERVILLE Department of Medical Genetics University of Alberta Edmonton
Czech Republic	**Ms. Alena BLAZKOVA** Ministry of Education, Youth and Sports Department of International Cooperation in Research and Development Prague
	Mr. Radim BRDICKA National Ref. Lab. DNA Institute of Hematology and Blood Transfusion Prague

Finland	**Mr. Mauri KEINANEN** Managing Director Labquality Helsinki
France	**Ms. Ségolène AYMÉ** INSERM Paris
	Mr. Marc DELPECHE Hôpital Cochin Paris
Germany	**Ms. Birgit SCHNIEDERS** Federal Ministry for Health and Social Security Bonn
	Mr. Clemens MÜLLER-REIBLE Institut für Humangenetik Biozentrum am Hubland Würzburg University
Ireland	**Mr. David BARTON** Chief Scientist & Honorary Lecturer in Molecular Genetics National Centre for Medical Genetics Our Lady's Hospital for Sick Children Dublin
Italy	**Ms. Domenica TARUSCIO** Istituto Superiore di Sanità Rome
	Ms. Giovanna FLORIDIA Istituto Superiore di Sanità Rome
	Mr. Giuseppe NOVELLI Università Tor Vergata Biopatologia e Diagnostica per Immagini Rome
Japan	**Mr. Hiroshi YOSHIKURA** Director-General Ministry of Health, Labour & Welfare National Institute of Infectious Diseases Tokyo

Norway	**Ms. Tonje BORCH** Senior Officer Norwegian Health Directorate Department of Specialised Health Care Oslo
	Ms. Vibeke DALEN Directorate for Health and Social Affairs Division for Health Care and Social Services Oslo
Portugal	**Mr. Jorge SEQUEIROS** UnIGENe – IBMC University of Porto
Spain	**Mr. D. Armando ALBERT MARTINEZ** Coordinator Cientifico Ministerio de la Ciencia y Tecnologia Consejo Superior de Investigaciones Cientificas (CSIC) Madrid
Sweden	**Mr. Ulf KRISTOFFERSSON** Associate Professor Department of Clinical Genetics, University Hospital, Lund
Switzerland	**Ms. Isabella BERETTA** Département Fédéral de l'Intérieur Office fédéral de l'éducation et de la science Bern
	Mr. Hansjakob MUELLER Dept. Klinisch-Biologische Wissenchaften Abd. Medizinische Genetik UKBB Basel
Turkey	**Mr. Meral OZGUC** Hacettepe University Faculty of Medicine, Department of Medical Biology and Turkish Scientific and Technical Research Council DNA/Cell Bank Ankara

United Kingdom	**Mr. Robert ELLES** Head, National Genetics Reference Laboratory Manchester
	Ms. Louise NEWPORT Department of Health London
United States	**Mr. Joe BOONE** Associate Director for Science PHPPO/CDC, Division of Laboratory Systems Atlanta, GA
	Mr. Ira LUBIN Geneticist Laboratory Practice Evaluation and Genomics Branch Division of Laboratory Aystems Atlanta, GA
	Ms. Margaret MCGOVERN Department of Human Genetics Mount Sinai School of Medicine New York, NY
European Commission	**Ms. Dolores IBARRETA** Institute for Prospective Technological Studies European Commission Edf. EXPO Seville, Spain
	Ms. Line MATTHIESSEN European Commission, DG Research Directorate E-Biotechnology, Agriculture and Food Policy Unit Brussels, Belgium
	Ms. Elisabetta BALZI European Commission, DG Research Directorate E-Biotechnology, Agriculture and Food Policy Unit Brussels, Belgium

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Genetic Testing

A SURVEY OF QUALITY ASSURANCE AND PROFICIENCY STANDARDS

This report presents the results of a survey of over 800 genetic testing laboratory directors in 18 OECD countries. It provides the first detailed overview of the availability and extent of molecular genetic testing across OECD member countries. The survey asked questions about what sorts or laboratory policies and practices are in place to to assure the quality of human genetic testing and the proficiency of those that carry out such tests. It includes information on policies regarding samples and genetic data handling, as well as the transborder flow of specimens

The survey allowed the OECD to compare practices in individual countries in order to inform international action in setting standards and developing guidelines for practice. Based on the survey results, the report puts forward recommendations for action for better quality assurance and proficiency of molecular genetic testing. It shows, for example, that requirements for licensing and accreditation/certification of diagnostic molecular genetic testing laboratories have not penetrated OECD countries to a high degree or with any consistency. Considerable variations exist in mechanisms of licensing, certification and accreditation, including the standards by which tests are performed, results are reported, and the qualifications for laboratory personnel.

This survey was carried out between June and October 2003 in 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. Over the following three years, based on the results of this survey, the OECD Working Party on Biotechnology developed Guidelines for Quality Assurance in Molecular Genetic Testing which were approved as an OECD Council Recommendation in May 2007. (See *www.oecd.org/sti/biotechnology/qualityassurance* for a free download of the Guidelines.)

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