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.

References

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