Genetic Testing

POLICY ISSUES FOR THE NEW MILLENNIUM

SCIENCE AND INNOVATION

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OECD Proceedings

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ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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LES ENJEUX DU NOUVEAU MILLÉNAIRE

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FOREWORD

This report summarises the topics, issues and policy considerations discussed at the OECD Workshop on "Genetic Testing: Policy Issues for the New Millennium". The Workshop was held in Vienna on 23-25 February 2000. It was co-sponsored by the European Commission, the Governments of Austria and the United Kingdom and was attended by some 150 experts and delegates from the 29 OECD countries.

The Workshop's aims and objectives were:

- To review the current situation in genetic testing and to explore the impact of new genetic technologies upon healthcare practice in the next few years.
- To consider the impact of commercialisation of new genetic technologies on healthcare economics and on the delivery of genetic testing.
- To consider best practice and make policy statements on:
    - The importance of genetic counselling.
    - Storage and confidentiality relating to samples and genetic data.
    - Facilitating access to genetic testing.
    - Appropriate involvement of patient/consumer groups in policy making, regulation and oversight.
    - Referring tests to accredited facilities.
- To consider the benefits of international harmonisation in the areas of:
    - Regulation of the validation of genetic tests.
    - International recognition of external quality assessment programmes.
    - Standards for recording of genetic data.
    - Evaluation of the efficacy of new genetic tests and technologies.
    - International recognition of laboratory accreditation.

Accordingly, there were 24 presentations on four topics of key international relevance:

- Access to genetic tests.
- Laboratory Quality Assurance.
- Impact of the free market and technological developments on service availability, service delivery and genetic support services.
- Ethical, legal and social aspects.

The report was prepared by Elettra Ronchi of the OECD Secretariat with the editorial assistance of Doranne Lecercle, and secretarial support of Sonia Guiraud, Alysia Ritter and Stella Horsin. It is based on presentations, transcripts of panel discussions and comments made at the Vienna Workshop. It has been updated to include significant material from recent reports and information on national and international regulatory developments. The assistance of the staff of the Documentation and Information Centre of the OECD, particularly Hilary Carroll and Peter Raggett, has been invaluable.

The report was submitted for comments to speakers, chairs, panel discussion members and rapporteurs who participated in the Vienna Workshop. Their support and advice is gratefully acknowledged. It was also submitted to the WPB Working Group on Human Health-related Biotechnologies and was discussed at its meeting of 2 October 2000. The Workshop programme can be found in Annex 2.

A number of the complete speeches will be published in the journal *Community Genetics* (S. Karger AG Basel: http://www.karger.com/journals/cmg/cmg_jh.htm) under the responsibility of their authors. The abstracts of the presentations will be published in the Journal *Bio-Law and Business* (http://www.biolawbusiness.com/) and are available on the OECD Web site: http://www.oecd.org/dsti/sti/s_t/biotech/prod/genetic_testing.htm.

The report is published on the responsibility of the Secretary-General of the OECD. The views expressed are those reported at the Workshop and do not necessarily reflect the views of the OECD or of its Member governments. Mention of industrial companies, trade names or commercial products or processes in this report does not constitute an endorsement or recommendation by the OECD or the various bodies mentioned above.

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GENETIC TESTING

POLICY ISSUES FOR THE NEW MILLENNIUM

"…...and I do not believe
that there were any such diseases
in the days of Asclepius".
Plato, *Republic*, Book III

Executive Summary

On 26 June 2000, the near completion of the map of the human genome was announced. This achievement, together with other major scientific and technical advances such as the production of a high-density map of genetic markers or single nucleotide polymorphisms (SNPs), the development of methods for high-throughput parallel processing (*e.g.* gene chips), robotics and bioinformatics, is significantly accelerating progress in genetic testing. Knowledge gained from the mapping of the human genome and from the SNPs map will lead to the systematic identification of virtually all disease-causing genes and to the development of tests to detect the mutations responsible for single-gene disorders, for susceptibility to many other common disorders and for inherited differences in drug response. The introduction of gene chips and other high-throughput processing methods will enable rapid parallel testing of many genetic markers and gene mutations.

Genetic tests are being developed at an impressive rate and many have already reached the market. The complexities of the process of determining what genetic tests to adopt and reimburse, when to test, who should be tested and how to devise appropriate strategies for counselling and treatment pose tremendous challenges.

Substantial involvement of the private sector has led to unprecedented growth in commercial genetic testing services and in trade of such services, which are based on patented genes and diagnostic processes. The potential impact on OECD countries' healthcare systems, on the performance and delivery of genetic services and on related healthcare outcomes is significant. Testing is now offered internationally, and human samples and related data are increasingly being exchanged across national borders, particularly for research purposes, not always with the knowledge of donors. Such samples and the genetic information they harbour can be stored in data banks and used for public health purposes or for further research and development.

Yet the international frameworks needed 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 have not yet been clearly established. Progress in genetic testing appears to have outrun the current ethical and regulatory frameworks.

It is against this background that the OECD Workshop, "Genetic Testing: Policy Issues for the New Millennium" was organised and hosted by the UK and Austrian Governments in Vienna, on 23-25 February 2000, with the support of the European Commission. Participants included experts from 17 OECD countries, representatives of patients' organisations, industry, non-governmental organisations and the World Health Organisation (WHO).

The Workshop's overall aim was "to consider whether the approaches of OECD Member countries for dealing with new genetic tests are appropriate and mutually compatible"

Among the many questions that surround genetic testing and were set forth by the OECD Steering Committee, a significant number were retained by the participants and discussed extensively in the relevant sessions (see Annex 3). On the basis of speakers' presentations, roundtable discussions, guidance documents and scientific papers released in OECD Member countries, five interlinked areas were identified as urgently requiring co-ordinated international action:

- Development of internationally recognised and mutually compatible best practice policies for analytical and clinical validation of genetic tests, including quality assurance and accreditation of genetic services.

- Exploration of strategies to enhance current counselling services, genetic training and public information (including the development of compatible electronic information systems in genetics), particularly as a means to provide the individual with accurate information and to protect his/her autonomy.

- Examination of possible impacts of restrictive licensing practices.

- Guidance on how existing privacy, security and cryptography guidelines can apply in the context of genetic testing, particularly to ensure adequate security of genetic databases.

- Exploration of broader implications of developments in pharmaco-genetics and in high-throughput processing methods.

In addressing these issues of global importance, the OECD will continue to strengthen co-operation in biotechnology with other international organisations, particularly the WHO, as highlighted in a Framework for Co-operation signed by the two organisations on 16 December 1999.

This executive summary reports on the main considerations, contained in the accompanying report, underlying the consensus achieved on the urgency for international co-operation in these areas.

Development of internationally recognised and mutually compatible best practice policies for analytical and clinical validation of genetic tests, including quality assurance and accreditation of genetic services

Today, genetic services and clinical laboratories face a proliferation of molecular genetic tests, the introduction of a bewildering array of methods to detect any single genetic mutation and potentially many different ways for reporting laboratory findings. Yet, across OECD countries, most regulations with which laboratories must comply are not specifically designed for molecular genetic testing. Often, clinical laboratories performing these tests are not specifically required to ensure the overall quality of molecular genetic testing. As a result, while many OECD countries have established adequate oversight or legislative authority for diagnostic laboratory practices, this oversight is not in fact being implemented for molecular genetic testing. Errors are therefore more common than is generally thought and some currently reported error rates could have very serious, irreversible implications for the testees, particularly in the case of predictive testing.

Proficiency testing is not part of the mandatory certification procedure in all OECD countries. To remedy this situation, most OECD countries have implemented a number of external quality assessment (EQA) schemes in the last five years. These are largely based on professional guidelines and on voluntary participation; only in a few OECD countries are EQA schemes mandated by government (*e.g.* the United States). EQA or proficiency testing gives an independent check on a laboratory's performance, measured against an external "gold standard". Existing EQA schemes are for the most part voluntary because it is assumed that, owing to the rapid pace of technological advances, quality in molecular genetic testing is best achieved by developing consensus among professionals directly involved in such testing. The advantage of this approach is that scheme organisers and assessors are well placed to observe different approaches and changes in technology and to assess, on a case-by-case basis, which ones yield the best results. The disadvantage of this approach is a lack of the necessary enforcement authority.

These considerations and the increasing trend for tests to cross national boundaries should encourage an international approach to quality assessment, harmonisation and mutual recognition of national and regional schemes. However, significant gaps in data and policy analysis may impede informed international action. Thus, valuable first steps towards such action might be to*:*

- Collect basic data to learn what quality assurance measures and proficiency testing schemes are being undertaken across OECD countries and in clinical laboratories that offer molecular genetic testing, and to compare these practices.
- Identify areas for international co-operation in developing standards, proficiency testing and interpretative guidelines.
- Develop international guidelines on general principles.
- Facilitate international collaboration among disease-specific consortia, particularly for the testing of rare diseases.

Exploration of strategies to enhance current counselling services, genetic training and public information

While the new knowledge from genetic testing gives patients hope, it can also create problems and fears if it is not applied appropriately and effectively. The major concern for patients is what the information gained from testing will mean for them. Will it be of sufficient quality and in a form understandable and

comprehensive enough to enable them to make decisions regarding their own health and welfare and possibly that of their children?

Genetic counselling is intended to address these concerns by providing individuals and families with an inherited disorder with accurate, full and unbiased information and by offering support in the decision-making process and in coping with the diagnosis. Yet, owing to the growing number of tests available (for both rare and common disorders), the development of easier and cheaper molecular techniques, as well as the increasing tendency of physicians to use such tests to replace more traditional diagnostic procedures, the demand for genetic testing is likely to exceed the supply of counsellors and genetic services. Most OECD countries do not expect to have enough counsellors to handle the expected growth. The ability of each healthcare system to cope with the increased demand for genetic tests and services will nonetheless depend on various factors: type of healthcare system and financial resources, curriculum of medical schools, availability of continuing education and organisation of genetic services. However, much of the responsibility for preparing medical professionals and the general population to deal effectively with the implications of genetic testing will necessarily fall on the public education system.

For these reasons, a number of pressing issues in genetic education and counselling need to be addressed. These include the development of training and educational programmes for genetic counsellors, healthcare practitioners and paramedical staff. The role of primary healthcare providers as gate-keepers for genetic referrals and in the provision of genetic tests might also need to be re-defined. Furthermore, in view of the quantity of information available and in order to tailor advice on specific genetic conditions, automated databases and powerful computers and software are becoming a basic feature of genetic services and the impact of computer-assisted programs which provide patients and medical professionals with information on genetic disorders, testing and screening programmes will need to be assessed. As our ability to test grows, the information technology needs of genetic services also increase. Health workers will require continuing updating in genetics and ready access to information on genetic mutations and related materials designed both for them and for their patients.

To meet these challenges, participants at the Workshop identified two specific areas where international guidance and co-operation would be particularly useful:

- Development of international agreements on genetic terminology and programmes to enable and sustain the development of advanced

computer technologies and electronic exchange to service patients, medical staff and healthcare workers.

- Comparative analysis of emerging patterns in the organisation of genetic services across OECD countries to facilitate an understanding of the factors influencing the availability of tests and services and the policies to be developed to meet the expected increase in demand.

Examination of possible impacts of restrictive licensing practices

No matter what aspect of genetic testing is discussed, it is almost impossible not to acknowledge the importance of the private sector's involvement in the development of genetic tests and databases and of the growth in commercial genetic testing services.

An obvious consequence of such involvement is that many current genetic tests are under patent protection and can be practised only under licensing agreements. With the award of patents for gene sequences from the human genome, SNPs or expressed sequence tags (ESTs) indicative of disease, this trend is likely to continue. Although the need for patent protection to encourage investment in R&D was recognised by Workshop participants, concerns were raised about the recent practice of exclusive and restrictive licensing of broad disease gene patents, which restricts full utilisation and wide diffusion of such tests. This practice may have – as yet unclear – impacts on access to genetic testing and on the current infrastructures for the provision of genetic services across OECD countries.

Such concerns are linked to current international discussions on the laws and procedures that govern the patenting of genetic material. This is emerging as an important and controversial international policy issue. The most visible questions relate to the conditions under which laws in various countries allow patenting of genetic sequences (*e.g.* genes) in addition to the traditionally patentable processes and novel materials derived from that information.

A lack of coherence in international biotechnology patent regimes and in licensing practices would have serious adverse impacts on economic development, trade, health and basic research. An initiative to review and identify the main issues underlying the current controversy and concerns could facilitate international discourse.

Guidance on how existing privacy, security and cryptography guidelines can apply in the context of genetic testing, particularly to ensure adequate security of genetic databases

Developments in public health genetics and molecular epidemiology, coupled with trends in bioinformatics and commercially available technologies for DNA collection, storage, mining and management, have led to increasing interest in and the collection and storage of DNA and related genetic data. The European Society of Human Genetics' Public and Professional Policy Committee highlighted at a recent workshop how indispensable DNA banking for medical and research purposes has become.

However, whether samples are identified, coded or anonymous, banking of DNA and of genetic information raises serious issues pertaining to access, informed consent, privacy and confidentiality of genetic information, civil liberties, patenting and proprietary rights. A key concern regarding stored genetic information is whether unauthorised third parties could gain access to or view genetic profiles or results of simple DNA tests. A related concern is whether samples or data are used for purposes different from those for which they were originally collected.

In considering the former concern, it appears that, despite the overwhelming agreement of international bodies and professional organisations on the need for "appropriate technical measures" to protect data, little progress has been made in clarifying what the term "appropriate" should signify and how this goal can be achieved in practice.

The future of genetic data banks as well as of healthcare sector databases will depend critically on good privacy and encryption policies, as the recent debate on the Icelandic Health Sector Database shows. Cryptographic methods need to be trustworthy if they are to generate confidence in the storage and use of sensitive genetic and health information. Government regulation, licensing and use of such methods may also encourage user trust. Evaluation of current methods, especially against accepted market criteria, could also generate trust. The OECD could use the experience gathered over the years in its work on privacy and confidentiality and particularly on cryptography to address the specific needs of this particular sector.

In particular, the OECD could address how its *Guidelines Governing the Protection of Privacy and Transborder Flows of Personal Data*; the *Guidelines for the Security of Information Systems* and the *Guidelines on Cryptography Policy* could apply in the context of genetic testing. This might involve:

- Exchange of information to identify practices currently available for protecting privacy and ensuring adequate security.
- Practical guidance (on the basis of exchange of information) on how to implement the OECD *Guidelines* on privacy, security and cryptography in the context of genetic testing.

In discussing secondary research and subsequent use of data or of human samples, participants agreed that this issue is highly relevant to current debates on the requirements and scope of informed consent, the rights of subjects to information on the purpose of research, the duration of the storage of data and especially the rights of subjects to withdraw or suppress personal data. This underscores the importance of an open and realistic international debate on the information required for consent, particularly against the background of increased global public/private research alliances and the likelihood that data will be increasingly transferred across borders and used for secondary purposes.

Exploration of broader implications of developments in pharmaco-genetics and in high-throughput processing methods

Pharmaco-genetics refers to the identification of genetic mutations and of polymorphisms involved in or responsible for variability in drug response, including drug metabolism and disposition and the development of what is often described as "the right medicine for the right patient".

The identification of polymorphisms, particularly of single nucleotide polymorphisms (SNPs), can be useful for finding disease susceptibility genes and for correlating a patient's genetic information with his or her probable response to medicine. At present, very few susceptibility genes for common, genetically complex diseases like diabetes have been definitely identified. However, it is thought that the DNA sequence mutations that confer susceptibility to common diseases will largely be minor changes that slightly alter a gene's activity. If so, susceptibility testing would need to look for only one or a few particular DNA sequence variants when testing a given gene. A number of simple, specific tests, covering dozens of different susceptibility genes or SNPs, could perhaps be run on a single gene chip to map a person's overall susceptibility to a given disease. Interpretation of the results would depend on epidemiological and genetic data defining the risk conferred by each combination of factors. This approach promises to be particularly useful for tailoring specific drug treatments to individuals, *i.e.* for personalising medicine.

These anticipated scientific and technological developments raise, however, a number of novel issues and could challenge current regulatory

frameworks governing clinical trials. The impact and consequences of changes in the design and practice of clinical trials and in post-approval surveillance and the need to ensure that abstracted SNP profiles do not give information concerning any genetic characteristic other than the response to medicine will be crucial. Finally, for a SNP mapping system to be useful across the industry, it must be standardised, readily available and amenable to good laboratory practices (GLP). Similar considerations apply to the technology that will ultimately enable SNP utilisation and testing, high-throughput parallel processing methods (*e.g.* gene chips).

Participants at the Workshop agreed that further exploration of the implications of developments in pharmaco-genetics and in high-throughput processing methods would be useful.

PART I

GENETIC TESTING: NEW DEVELOPMENTS AND SOCIO-ECONOMIC IMPACTS

Introduction

Genetic testing is a field whose importance for and impact on medicine and society can hardly be overstated. As this report will show, the process of drug discovery as well as the practice of medicine are undergoing major changes because of the information generated by the human genome mapping project and related advances in science and technology.

This new knowledge will ultimately be applied to gain a finer understanding both of the health status of the individual and of health trends in entire populations. It will make it possible to tailor treatments to the needs of the single patient or to design therapies for patients with a common aetiology. As knowledge about genetic predisposition to specific conditions advances, so will the development of diagnostic tests and preventive therapies. At the same time, as new genetic tests enter commercialisation, the decision-making process and the issues facing healthcare providers become increasingly complex.

It is a primary duty of policy makers to develop appropriate quality control and quality assurance schemes for establishing the efficacy, effectiveness and utility of the new predictive technologies and services on the market. However, concerns about the potential social, legal and economic implications are equally important. It is not enough to know that a technology is safe or that it does what it promises to do. It is necessary to know whether it provides additional benefits as compared to an older technology and improved outcomes for the individual patient and society as a whole.

Given these considerations, the principal objective of the Vienna Workshop was to consider whether the various approaches of OECD Member countries for dealing with new genetic tests are appropriate and mutually compatible. As this report highlights, participants from OECD Member countries identified a number of policy areas requiring international co-ordination and the establishment of coherent international policies.

What is genetic testing?

There are several possible interpretations and definitions of genetic testing. In order to delineate the issues to be discussed at the Workshop, the OECD Steering Group charged with the organisation of the Workshop developed the following ***ad hoc working definition*** and related explanatory notes:

Genetic testing is testing for variations in germline DNA sequences, or for products/effects arising from changes in heritable sequences, which are predictive of significant health effects.

- This is a working definition, intended to set the boundaries of the issues for discussion at the Workshop.
- It is worded to allow for the discussion of issues beyond science and technology at the Workshop.
- It specifically excludes identity testing and acquired changes in a person's DNA.
- It covers genetic testing that is diagnostic of a particular disease or condition as well as predictive genetic testing carried out prior to the appearance of clinical signs of the disease or condition.
- It refers to testing for germline changes in the individual.
- It may be relevant both to the individuals being tested and their wider family and offspring.

As such, this definition does not include the tests involved in the analysis of the many non-heritable changes in the genes of cancer cells, in paternity and forensic testing and in the DNA analysis of pathogenic organisms involved in human disease. These tests, however important, do not raise the same social and ethical issues. They do not, in general, differ from most other medical tests, whereas genetic testing, as defined above, may well differ. It may reveal important information not only about the tested individual, but also about family members, and may ultimately have a great impact upon an individual's life and lifestyle, including reproductive choices. In addition, genetic information is permanent; it is not something one may recover from. It may affect an individual's relatives, both living and as yet unborn, long after that individual is dead. Moreover, many such tests have the potential to predict predisposition to disease in a "pre-symptomatic" or otherwise healthy individual. Such genetic testing raises fundamental policy issues that have not yet been fully debated or resolved. The working definition includes yet another application of genetic testing, *i.e*. testing to predict the response profile of an individual to a drug or course of therapy, as will be discussed in the next section.

Thus, genetic testing may mean different things to different people, and the term, depending on the applications and purposes of the tests, may have several

possible definitions. One or the other may be most appropriate in a specific context and may raise specific and distinct ethical, legal and social issues.

Genetic testing and pharmaco-genetics: revolutionising drug development

The terms "pharmaco-genomics" and "pharmaco-genetics" are often used interchangeably. However, pharmaco-genomics refers to the application of molecular tools to R&D, including, but not limited to, differential gene expression (DGE), proteomics, tissue immunopathology and histopathology, etc. Pharmaco-genetics refers to the identification of genetic mutations and polymorphisms involved in or responsible for the variability in drug response including drug metabolism and disposition and the development of what is often described as "the right medicine for the right patient".

The identification of polymorphisms,[1] particularly of single nucleotide polymorphisms (SNPs) can also be useful for finding disease susceptibility genes.

Susceptibility gene identification and SNPs

Some mutations in a single gene alter function sufficiently to result in a specific phenotype or disease (monogenic disease). Many common human diseases, however, appear to be due to alterations in more than one gene (polygenic diseases) and in the environment, *i.e*. they are the result of complex interactions among various genes and environmental factors. With current methods and on the basis of family history and DNA samples, it is today possible to identify the gene mutations responsible for monogenic diseases efficiently. Determination of the gene alterations involved in the more common polygenic or multifactorial diseases (*i.e*. of genes that underlie predisposition to such diseases, or susceptibility genes) is more complex. In general, scientists have been able to provide, at best, a comparatively large linkage area with indistinct boundaries. These large linkage areas may include hundreds of genes and their variants, which are usually examined one by one to determine whether they are associated with the disease. These variants may exist at high frequency in a population and in such cases they are referred to as polymorphisms. Today we know that individuals are likely to carry variants even at a single nucleotide base, *i.e*. in the very smallest molecule or building block of the genome. These minimal variants are called single nucleotide polymorphisms (SNPs), can result in a particular version of a gene and can be used as "genetic" markers because

1. Genetic polymorphism is a Mendelian trait that exists in the population in at least two phenotypes, with each phenotype showing a frequency of at least 1%.

of their high density and even distribution throughout the genome. The first polymorphism observed in humans was the ABO blood group polymorphism, identified by Landsteiner in 1900.[2] Although the reason for the variation was obscure at the time, we now know that the variability in the A, B, O alleles is due to a few single base DNA substitutions.[3]

Polymorphisms or SNPs such as those that lead to different blood types are frequent throughout the genome. One SNP is estimated to occur about every 1 000 base pairs. Hundreds of thousands of such SNPs can now be identified and precisely ordered in a map. The map can be used to find disease susceptibility genes and also to correlate a patient's genetic information with his or her probable response to medicine.

In 1999 a SNP Consortium initiative was launched. The goal of the Consortium, funded by the Wellcome Trust, a number of pharmaceutical and bioinformatic companies, is to produce a high-density SNP map of the human genome, which will be released into the public domain to foster and enable clinical research. The SNP map will be used to identify causative genes of monogenic and complex diseases, to develop novel diagnostic tools and "personalised" medicine based on SNP profiles that predict response to therapy. By August 2000, the Consortium[4] had identified over 450 000 candidate SNPs and had released over 40 000 SNPs into the public domain (see Box 1). In the United States, the National Center for Biotechnology Information (NCBI) of the National Institutes of Health maintains a publicly accessible database of SNPs, including those identified by the SNP Consortium. As of September 2000, NCBI's SNP database contained more than 1.4 million SNPs. In parallel with these public efforts, a private sector company, Celera Genomics, recently announced that it had identified 2.4 million SNPs. Access to this data is limited to Celera subscribers.

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2. Landsteiner, K. (1900), "Zur Kenntnis der antifermemtativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe", *Zbl. Bakt.* 27, pp. 357-362.

3. Yamamoto, F., H. Clausen, T. White, J. Marken and S. Hakomori (1990), "Molecular genetic basis of the histo-blood group ABO system", *Nature* 345, pp. 229-233.

4. The Consortium's SNP data set as well as the TSC Requests For Application (RFA) for the determination of SNP allele frequencies in major populations are available via the Internet through the SNP Consortium's Web site (http://snp.cshl.org/).

Box 1. **Using SNPs in clinical trials: feasibility and policy implications**

Assuming that a whole genome SNP map with a density of 15 Kb on average were to be used for patient profiling, this would represent approximately 200 000 SNPs. Each SNP genotype would require at least two reactions, one for each allele, or 400 000 tests per person. In a phase 2 trial of 500 people of whom 100 were drug responders, 200 million genotypes would be required. This one experiment, at USD 0.01 each, would cost USD 2 million. Clearly, for such experiments to be affordable for development of early phase drugs, the cost and speed of genotyping will need to be significantly different from what current methods allow. The current goal is to be able to measure 200 000 SNPs in 500 people over a two-week period at reasonable cost, since pharmaceutical companies generally perform in excess of 25 such clinical trials annually. Technological advances in high-throughput processing, *e.g*. high-throughput SNP genotyping, gene chips, robotics and bioinformatics, will be crucial to reducing costs, as today's molecular biology methods generally are on a "one gene–one experiment" basis, which means that throughput is very limited and costs are very high. In the past few years, a new parallel processing technology, DNA microarray, has attracted tremendous interest among biologists.

An array is an orderly arrangement of DNA samples. DNA microarray, or DNA (gene) chips are fabricated by high-speed robotics, generally on glass but sometimes on nylon substrates. These are then tested with probes with known identity to determine complementary binding, thus allowing parallel gene expression and gene discovery studies. An experiment with a single DNA chip can provide researchers with information on thousands of genes simultaneously, a dramatic increase in throughput.

These anticipated scientific and technological developments raise, however, a number of novel issues and could challenge current regulatory frameworks governing clinical trials. The impact and consequences of changes in the design and practice of clinical trials, in post-approval surveillance and the need to ensure that abstracted SNP profiles do not give information concerning any genetic characteristic other than the response to medicine will be crucial. Finally, for a SNP mapping system to be useful across the industry, it must be standardised, readily available and amenable to good laboratory practices (GLP). Similar considerations apply to the technology that will ultimately enable SNP utilisation and testing, high-throughput parallel processing methods.

"The right medicine for the right patient"

A patient's response to a drug may depend on one or more factors that vary according to his or her alleles. Such factors include absorption, distribution, metabolism and elimination, concentration at the target site, etc. Can genetic testing/profiling be used to identify patients who will respond positively to a particular medicine? Can it be used to identify patients who will have an adverse event if they take a particular medicine? Can it be performed at reasonable cost using a standardised genetic map?

With the information obtained through the Human Genome Project and SNP mapping, it will be increasingly possible to understand and define the

heterogeneity of the causes of disease and of patients' response to medication. Several gene variants that encode for drug-metabolising enzymes, which may affect effective drug dose or lead to adverse drug reactions, have already been identified. In some instances, the response to drug treatment may be correlated with gene variants involved in the drug's mode of action. Testing for these variants could allow physicians to write prescriptions based on a patient's genetic predisposition to tolerate specific medicines and thus to avoid drugs likely to be ineffective or harmful. This could have a major impact on healthcare systems. Underdosing, overdosing and missed dosing account for more than USD 100 billion yearly in increased hospital admissions, lost productivity, and premature deaths, particularly in the elderly population.[5]

Genetic programmes and services: the likely consequences of a rapid expansion of genetic testing

Lessons learned from screening programmes

Prenatal screening for Down's syndrome as well as genetic reproductive risk of haemoglobin disorders has been widely practised for 20 years. Such screening offers an excellent opportunity for studying and assessing the requirements for delivering genetic services to populations and the underlying reasons for variability in the uptake and performance of such services.

Prenatal testing for Down's syndrome

Down's syndrome, which affects one in 700 live births, occurs when three copies of chromosome 21 are inherited instead of two. The condition is the most common known cause of mental disability and the leading cause of congenital heart disease and results in a wide variety of other developmental and health problems. Prenatal testing for Down's syndrome was first introduced in the mid-1970s for high-risk couples who were aware of their risk and of the consequences. In the 1980s, prenatal screening began in many countries and was offered more or less systematically to women aged 35 and older. Soon after, with the introduction of ultrasound technology and serum marker screening, the possibility of testing for high-risk pregnancies was extended to younger persons.

Despite the availability of the necessary technologies, practices and policies differ significantly from one country to another. In Europe, certain

5. Larkin, M. (1998), "'Personalised' drug therapy could be near", *The Lancet* 351, p. 1937.

countries use prenatal screening widely but do not offer clear recommendations, others have a national policy and still others offer testing only on request. As a consequence, the detection rate ranges from 18 to 70% across Europe. The termination rates after prenatal diagnosis of Down's syndrome range from 67 to 95%. This reflects the fact that culture, religion, provision of services and national laws differ and influence attitudes towards termination of pregnancy and towards the disabled. This highlights the importance of organising screening programmes to provide equitable services and appropriate information and of developing social and medical services for the disabled, without ignoring the need for alternatives and with full respect for different views.

In the absence of clear policy, key issues – access to testing, the choice of universal or targeted testing, quality of the information delivered, quality of the screening procedure, counselling and options for patients who test positive – remain unresolved. This may lead to problems in uptake of the technology, inequitable access, variability in the performance of preventive programmes and ultimately may affect health outcomes in populations.

Screening for haemoglobin disorders (thalassaemias and sickle cell disorders)

Problems related to information, access and choice occur also in the case of testing for haemoglobin disorders, a group of inherited diseases of the blood. Worldwide, about 325 000 babies are born with severe haemoglobin disorders each year, about 250 000 with a sickle cell disorder and 60 000 with serious thalassaemia. Thalassaemia occurs most frequently in people of Mediterranean, Middle Eastern, and South and South-East Asian ancestry. Sickle cell disorders are common among people of African ancestry. The disorders are inherited recessively. From 3 to 25% of the population in the above areas of the world are symptomless carriers of one variant gene. When both members of a couple are carriers, each child has a one in four risk of inheriting a variant gene from both parents: in most cases, such a child will suffer from a severe inherited anaemia, thalassaemia major or a sickle cell disorder.[6]

It is possible to detect carriers of haemoglobin disorders by simple, cheap and reliable blood tests, and to provide carrier couples so detected with genetic counselling, including the offer of prenatal diagnosis before they have children.

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6. In the United States, thalassaemia major is also called Cooley's anaemia, after the doctor who first described it in 1925.

When performed as recommended,[7] the "haemoglobinopathy screen" is an almost ideal screening test. Sensitivity is 100% for common abnormal haemoglobins and over 96% for thalassaemias, and specificity is 100% for both. It is national policy to provide carrier screening and counselling in a growing number of countries, including Italy, Greece, Cyprus, Cuba, Iran, Singapore and the Maldives. There is no formal national policy but screening is considered standard practice in the United Kingdom and many other OECD countries. The delivery of the service has recently been audited in the United Kingdom (see Box 2). In the United States, almost all newborns are screened for sickle cell anaemia.

Box 2. **Haemoglobin disorders in the United Kingdom**

In the United Kingdom 7% of the population and 11% of infants born are carriers. In 1999, there were about 9 000 living patients with sickle cell disorders, and 800 with beta thalassaemia. Every year at least 75 000 infants are born to women in ethnic groups at risk for haemoglobin disorders (11% of the total): about 7 120 of these women carry a haemoglobin disorder, as do about 870 of their partners. A random 25% of these pregnancies at risk (about 218 a year) are affected and end either in an affected liveborn infant or in termination of pregnancy after prenatal diagnosis. About 20% of the liveborn have major thalassaemia. This subset of affected infants is reported in national registers, and this provides a means to audit performance of the entire genetic service.

Where there is clear policy and multidisciplinary co-operation, it is possible to identify practically all couples at risk at their first pregnancy. However, this is rarely done before the second trimester.* This is of particular concern for thalassaemia, since there is evidence of high demand for the service and a strong preference on the part of parents for risk detection and prenatal diagnosis as early as possible in pregnancy.

* Modell, B., R. Harris, B. Lane and M. Khan (2000), "Informed choice in genetic screening for thalassaemia during pregnancy: Audit from a national confidential inquiry", *BMJ* 320, pp. 337-341.

A child with beta thalassaemia major becomes unwell between three and 18 months of age. The child becomes pale and does not eat, sleep or grow well. The spleen may become enlarged. If they are not treated, children with beta thalassaemia major become chronically ill and die at between two and seven years of age. Treatment requires regular monthly blood transfusions to keep the haemoglobin in the normal range. Regular transfusion greatly improves quality of life, but leads to transfusional iron overload. If untreated, this causes death

7. The WHO has published recommended guidelines for screening programmes.

from cardiac complications at between 12 and 24 years of age; it can be controlled by nightly subcutaneous infusion of the iron-chelating agent desferrioxamine, using a portable syringe driver. Patients born today are expected to live a nearly normal length of life with this combined treatment, but up to 50% of patients cannot tolerate the subcutaneous infusions. The main cause of death from thalassaemia in developed countries today is non-adherence to treatment.

Sickle cell disorders cause anaemia from around six months of age, increased susceptibility to infection and unpredictable attacks of very severe pain anywhere in the body. There may eventually be damage to bones, joints or eyesight or stroke. The condition is unpredictable. There is a risk of sudden death, but in developed countries most patients live past the age of 20, and at least half live to age 45-50.

It is important for medical and ethical reasons to provide full information and counselling to the patient. Different mutations may interact to produce either no effect or serious effects. It is possible to use informatics to support accurate, mutation-specific genetic counselling at national (and international) level for these disorders. To provide full information on these complex genetic conditions, matrices for the various mutations can be set up on data sheets for particular cases and be accessed by all interested parties, *i.e.* patients, medical staff and healthcare workers. However, for haemoglobin disorders, a relatively "simple" 12 x 12 matrix (one parent against the other, 12 mutations) may produce a total of 507 documents with information on the different combinations. This is a challenging task and in order to tailor advice on specific combinations, automated databases and powerful informatics are needed.

The complexities of testing and counselling for thalassaemia are not unique, since many common human diseases appear to be due to more than one mutation in more than one gene and are the result of complex genetic interactions. Thus, as our ability to test grows, the informatic needs of genetic services also increase. To meet this challenge, health workers will require continuing updating in genetics and ready access to information on genetic mutations and related materials designed for them and for their patients. International guidance to enable and sustain the development of advanced informatic technologies and electronic exchange as well as international agreements on genetic terminology could enormously facilitate this process.

Genetic counselling: forecasting the needs

Genetic counselling provides individuals and families with an inherited disorder with accurate, full and unbiased information and offers support in the

decision-making process.[8] It is a complex process, which stands in opposition to eugenic principles and seeks to help families to cope with the diagnosis of an inherited disorder, to face its implications and to make decisions on the basis of their medical and non-medical options. As genetic testing is involved in the diagnosis of inherited disorders, counselling becomes an integral part of it; it aims at encouraging the autonomy of those involved and reducing the adverse consequences of testing. The need for counselling derives from: *i)* the peculiarities of genetic information, as compared to other biomedical tests, particularly in terms of its predictive and complex character; *ii)* the gap between the ability to diagnose and to treat an inherited disorder; *iii)* the social value attributed to heritable characteristics; and *iv)* the psycho-social and ethical problems often arising in testing situations. Counselling is traditionally performed by healthcare professionals specifically trained to use procedures different from those used in everyday clinical practice.

The growing number of available tests (for both rare and common disorders), the development of easier and cheaper molecular techniques, as well as the increasing tendency of physicians to use such tests to replace or supplement more traditional diagnostic procedures are expanding the demand for genetic testing beyond the availability of counsellors and genetic services. This is a problem for all OECD countries, as the rate of increase of healthcare professionals trained and certified in medical genetics or in genetic counselling has not kept pace with the rate of genetic discoveries. Some studies[9] claim that population carrier screening for just one condition, *e.g.* cystic fibrosis, could overwhelm the system.

The ability of each healthcare system to respond to an increased demand for genetic tests and services will depend on various factors: type of healthcare system and financial resources, genetic *curricula* in medical schools, availability of continuing education and organisation of genetic services. However, data on the availability of genetic services across OECD countries are relatively scarce and suffer from several limitations. An analysis of the emerging patterns in the organisation of genetic services could help understand the factors influencing the availability of tests and services and the policies to be developed to meet the expected increase in demand.

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8. Ad Hoc Committee on Genetic Counseling (1975), "Report to the American Society of Human Genetics", *Am. J. Hum. Genet.* 27, pp. 240-242. T.M. Marteau, B.B. Biesecker (1999), "The future of genetic counselling: An international perspective", *Nature Genetics,* Vol. 22, No. 2, pp. 133-137.

9. Wilfond, B.S. and N. Fost (1990), "The cystic fibrosis gene: medical and societal implications for heterozygote detection", *JAMA* 263, pp. 2777-2783.

Recently, a small survey of managed care organisations in the United States suggested that medical directors rely on primary care providers to serve as "gate keepers" for genetic referrals.[10] This appears to be an emerging pattern across OECD countries.

Because of the limited supply of geneticists and genetic counsellors, primary care and other non-geneticist practitioners are being relied on to help cope with the increased demand for genetic testing. Although general physicians are educated about inherited genetic susceptibilities, they may not be prepared to counsel their patients, particularly in the case of pre-symptomatic and prenatal testing, which often poses complex psychological and ethical problems.[11] This highlights the importance of developing targeted educational programmes for healthcare practitioners and paramedical staff, on the one hand, and of increasing the availability of training programmes for professional counsellors, on the other. However, any long-term sustainable solution would require an assessment of the options available for overcoming expected problems in the provision of genetic counselling. Comparative analysis of models across OECD countries and the institution in each country of an advisory committee on genetic testing[12] could help policy makers in this challenging task.

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10. Musial, A. (1995), "A movement towards managed health care and the role of the genetic providers: A survey of medical directors of managed care programmes in New York State", a poster presentation at the American Society of Human Genetics meeting, Minneapolis, Minnesota.

11. Maylick, S.J., M.P. Eiff, L. Carpenter and J. Steinerger (1998), "Primary care physicians' utilization and perception of genetic services", *Genet. Mod.* 1, pp. 13-22.

12. Harper, P.S. (1997), "What do we mean by genetic testing?", *J. Med. Genet.* 34, pp. 749-752.

PART II

SAFEGUARDING QUALITY AND EQUITABLE ACCESS

Genetic testing for susceptibility genes

The discovery of the genes responsible for hereditary cancer syndromes illustrates how genetic research can result in improved patient care. At the same time, it offers a striking example of the ethical and policy issues raised by genes that confer susceptibility to a disease and of the need to safeguard rigorous standards of quality.

BRCA1, the first hereditary breast cancer susceptibility gene, was isolated in 1994.[13] By the end of 1995, BRCA2 was found. Their discovery has tremendous implications for diagnosing and treating breast cancer, as 5 to 10% of breast cancer may be caused by genetic mutations. In the United States alone, it is estimated that about 183 000 women develop breast cancer each year, 41 000 of whom will die from it. The economic burden is considered to exceed USD 10 billion.

Taken together, mutations in the two genes have been estimated to account for around 70% of the high-risk families with breast cancer. High-risk families are usually those with several affected members (more than four) in several generations. In some genetically distinct populations, *e.g.* Ashkenazi Jews, the combined frequency of BRCA1 and BRCA2 mutations exceeds 2%.[14]

However, even in such cases, the interpretation of results from BRCA1-2 tests is not always simple.[15] Although a positive result indicates an increased risk of cancer, it does not predict when, during the person's lifetime, cancer may appear. In addition, the large size of the BRCA1 and BRCA2 genes, the dispersed locations of the more than 700 mutations identified to date,[16] and the lack of functional assays hamper direct estimation of carrier frequencies and

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13. Miki, Y. *et al*. (1994), *Science* 266, pp. 120-122.

14. Roa, B.B., A.A. Boyd, K. Volcik and C.S. Richards (1996), "Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2", *Nat. Genet.* 14, pp. 185-187.

15. Hubbard, R. and R.C. Lewontin (1996), "Pitfalls of Genetic Testing", *New Engl. J. Med.* 334, pp. 1192-1193.

16. Couch, F.J. and B.L. Weber (1996), "Mutations and polymorphisms in the familial early-onset breast cancer (BRCA1) gene. Breast cancer information core", *Hum. Mutat.* 8, pp. 8-18. Tavtigian, S.V., J. Simard, J. Rommens *et al*. (1996), "The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds", *Nat. Genet.* 12, pp. 333-337. http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/.

cancer risks in the general population.[17] New methods of gene analysis, such as high-throughput parallel testing and rapid automatic sequencing have been recently developed that can overcome many of these technical obstacles.

What then is the efficacy of genetic testing and preventive treatment for women who test positive for these genetic mutations? Who should be tested? One approach has been to use computer modelling to determine the cost-effectiveness of screening for BRCA1-2 in a population where the frequency of mutations is high, *e.g.* Ashkenazi Jews (see Box 3);[18] another has been to compare the benefits and cost-effectiveness of preventing breast cancer in women who test positive for these mutations (either with chemo-prevention or prophylactic surgery). The benefits have been reported in terms of life years saved. The results of screening studies show that in the Ashkenazi Jewish population, with a high prevalence of BRCA1-2 mutations, genetic screening may increase average survival (up to four years) and, depending on costs and screening/treatment strategies, be cost-effective by the standards of accepted cancer screening tests (for the strategies to be cost-effective, women tested need to be willing to have prophylactic surgery if they test positive). The model for the second approach suggests that although surgery may yield more substantial survival and cost benefits, quality of life issues may make chemo-prevention a more attractive option for young women at high risk. The estimates require confirmation through clinical trials, however, and clearly have broad implications both for policy makers and for patients.

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17. Struewing, J.P., P. Hartge, S. Wacholder *et al.* (1997), "The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews", *New Engl. J. Med*. 336, pp. 1401-1408.

18. Grann, V.R. (1999), "Benefits and costs of screening Ashkenazi Jewish women for BRCA1 and BRCA2" *J. Clin. Oncol.* 17, pp. 494-500. Grann, V.R. (2000), "Prevention with tamoxifen or other hormones versus prophylactic surgery in BRCA1/2-positive women: A decision analysis", *Cancer J. Sci. Am.*, Vol. 6, No. 1, pp. 13-20. Grann, V. (2000), "Benefits and costs of genetic testing: The case of breast cancer", OECD Vienna 2000 presentation.

Box 3. **Estimates of cancer risk in BRCA1 and BRCA2 mutation carriers**

In the general population, breast cancer is rare at age 50, with 12% contracting it by age 80. However, in BRCA1/BRCA2 carriers primary breast cancer risk may amount to 56 to 87% by age 70 and 33 to 50% by age 50 (Table 1). In Ashkenazi Jews, the figures, among carriers, are 40% at age 50, and 50% at age 80. The relatively higher risk in the Ashkenazi population appears due to two specific variants or ancestral mutations of the BRCA genes, BRCA1 185delAG and BRCA2 6174delT, which appear in the general population at about 1% frequency; and to a third mutation, BRCA1 538lnsC, which occurs at a frequency of 0.11%.* Although a significant proportion of breast and ovarian cancer in Ashkenazi Jews is attributable to these mutations, about 52% of high-risk breast and/or ovarian cancer families do not carry these mutations.**

Knowledge of specific mutations can help physicians decide on appropriate preventive approaches, but the outcomes and cost-benefit of prophylactic interventions may vary considerably and raise major ethical considerations. Prophylactic interventions may be chemical (tamoxifen, ralixifene or oral contraception) and/or surgical, *i.e.* prophylactic mastectomy.

In Ashkenazi Jews, the life years saved appear to be 1.6 for tamoxifen, 2.2 for ralexifene, 0.9 for oral contraceptives, 3.4 years for prophylactic mastectomy and 4.2 years for prophylactic mastectomy with removal of the ovaries. Cumulatively, the extra years gained would be about 10% by age 40. Prophylactic mastectomy and removal of the ovaries at age 30 was predicted to give 4.5 years of extra life (also at around 40) to an individual with appropriate mutations in BRCA1 or BRCA2.***

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* Roa *et al.*, *op. cit.*

** Levy-Lahad, E., R. Catane, S. Eisenberg, B. Kaufman, G. Hornreich, E. Lishinsky, M. Shohat *et al*. (1997), “Recurrent BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: Frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families”, *Am. J. Hum. Genet*. 60, pp. 1059-1067.

*** Grann, V. (2000), “Benefits and costs of genetic testing: The case of breast cancer”, OECD Vienna 2000 presentation.

Table 1. **Published estimates of cancer risks for *BRCA1-2* mutation carriers**

Site	Risk	Reference
Breast	*Risk of primary breast cancer:* *BRCA1* and *BRCA2:* 56-87% by age 70 33-50% by age 50 *Risk of contralateral breast cancer:* *BRCA1:* 48% risk by age 50, 64% by age 70 *BRCA2:* 37% by age 50, 50% by age 70 *BRCA1:* 20% within 5 years of first diagnosis *BRCA2:* 12% within 5 years of first diagnosis	[1,2,] [2,3] [1] [12] [10] [14]
Ovary	*BRCA1*: 28-44% by age 70-80 *BRCA2*: 27% by age 70 Ten-fold increased risk following breast cancer 16% following breast cancer (*BRCA2*)	[1,5] [4] [11] [12]
Colon	Recent studies: no apparent increase in risk	[13]
Prostate	*BRCA2:* three- to seven-fold increase in relative risk 8% by age 70, 20% by age 80	[1,6,12]
Male breast cancer	*BRCA2*: 6%	[6,7]
Pancreatic cancer	*BRCA2:* three- to four-fold increase in relative risk; Pancreatic cancer: 1-2% by age 70	[8,9,12]

References (*source:* T.S. Frank, Myriad Genetic Laboratories):

1. Ford, D., D.F. Easton, D.T. Bishop *et al.* (1994), " Risks of cancer in *BRCA1*-mutation carriers", *Lancet* 343, pp. 692-695: (87% risk of breast cancer by age 70) (44% risk of ovarian cancer) (48% risk of contralateral breast cancer by age 50, 64% by age 70).
2. Struewing, J.P., P. Hartge, S. Wacholder *et al.* (1997), "The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews", *New England Journal of Medicine* 336, pp. 1401-1408: (33% risk of breast cancer by age 50, 56% risk by age 70).
3. Easton, D.F., D. Ford, D.T. Bishop,*et al.* (1995), "Breast and ovarian cancer incidence in BRCA1-mutation carriers", *Am. J. Human. Genet.* 56, pp. 265-271: (50% risk of breast cancer by age 50).
4. Ford, D., D.F. Easton, M. Stratton *et al.* (1998), "Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families", *Am. J. Hum. Genet.* 62, pp. 676-689.
5. Whittemore, A.S., G. Gong, J. Itnyre (1997), "Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: Results from three US population-based case-control studies of ovarian cancer", *Am. J. Hum. Genet.* 60, pp. 496-504: (28% risk of ovarian cancer).
6. Easton, D.F., L. Steele, P. Fields *et al.* (1997), "Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12-13", *Am. J. Hum. Genet.* 61, pp. 120-128.
7. Couch, F.J., L.M. Farid, M.L. DeShano *et al.* (1996), "BRCA2 germline mutations in male breast cancer cases and breast cancer families", *Nature Genetics* 13, pp. 123-125.
8. Goggins, M., M. Schutte, J. Lu *et al.* (1996), "Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas", *Cancer Re*s. 56, pp. 5360-5364.
9. Phelan, C.M., J.M. Lancaster, P. Tonin *et al.* (1996), "Mutation analysis of the BRCA2 gene in 49 site-specific breast cancer families", *Nature Genetics* 13, pp. 120-122.
10. Verhoog, L.C., C.T.M. Brekelmans, C. Seynaeve *et al.* (1998), "Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1", *Lancet* 351, pp. 316-321 (20% risk of contralateral breast cancer).
11. Frank, T.S., S.A. Manley, Ol. Olopade *et al.* (1998), "Sequence analysis of BRCA1 and BRCA2: Correlation of mutations with family history and ovarian cancer risk", *J. Clin. Oncol.* 16, pp. 2417-2425 (ten-fold increased risk of ovarian cancer following breast cancer).
12. The Breast Cancer Linkage Consortium (1999), "Cancer risks in BRCA2 mutation carriers", *JNCI* 15, pp. 1310-1316.
13. Lin, K.M., C.A. Terment, D.R. Adams *et al.* (1999), "Colorectal cancer in hereditary breast cancer kindreds", *Dis Colon Rectum* 42, pp. 1041-1045.
14. Verhoog, L.C., C.T.M. Brekelmans, C. Seynaeve *et al.* (1999), "Survival in hereditary breast cancer associated with germline mutations of BRCA2", *J. Clin. Oncol.* 17, pp. 3396-3402.

The decision to test

For patients, while the new knowledge from genetic testing brings hope, it can also create problems and fears if it is not applied appropriately and effectively. In order to ensure that the beneficial uses of this new knowledge are available to all who need them, and at the same time prevent abuse and unfair discrimination, a number of issues will need to be addressed. In addition, concerns expressed by patients and by the broader public should be adequately considered – as the European Alliance of Genetic Support Group reported at the Vienna 2000 Workshop (Annex 1).

The major concern for patients is the question of what the information gained from being tested will mean for them. Will it be of sufficient quality and in a form understandable and comprehensive enough to enable them to make decisions regarding their own health and welfare and possibly that of their children?[19] There is also the issue of access to the services and the support necessary to avail themselves of this information. For the policy maker, the critical issues are which tests to adopt and how to ensure access, accuracy, quality of care and cost-effectiveness; particularly since most common human diseases appear to be due to more than one gene and are the result of complex interactions among various genes. In many cases these diseases are also or principally caused by environmental and life-style factors, such as smoking, malnutrition or infection. In addition, some genes may be very common in a given population, others rare.

If the prevalence of the mutation in the population is low – even where effective preventive/therapeutic means are available – genetic testing of whole populations is unrealistic, since hundreds of thousands of individuals would have to be screened to find one true positive, usually along with a large number of false positives. So, it is more reasonable to seek mutations in families (where they are concentrated), rather than in the general population.

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19. This is particularly important in the case of predictive tests such as BRCA1/2, which are reported to the patient in statistical terms or as probability of occurrence of the disease and for conditions for which there are no therapies. Research evidence indicates that while the nature of genetic information is probabilistic, human perceptions tend to be binary, *i.e.* an event will or will not happen. See Lippman-Hand, A. and F. Fraser (1979*a*), "Genetic counseling: Provision and perception of information", *Am. J. Med. Genet*. 3, pp. 113-127.

Another determining factor is penetrance.[20] Penetrance is the likelihood, or probability, that a condition or disease phenotype will, in fact, appear when a given genotype known to produce the phenotype is present. If every person carrying a gene for a dominantly inherited disorder has the mutant phenotype, then the gene is said to have 100% penetrance. Similarly, if only 30% of those carrying the mutant exhibit the mutant phenotype, the penetrance is 30%.

A variety of genes associated with cancer appear to have less than 100% penetrance. For genetic counsellors, this makes the question of genetic testing more complex than would be the case for a fully penetrant gene.[21] Variable expressivity, or the likelihood that symptoms will vary among individuals with similar genotypes, further complicates decisions to test. All these factors and the therapeutic and preventive options available to patients should guide the decision to test.

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20. Short glossary of terms used in this chapter. *Penetrance* is the proportion of individuals with a specific genotype who manifest that genotype at the phenotype level. *Expressivity* is the degree to which a particular genotype is expressed in the phenotype. It also means the degree of expression of a genetically controlled trait. *Phenotype* is *i)* the form taken by some character (or group of characters) or genes in a specific individual*; ii)* the detectable outward manifestations of a specific genotype; *iii)* the observable attributes of an organism. *Genotype* are the genes that an organism possesses, the specific allelic composition of a cell.

21. "Let us imagine we have two different genetic traits, one with low penetrance (1.4% of cumulative lifetime risk in the carriers) and one with high penetrance (37% cumulative risk). Let us suppose that screening allows us to reduce the risk of cancer by 58% in both cases. This means that the absolute risk goes down to six per thousand in category A and to 15.5% in category B, with an absolute reduction of eight per thousand and 21.5%, respectively. The Number Needed to Treat (NNT) is the inverse of such figures, *i.e.* 125 in category A, while it is sufficient to treat 4.5 individuals in category B to achieve the same result. These are the numbers that are needed to treat after we have identified the carriers. In order to identify carriers, of course, we have to screen many more subjects. (Low penetrant genes tend to show frequent polymorphisms. For example, the polymorphisms for GSTM1, a gene encoding Glutathione-S-Transferase isoenzyme, a drug-metabolising enzyme, has a frequency of 50%, so that the number needed to screen becomes approximately double compared to the NNT). In contrast, highly penetrant mutations have low frequency in the general population (in the order of less than 1%), which means that the number needed to screen is 100 or more higher than the NNT. In families where the prevalence is high, the number needed to screen is much closer to the NNT." Vineis, P. (2000), "Genetic screening for cancer: False positives and predictability", Vienna 2000 Workshop presentation.

Safeguarding the quality of genetic testing and services

The advent of molecular genetic testing in clinical laboratories has led to the introduction of a bewildering array of tests for many hundreds of genetic disorders. With the completion of the human genome project, the number is expected to increase significantly since in clinical practice one of the first applications of knowledge about the molecular basis of a particular disorder is the ability to develop diagnostic tests. As for all new medical technologies, new genetic tests should be thoroughly evaluated prior to their introduction into general practice. Likewise, laboratories performing such tests should meet specific standards of quality of service, including the safeguard of patients' rights to informed consent and confidentiality.

However, often the clinical laboratories performing these tests act under no specific requirement to ensure the overall quality of molecular genetic testing. One reason for this is that most regulations with which laboratories must comply are not specifically designed for molecular genetic testing. In addition, much clinical molecular genetic testing is carried out in research centres or in laboratories in transition from a research to a service function. Research centres are not submitted to the same regulations relating to clinical laboratories and often might not be familiar with such regulations. Another problem is that clinical genetic laboratories across OECD countries work under different norms and conditions. For example, not all countries require accreditation of genetic laboratories or proficiency testing, and supervision by and involvement of appropriately trained scientific and medical staff in diagnostic and laboratory services vary widely. In addition, there are major problems and concerns about home-brew tests, which are primarily available in clinical research laboratories, particularly predictive tests and tests for rare diseases and their standardisation, and the adequacy of interpretation of the results of these tests; and a lack of independently certified reference materials as controls for tests.

How can quality assurance in molecular genetic testing be guaranteed?

Validation is the procedure by which possible errors in the diagnostic process are identified, measured and evaluated so as to minimise the risk of an erroneous outcome of the test procedure. More specifically, validation of a laboratory test establishes by systematic laboratory studies that the test is fit for the purpose, *i.e.* its performance (measured in terms of specificity, sensitivity and robustness) is capable of producing results that meet the needs of the analytical problem.[22] However, the design of the counselling process is equally

22. Saunders, G.C. and H.C. Parkes (eds.) (1999), *Analytical Molecular Biology Quality and Validation*, LGC Teddington.

relevant to the performance of a test, particularly in the case of molecular genetic testing. This is because molecular genetic testing requires complex interpretation, as noted above. For example, in the case of cystic fibrosis, the interpretation of a negative result on a standard test is highly dependent upon the ethnic origin of the subject, their family history of cystic fibrosis, and whether or not they present relevant symptoms. In most cases, patients expect genetic tests to be 100% reliable. However, errors may be more common than is thought, as recent surveys reveal (Boxes 4 and 5).

The types of errors found have to do with sample/information handling, are technical (controls, interpretation) or inherent to the reagents or assays or lie in the overall interpretative conclusions in the light of clinical data. The most common errors are technical failures and interpretative errors.[23] Thus, in validating a genetic test, special consideration must be given to pre- and post-test genetic counselling. The test itself is only one part of the testing procedure and cannot be completely validated on its own. It follows that the validation process should address the development both of technical standards and of counselling procedures, possibly in collaboration between medical professionals, lay persons and state authorities.

Technically, quality assurance of the whole diagnostic process includes laboratory accreditation, external quality assessment (EQA) internal quality control, use of standard operating practices (SOPs), and comparison with other tests predictive of disease. Most OECD countries have developed some form of relevant regulation to ensure QA based either on professional guidelines or on government regulations. Aspects of QA relevant to genetic testing can be readily incorporated into existing general regulations of medical laboratories (*e.g.* EN 45001 and ISO 17025). However, other aspects will strictly depend on international co-operation because of the very nature of the field. Many genetic diseases are rare, which makes national approaches to QA difficult, since QA relies on the possibility of comparing practices and thus, on the participation of a minimum number of centres and on a critical volume of testing. This and the increasing trend for tests to cross national boundaries should encourage an international approach to QA, harmonisation and mutual recognition of national and regional schemes. International guidelines on general principles would be a valuable first step towards this goal.

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23. Dequeker, E. and J.J. Cassiman (2000), "Genetic testing and quality control in diagnostic laboratories", *Nature Genetics* 25, pp. 259-260.

Box 4. **Quality assurance in Europe**

External quality assurance (EQA) or proficiency testing gives an independent check on a laboratory's performance measured against an external "gold standard". A number of EQA schemes have emerged in the last five years across OECD countries. In Europe some EQA systems have developed schemes to enable the assessment of the whole analytical process, including professional qualifications.* These EQA systems rely on a disease-specific approach which tests the laboratory's proficiency in generating accurate results but also in interpreting genotype results within a specific clinical context and in issuing clear reports. This enables the development and application of best practice guidelines and encourages a convergence of methodology and practice. For example, in Germany a quality assessment scheme for cytogenetic and molecular testing was initiated by the *Berufsverband Medinische Genetik* in 1993 and has the participation of laboratories in Austria and Switzerland. The scheme is based on three main pillars: *i)* definition of the professional qualifications for the laboratory directors; *ii)* publication of general and specific guidelines for genetic testing in the journal Medizinischer Genetik; and *iii)* implementation of an external quality assessment scheme.

In the United Kingdom, the experience of organising pilot EQA schemes in molecular genetics led to the holding of consensus-building workshops, where representatives of each testing laboratory participated in drawing up agreed guidelines for best practice for a particular inherited disorder. The reports from these workshops formed the framework for the development of a set of guidelines published on the Web site of the Clinical Molecular Genetics Society (http://www.cmgs.org). The guidelines offer advice on appropriate reasons for referral, contain links to key references in the literature and to sites where detailed information on primers, mutations and clinical information may be found. Importantly, the guidelines also contain advice on how to interpret and report the results. The guidelines now act as a resource to which laboratories can refer, when necessary, and which guides EQA assessors in their work.

These guidelines have now been adopted as a starting point for the development of European guidelines through the European Molecular Genetics Quality Network EMQN (http://www.emqn.org/emqn.htm). The EMQN is a network funded by the European Commission to develop disease specific external quality assurance (EQA) or laboratory proficiency schemes across Europe. One of the goals is to facilitate harmonisation of pre-existing national EQA schemes. This is done by convening workshops and by establishing consensus on best practice. The EMQN has also adopted an approach to assist in measuring the quality of the whole analytical process, *i.e.* interpretation of data in its clinical context as well as the accuracy of interpreting genotype results.**

Despite its performance to date, the EQA approach has some shortcomings. EQA can both measure and encourage improved performance and forms an important part of "total quality" laboratory management; however, QA schemes are also needed for definition of tests and validation prior to introduction into the clinical setting and for rare diseases which might not be represented in the network. In addition, EQA is largely a voluntary system. This is based largely on the assumption that because of the rapid pace of technological advances, quality in molecular genetic testing is best achieved by developing consensus among the professionals involved directly in testing.

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Box 4. **Quality assurance in Europe** *(cont'd.)*

The advantage of this approach is that the scheme organisers and assessors are in a good position to observe the different approaches used and the changes in technology and to assess on a case-by-case basis which approaches yield the best result. The downside of this approach is that there is no pressure for laboratories to participate in and pay for EQA nor to integrate changes in diagnostic practice or methodology which may be suggested. The introduction of accreditation or certification for service, through *e.g.* existing systems such as CLIA (US), Clinical Pathology Accreditation (UK) or ISO 17025, could change this and could oblige laboratories to join a recognised EQA scheme and to pay for it, thereby allowing the development of well-founded and administered schemes. At present, proficiency testing is an entirely educational process. This is helpful when there is a variety of standards among centres. However, only accreditation will give EQA organisers the authority to sanction centres that perform poorly. This would imply, though, that international EQA organisers should be officially recognised by the official authorities of each of the participating countries.

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* For a review, see proceedings of the EC Workshop on "Genetic Testing in Europe: Harmonisation of Standards and Regulations", Vienna, 30 October 1998.

** For the EMQN, QA in molecular genetic testing consists of EQA, comprising a comparison of technical performance against a validated "gold standard" and an assessment of results by an expert panel, as well as of an internal quality assurance, such as standard protocols or procedures, reagents and reporting, established by operational best practice.

Box 5. **Ensuring the quality of genetic testing in the United States**

In the United States, laboratories performing chromosomal, biochemical and/or DNA-based tests for genetic disease are accredited under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) which is federal in character. It has input from the US Health Care Financing Administration (HCFA) and the Centres for Disease Control and Prevention (CDC) (*i.e.* not the FDA). The regulations apply to all laboratories from which clinical information is fed back to practitioners, whether commercial, clinical or research-based. CLIA regulations are based on a complexity model of testing; clinical molecular genetic analyses are considered to be in the high-complexity category, tests that can be performed in a GP's office considered easy and tests such as blood chemistry of moderate difficulty. The regulations cover personnel and include biennial inspection, some proficiency testing (albeit not for genetics and cytogenetics) and requirements involving the speciality for which the laboratory is certified. As an alternative to CLIA, state schemes can be deemed satisfactory, provided that they exceed CLIA requirements.

For New York, for instance, state regulations cover the qualifications of the director, requirements related to informed consent forms, approval of tests performed and affiliation with a genetics professional. A number of voluntary professional organisations have issued guidelines and operate to safeguard quality of testing, including the College of American Pathologists (CAP), which has a programme on molecular and cytogenetic tests, the Association for Molecular Pathology, which runs a sample exchange for PCR tests, and the American College of Medical Genetics, which provides a number of QA standards. The International Organisation for Standardisation (ISO) has a programme of internal and external QA and inter-laboratory comparison as part of its guidelines. However, problems and concerns have recently been identified* in regard to home-made tests, their standardisation, adequacy of interpretation, quality assessment for esoteric testing, cost of the regulatory process, especially for low-volume testing which must nonetheless be maintained, and related issues such as confidentiality, informed consent and counselling.

A QA assessment was done under the auspices of CDC to assess compliance with minimum standards.** It considered 245 laboratories, covering the laboratory setting, personnel, types and numbers of tests, QA practices, types of specimen and licensing and proficiency testing and addressed some clinical issues. Of the laboratories tested, 64% were hospital-based, 18% research and 18% independent or commercial. All heads of laboratory were qualified to doctoral level, and most were board certified. The number of test types offered ranged from one to 27 (mean 4.68) and the number performed annually from ten to 31 500 (mean 872); 59% performed fewer than 225 tests a year and 8% more than 1 600. A QA score was assigned based on minimum standards set by the American College of Medical Genetics Laboratory Practice Committee. The results revealed that a number of laboratories had QA scores that may indicate sub-optimal laboratory practices. Scores (which should have been 100% as the criteria are minimal) ranged from 44 to 100%, with a mean of 90%. Research laboratories performed the worst. Participation in proficiency testing schemes or CLIA certification improved performance, as did the volume of testing. Issues related to counselling and informed consent were also considered; 70% of laboratories provided access to genetic counselling, 69% had a confidentiality policy and 45% required informed consent prior to testing.

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Box 5. **Ensuring the quality of genetic testing in the United States** *(cont'd.)*

Following these results, the CDC recently sponsored a meeting and convened an expert panel on molecular genetic testing (MGT). The panel identified three immediate needs for ensuring QA for MGT. These included: *i)* sample and positive control development; *ii)* the development of performance evaluation programmes for diseases and methods not covered by the College of American Pathologist programmes; and *iii)* the establishment and support of disease-specific, laboratory-oriented consortia.

It was recognised that international collaboration and exchange of information would facilitate the development of programmes on the latter two recommendations, in particular as they relate to testing for rare diseases.

In June 1999, the Secretary's Advisory Committee on Genetic Testing (SACGT)*** was charged with conducting a comprehensive assessment, in consultation with the American public, of the adequacy of oversight of genetic tests. A key recommendation resulting from such assessment**** was that the Food and Drug Administration (FDA) be the agency responsible for the review, approval and labelling of all new genetic tests that have moved beyond the research phase. SACGT also recommended that FDA, in collaboration with other agencies and relevant private sector organisations, develop innovative review processes for genetic tests, minimising the time and costs of review without compromising the quality of assessment of test validity. To address the quality of laboratories conducting genetic tests, SACGT recommends that the CLIA regulations be augmented to provide more specific provisions regarding genetic tests. Activities related to the implementation of this recommendation are under way.

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* Holtzman, N.A. and M.S. Watson (eds.) (1997), *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing*, The National Human Genome Institute.

** McGovern, M.M., M.O. Benach, S. Wallenstein *et al.* (1999), "Quality assurance in molecular genetic testing laboratories", *JAMA*, Vol. 281, pp. 835-840. In this survey, QA practices were assessed using the standards defined by the American College of Medical Genetics Laboratory Practice Committee (http://www.arvo.org/genetics/acmg). These guidelines establish minimum standards for each of the common methods used in clinical molecular genetic testing.

*** SACGT was established in 1998 by the Department of Health and Human Services to provide advice on the medical, scientific, ethical, legal and social issues raised by the development and use of genetic tests.

**** SACGT (2000), "Enhancing the oversight of genetic tests: recommendations of the secretary's advisory committee on genetic testing".

PART III

INCENTIVES AND BARRIERS TO DIFFUSION OF NOVEL GENETIC TESTS

Impacts of stringent licensing agreements

The limitations on access to materials and processes indispensable for research by restriction of licensing has recently been raised as an issue of concern in several OECD countries.[24] The possible award of patents – in the thousands – for SNPs or expressed sequence tags (ESTs)[25] indicative of disease[26] and the recent practice of exclusive licensing of broad disease gene patents to a limited number of clinical laboratories have raised similar concerns. In the latter case, the concerns relate to the possibility that such licensing agreements could restrict the full utilisation and wider diffusion of such tests. Indexing of familial cases, for example, may not be allowed because most companies are in the business of full sequence analysis and could be reluctant to permit screening of new mutations, which might lead to new diagnostic tests and competitive commercial applications. In addition, companies usually set a fee for use of their tests unless these are used for research purposes; and even in such cases restrictions and fees often apply. Fees levied for various tests could add up and make clinical research, generally performed on tight budgets,

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24. *Intellectual Property Restrictions on Access to and Use of Research Tools in Biomedical Research*, report of the National Institutes of Health (NIH) Working Group on Research Tools (1994) chaired by R. Eisenberg. Available at the NIH's Web site: http://www.nih.gov./news/researchtools/index.htm#exec.

25. More than 10 000 applications for patents on discoveries involving the DNA stretches known as ESTs have accumulated since 1991 at the USPTO. However, only about 7 000 of these will likely be awarded a patent. This is because EST-related applications may be subdivided into three groups: 500 to 600 first-generation applications are DNA fragments vulnerable to rejection under the new USPTO guidelines because applicants asserted utility in a non-specific "shotgun-type disclosure". In about 2 500 second-generation applications, scientists used ESTs to discover entire genes or full-length cDNAs. One-quarter of these discoveries may be unpatentable because the utility of the gene or gene product was poorly characterised or incorrectly stated. The remaining applications, *i.e.* some 7 000, belong to a patentable third generation, in which inventors had correct, complete information about genes and gene products.

26. As a consequence of these concerns, the USPTO, burdened by thousands of applications for gene patents, is now proposing new guidelines under which it could reject many pending and future applications. In addition, the US Congress has recently enacted the most extensive revision of the patent statute since 1984. Thus, it may well be that the new examination guideline for utility and written description of the USPTO, as well as the revised guidelines for examination in the European Patent Office will have an impact and prevent extensive patenting.

unaffordable. The consequence may be a *de facto* monopoly on testing and research. Many scientists and clinicians have therefore called for changing a system which, they contend, denies them affordable access, if any, to disease-linked genes.

Although the need for patent protection to encourage investment in R&D was recognised by Workshop participants, concerns were raised that at international scale, stringent licensing may have other – as yet undefined – consequences on genetic services across OECD countries as well as on global competition in this sector. Many OECD countries have traditionally offered comprehensive genetic services, delivered either through specialised regional centres or, more broadly, in clinical settings. Exclusive licensing may have some or more of the following infrastructure effects:

- Genetic testing may become concentrated in a few centres (or excellence centres).
- Centres may be licensed to test only for specific disease genes, leading to a disaggregation of genetic services into disease-specific testing centres.
- Since a single commercial company may not hold the licence for all the genes involved in any one disease, the result might be further disaggregation of genetic services and the need for multiple referrals.

The potential impact on the performance of genetic services and related healthcare outcomes is not known. In some countries, such as the Netherlands, genetic testing is delivered by few accredited centres. These centres, however, are linked to clinical genetic and research centres and usually offer testing for all known genetic conditions.

Another issue relates to the restrictions on full sequence testing which some companies might impose. As mentioned above, a company might retain the right to key parts of the testing process, *e.g.* scanning for the causative mutation in a family. Since testing is likely to take place on an international scale, human samples will increasingly be exchanged across national boundaries. To protect the rights of individual patients will require setting up clear material transfer agreements, international standards for quality assurance and agreements on privacy and confidentiality, in particular on informed consent and use and release of data. Another consequence of international commercialisation or trade in genetic testing under such restrictions is that knowledge as well as know-how might ultimately be retained within a few companies or centres, most likely located in the few OECD countries that

already possess a competitive advantage in this area. In the long term, this would affect R&D and skills.

Issues such as these raise important questions for the future of genetic testing services, the diffusion of the technology and the need for coherent international policies.

Likely trends in demand: marketing directly to the patient/consumer

In 1997 the Task Force on Genetic Testing created by the National Institutes of Health (NIH)/Department of Energy (DOE) Working Group on Ethical, Legal and Social Implications (ELSI) of Human Genome Research reported that, as early as 1995, over 50 biotechnology companies in the United States were developing or providing tests to diagnose genetic disorders or predict the risk of their future occurrence. A significant proportion of these companies were developing or offering tests for three of the most common complex disorders (Alzheimer's disease, breast cancer and hereditary non-polyposis colon cancer). The remaining addressed frequent single-gene disorders (cystic fibrosis, fragile X, muscular dystrophy).

To date, most of the US companies that have developed genetic tests to predict or diagnose common complex disorders market these tests as services and aim their marketing at geneticists, genetic counsellors and general physicians as well as managed care organisations. Few companies market directly to patients and consumers. However, this trend is likely to increase.

In recent years, as a consequence of concerns over escalating public expenditure on healthcare, most OECD countries have encouraged the introduction of competition and a free market in healthcare services and goods. This has affected the private/public mix of responsibilities in the healthcare sector. A commonly used strategy has been to increase the level of cost sharing specified in insurance policies by raising co-payments or co-insurance rates. Another has been to require people to pay out of pocket the additional premiums required to purchase health insurance coverage. The assumption behind these measures is that an important element of cost containment is cost consciousness on the consumer's part. These measures have changed the classical relation between physicians and patients and are encouraging patient autonomy.

Today's patients are better informed and better educated. As a consequence of the new "empowerment" of patients, they have embraced the concept of self-medication and of increased availability of over-the-counter

medication, particularly to treat or diagnose less severe health conditions. Among over-the-counter products are analytical test kits packaged for use on a single-test basis for a wide variety of conditions. The major trend here is expansion of the at-home testing market to include greater use of established types of tests and the addition of new tests for measuring cholesterol, prostate specific antigen and faecal occult blood. As part of this expansion, there is the increase in direct-to-consumer marketing of generic drugs and diagnostic services over the Web and mail-order tests.

Whether this market continues to expand and will soon include genetic test kits will depend on several factors, among which are trends in preferences, the extent of government intervention to allow or restrict direct-to-consumer marketing and over-the-counter genetic tests, and the price of tests or services, *including* whether the tests are reimbursed, as well as the available options and price of alternatives.

The public's preference can be assessed through surveys. The most recent surveys show that across countries the public unanimously values the application of genetic engineering in medical research, particularly for genetic testing, more highly than its use in other areas of activity. The European Commission's *Eurobarometer*, for example, regularly surveys public opinion on various issues. Data for 1998[27] indicate that about 80% of the European population agreed on the usefulness of new genetic testing but that 60% are also concerned about the consequences of the diagnosis. Data for 1999, however, and perhaps in the background of the controversy over GM foods, show a drop of 11% in the overall positive response to the usefulness of genetic testing, to 72% (*Eurobarometer 2000*: 52.1).

The lack of available therapy is a deterrent for many patients and the risk of release of information to third parties is another reason for the observed ambivalence about genetic tests, although the latter reason might favour an over-the-counter "testing-kit" market.

Surveys in Japan reported by Macer show that 88% of the Japanese public also view medical applications of biotechnology positively. In the United States, 93% of those polled in 1998 showed approval for genetic testing. Interestingly, there did not appear to be a relation between approval of genetic testing and whether the disease or condition could be treated. Increased options for disease prevention were considered a good enough reason to test. Altogether

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27. Durant, J., M. Bauer and G. Gaskell (eds.) (1998), *Biotechnology in the Public Sphere: A European Sourcebook*, Science Museum, London.

this indicates that the extent of demand will depend on the strength of demonstrable associations between the results of genetic testing and disease (*i.e.* clinical validity) on evidence of the safety and effectiveness of interventions to reduce risk and/or improve outcomes (utility), and ultimately on the trust of the public in government oversight on this and other biotechnology applications. The willingness of health insurers and social security schemes to cover predictive genetic tests will also affect demand, although this will also be influenced by data on validity and utility.[28]

At the same time, in most OECD countries, governments have either intervened or may intervene to regulate genetic tests, particularly for susceptibility genes.[29] However, public preferences, particularly if only certain tests are to be listed for reimbursement, might ultimately dictate trends.

Private insurance and genetic testing

A troublesome concern with new genetic testing is the possibility that employers and health, life and disability insurers might use this information to deny coverage, raise rates or limit the extent of coverage. Private insurance is an industry which sells financial coverage against unexpected harmful events or loss. Private insurance can cover disability, long-term care, annuity products, life insurance, etc. For most people, life insurance is linked to home purchase and the protection of dependants. As a result, the availability of affordable insurance, in particular of affordable life insurance, is a matter of interest to many.

Insurance is based on uncertainty, and insurance companies have developed methods for assessing and forecasting risk, many of these based on actuarial models and stochastic analysis. A fundamental principle of private insurance is that individuals in the same risk category should pay the same premium. It follows that private insurance companies demand disclosure of known medical information in order to assess risk. Most "traditional" medical tests are used to detect evidence of a disease process that is already present. In the presence of symptoms or serious disease, private insurers may, in extreme cases, reject the application or require a much higher premium. Insurance

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28. Schoonmaker, M.M., B.A. Bernhardt and N.A. Holtz, (2000). "Factors influencing health insurers' decisions to cover new genetic technologies", *Int. J. Tech. Assess. Health Care*, Vol. 16, No. 1, pp. 178-189.

29. An overview of current regulatory developments in OECD countries is available on the OECD Web site: http://www.oecd.org/dsti/sti/s_t/biotech/act/healthhome.htm.

contracts entered into on this basis are said to reflect the utmost good faith (*uberrima fides*) on the part of both parties.

In this context, the issue of adverse or anti-selection is a serious one. Adverse selection is a term used by insurers to describe situations in which insurers know less than the applicants about their health status. This might be the case if an individual, following a positive genetic test for a serious disease, exploited this information by purchasing a disproportionate amount of life insurance. The converse is also possible, as insurance companies, if allowed access to the information, could select applicants on the basis of their own goals and strategic needs. In yet another scenario, people who could show their good health with favourable genetic tests might use this information to increase their chances of obtaining coverage at a low premium. For example, an individual with a family history of Huntington's disease, and for whom the family disease has been used adversely by insurers, could exploit a favourable genetic test to overturn the insurer's perception of his/her category of risk.[30]

Insurance companies therefore have every reason to wish disclosure of existing information on genetic tests that is accurate, clinically valid and relevant to the cover/product applied for. Incorrect information, one way or the other, harms the industry. Yet, there are serious concerns about the extent of the disclosure that should be allowed, in particular when, as in the United States, a strong correlation exists between employment and provision of health insurance.

For the above reasons, several European countries, the European Council and UNESCO have recently enacted guidelines on the use of genetic information. In the United States, over half of the states have imposed sweeping restrictions on health insurers' use of genetic information.[31] In 1996, a federal law known as HIPAA (Health Insurance Portability and Accountability Act) prohibited group health insurers from applying "pre-existing condition" exclusions to genetic conditions that are indicated solely by genetic tests and not by actual symptoms. In February 2000, US President Clinton signed, at an event at the American Association for the Advancement of Science, an executive order that prohibits US federal departments and agencies from using genetic information in any hiring or promotion action. This action ensures that health information obtained from genetic tests is not used against federal

30. However, this cannot result in preferred rates (lower than standard rates).

31. Hall, M.A. and S. S. Rich (2000), "Laws restricting health insurers' use of genetic information: Impact on genetic discrimination", *Am. J. Hum. Genet*. 66, pp. 293-307.

employees. The President also endorsed the Genetic Non-discrimination in Health Insurance and Employment Act of 1999, which extends this protection to the private sector and to individuals purchasing health insurance. The purpose of the legislative action is two-fold: to prevent misuse or abuse of genetic information and to encourage genetic testing for research and medical purposes.

In Europe, in the past few years, there has been a trend to allow access, under clearly defined circumstances, to certain tests, for specific products/use. For example, the Association of British Insurers has drawn up guidelines and a Code of Practice on how member offices should use genetic information and request disclosure of known genetic tests. This was in response to the fact that though the impact of genetic testing is considered as relatively slight for life assurance, it could have a serious impact on other classes of insurance in future years – medical fees insurance and long-term care insurance have been quoted as particular cases.

However, legislation is being enacted at different rates across OECD countries and is fragmented. This has an impact both on the insurance industry, which fears unfair competition and unclear regulation, particularly at a time when healthcare and health insurance can be purchased globally, and on the individuals, whose fundamental rights, in the absence of clear policies, may be endangered.

PART IV

BANKING DNA

Genetic databases: trends and policy issues

Repositories of biological samples have existed for decades in public and private research laboratories, pathology departments and clinical healthcare settings. Recently, however, the perceived value of stored human samples and materials, particularly of human DNA, has escalated. Developments in public health genetics and molecular epidemiology, coupled with trends in bioinformatics and commercially available technologies for DNA collection, storage, mining and management, have led to increasing interest in and the collection and storage of DNA. Recently the European Society of Human Genetics Public and Professional Policy Committee highlighted at a workshop how DNA banking for medical and research purposes has become indispensable.[32]

However, banking of DNA, whether samples are identified, coded or anonymous, raises extremely serious ethical and legal issues pertaining to access, informed consent, privacy and confidentiality of genomic information, civil liberties, patenting and proprietary rights.

In the past few years, several international organisations, professional associations and advisory bodies have developed guidelines to address ethical and legal concerns related to developments in DNA banking. Of particular relevance is the work of UNESCO, the Council of Europe and the HUGO Ethical, Legal and Social Issue Committee.[33]

The aim of this section is not to cover familiar ground but to advance international debate and understanding, particularly on the protection of data (and of data subjects), on the impact of commercial use and on the transfer of data across national borders.

Security of DNA and healthcare data banking facilities

In 1996, the HUGO Ethics Committee released a statement on the Principled Conduct of Genetic Research (http://www.gene.ucl.ac.uk/hugo/conduct.htm) in which a series of recommendations is made. Specifically

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32. Workshop on DNA banking, 7-8 April 2000, EUROGAPPP Project 1999-2000.

33. A list of the major publications and URL sites of these bodies is available at the OECD Web site: http://www.oecd.org/dsti/sti/s_t/biotech/prod/genetic_testing.htm.

addressing the need to develop adequate encryption technology and related mechanisms for review, the HUGO-ELSI Committee recommends:

- That recognition of privacy and protection against unauthorised access be ensured by the confidentiality of genetic information. Coding of such information, procedures for controlled access and policies for the transfer and conservation of samples and information should be developed and put into place before sampling. Special consideration should be given to the actual or potential interests of family members.

- That continual review, oversight and monitoring are essential for the implementation of these recommendations. Such review should include, where possible, representatives of participants in this research. Indeed, without continuing evaluation, the potential for exploitation, for duplicity, for abandonment and for abuse by all cannot be ignored. Like competence, continual review is imperative to respecting human dignity in international collaborative genetic research.

Similar statements have been made by the Council of Europe, in its Recommendations on the Protection of Medical Data (1997),[34] by the American College of Medical Genetics (1994),[35] by UNESCO and most recently by the US National Bioethics Advisory Commission (1999).[36]

Despite the overwhelming agreement of international bodies and professional organisations alike on the need for "appropriate technical

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34. The Council of Europe's Recommendation on the Protection of Medical Data (1997): "Appropriate technical and organisational measures shall be taken to protect data against accidental or illegal destruction, accidental loss, as well as against unauthorised access, alteration, communication or any other form of processing. Such measures shall ensure an appropriate level of security taking account on the one hand, of the technical state of the art and, on the other hand of the sensitive nature of medical data and the evaluation of potential risks." Council of Europe Committee of Ministers, Recommendation No. R.(97)5 of the Committee of Ministers to Member States, February 1997. Available on the Council of Europe's Web site at http://www.nih.gov./news/researchtools/index.htm#exec.

35. American College of Medical Genetics, Laboratory Practice Committee, Quality Assurance Subcommittee (1994), *Standards and Guidelines: Clinical Genetics Laboratories*, Bethesda, Maryland.

36. US National Bioethics Advisory Commission (1999), "Research involving human biological materials: ethical issues and policy guidance", http://bioethics.gov/cgi-bin/bioeth_counter.pl.

measures" to protect data, little progress has been made in clarifying what the term "appropriate" should signify and how this goal can be achieved in practice. In addition, little discussion has gone to addressing the possible consequences of irreversible anonymisation of key health data and whether this is truly desirable.

A 1997 report to the US Secretary of Health and Human Services on privacy and health research[37] provides a compelling review of security issues. As this document highlights: "security has many dimensions; the special challenge (in the health sector) is to keep data sequestered and protect its integrity, but at the same time to keep it accessible for authorised users who have legitimate need to use it".

The OECD has been building its expertise in privacy and confidentiality issues for more than a decade and has brought a science- and rules-based approach to these issues. Benchmark principles on data protection were developed by the OECD in 1980[38] and have been integrated in laws and regulations in many countries. The OECD principles address: collection limitation, data quality, purpose specification, use limitation, security safeguards, openness, individual participation, and accountability. All are relevant to genomic data. These principles were incorporated in the 1981 "Convention for the Protection of Individuals with Regard to Automatic Processing of Personal Data" of the Council of Europe and in the 1995 "Directive on Data Protection" of the European Union [95/46/EC].

Building on these principles, the OECD developed in 1997 a set of guidelines on cryptography policy[39] (see Box 6), which provides a comprehensive approach to international cryptography policy by identifying the basic principles that governments should take into consideration when developing policies on cryptography. In 1998, the OECD advanced this work by surveying international and national instruments relating to controls on the export, import and domestic use of cryptography technologies in OECD Member countries.

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37. W.W. Lowrance (1997), "Privacy and health research", report to the US Secretary of Health and Human Services.

38. OECD (1980), "Recommendation concerning Guidelines governing the Protection of Privacy and Transborder Flows of Personal Data"; and OECD (1992), "OECD Guidelines for the Security of Information Systems", http://www.oecd.org/dsti/sti/it/secur/prodpriv-en.htm.

39. OECD (1997), "OECD Guidelines on Cryptography Policy", http://www.oecd.org/dsti/sti/it/secur/prod/crypto2.htm .

It goes without saying that the future of genetic databanks as well as of healthcare sector databases depends, among other things, on good encryption policies, as the recent debates on the Icelandic Health Sector Database highlighted (see below). Cryptographic methods need to be trustworthy in order to generate confidence in the storage and use of sensitive genetic and health information. Government regulation, licensing and use of such methods may also encourage user trust. Evaluation of current methods, especially against market-accepted criteria, could also generate trust. The OECD could use the experience gathered over the years in its work on privacy and confidentiality and particularly on cryptography to address the specific needs of this particular sector.

Box 6. **What is cryptography?***

Cryptography is a discipline that embodies principles, means and methods for transforming data to hide their information content, establish their authenticity, prevent their undetected modification, prevent their repudiation and/or their unauthorised use. It is one of the technological means of providing security for data on information and communications systems. It is based on the developments of complex mathematical algorithms for transforming data to render them unintelligible to anyone who does not possess certain secret information (the cryptographic key) necessary to decrypt the data. Cryptography can be used to protect the identity of individuals or the confidentiality of data, such as financial or personal data, whether the data are in storage or in transit. Cryptography can also be used to verify the integrity of data by revealing whether the data have been altered and identifying the person or device that sent the data. Individuals or entities who own, control, access, use or store data may have a responsibility to protect the confidentiality and integrity of such data, and may therefore be held responsible for using appropriate cryptographic methods.

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* Extracts from OECD (1998), *Cryptography Policy: The Guidelines and the Issues*.

Transborder flow of data, secondary use of data and consent[40]

Today, much research (basic, clinical epidemiological, etc.) is performed on transferred data, and this practice, given the range of electronic technologies in existence, is expected to increase. Research on transferred data is usually considered secondary research if it entails the re-use of data for purposes either similar to, or different from, the purpose for which the data were originally collected. Judgements as to whether a purpose is similar to the original purpose (and thus meets the OECD "purpose specification" and use "limitation

40. Part of this section draws on W.W. Lowrance (1999), "Data protection in transborder flows of health research data", drafted for the OECD.

principles") can be contentious. So can judgements as to whether consent should be obtained again from the data subjects.

As the "distance" of a new use from the original point or time of data collection, or from the data subject, increases, it probably becomes more difficult to guarantee the respect of data-subject rights. Secondary research and subsequent use of data or of human samples is an issue that is highly relevant to current discussions on the requirements and scope of informed consent, the rights of subjects to information on the purpose of research, the duration of the storage of data and especially to the rights of subjects to withdraw or suppress personal data.

Opinions on these questions differ widely, although there appears to be at least some consensus that policies will vary according to whether data or samples are identifiable and/or have been processed and de-identified and whether they will be archived. Furthermore, a distinction should be made in policy making regarding medical data, *e.g.* data obtained from medical records, versus biological samples. Most health data begin as identified data. But they can be de-identified either:

- Irreversibly, by discarding identifying information or by aggregating (averaging) sets of data.
- Reversibly, by removing identifying information and assigning an arbitrary pseudonym (usually a code) connecting the substantive data with the identifiers (key coding) and safeguarding the key separately.

In the case of reversible information, several professional bodies, such as the American Society for Human Genetics,[41] consider that a blanket consent for all future unspecified genetic research projects is inappropriate. However, it must be recognised that fully informed, specific consent for secondary future research might be difficult to achieve. Another solution may be to recommend limited storage times or include provisions for specific destruction of samples at the request of the individuals to whom samples or data pertain. However, both solutions present ethical or technical dilemmas. For the former, for example, the World Health Organisation (WHO) (1998) recommends that DNA be stored for as long as it can benefit living or future relatives. For the latter, it is fairly apparent that samples or data that have been processed or provided to other research centres can sometimes be neither traced nor destroyed. An additional troublesome set of issues has to do with how effectively, in a practical sense,

41. American Society for Human Genetics (1996), "Statement on Informed Consent for Genetic Research", *Am. J. Hum. Genet.* 59, pp. 471-474.

data transfer contracts can preserve data-subjects' rights when data are transferred outside the country in which the subjects entered into an agreement with the data collector.[42]

Box 7. **The Icelandic Health Sector Database**

The Icelandic Parliament, the *Althingi*, is one of the world's oldest national parliaments. In 1998, a legislative bill to establish a Health Sector Database (HSD) was submitted to the *Althingi*. The objective of this legislation was to authorise the creation and operation of a centralised database of personally non-identifiable health data in order to increase knowledge and improve health and health services.

During the 122nd session of the Icelandic Parliament in March 1998, the bill was subjected to intensive discussions and was not passed. A working group was appointed by the Ministry of Health and Social Security to revise the bill in the light of these discussions, and a new bill was presented to Parliament during its 123rd session in October 1998. After a few weeks of deliberations in both the Parliamentary Committee on Health and in the general session, Parliament passed the bill on 17 December 1998. Prior to these deliberations, a survey/referendum had indicated that 58% of the Icelandic population were in favour of the project, 23% had no opinion and 19% were opposed.

Under the legislation, people may opt out of the Health Sector Database, but the collection of unidentifiable medical data does not require informed consent. On 10 July 1999, 18 000 people had exercised that right. The legislation includes strong provisions on encryption (http://brunnur.stjr.is/interpro/htr/ htr.nsf/Files/security), although there has been much discussion on whether the source of information in the Health Sector Database is nonetheless identifiable. The Data Protection Commission, which serves under the Ministry of Justice, has been given the task to secure the personal privacy of the data and act if any doubts arise regarding the possibility of identification. The Data Protection Commission also has the power to stop the operation of the database and destroy data if necessary to protect personal privacy.

In accordance with the bill, a Monitoring Committee was appointed to oversee the establishment and management of the database. In January 2000, the Ministry of Health and Social Security awarded a biotechnology company, deCode Genetics, the exclusive 12-year licence to develop, operate and use the database for applied clinical research purposes. Transfer of data onto the Health Sector Database is subject to the consent of the health institutions, which retain the right to maintain and store the original medical records. Once the HSD becomes operational, it will be possible, if the standards of the Data Protection Commission are met, to link it to a genealogy database called *Islendingabok* (Book of Icelanders) and to a genetic database, obtained through individual informed consent. The data stored in the Health Sector Database is coded in multiple steps, one of which is irreversible. The use of the database is monitored by Iceland's data protection and ethics committees. All of the company's operations are in Iceland and the company is majority owned by Icelanders.

Iceland is developing a pioneering project in this area, one which focuses on a number of ethical and technical issues that are central to the debate on the

42. W.W. Lowrance (1999), *op cit.*

primary and secondary use of medical and genetic data (Box 7). This project is consequently receiving worldwide attention from many and diverse interested parties particularly since similar initiatives are now considered in other parts of the world, *e.g*. Sweden, Estonia and the United Kingdom. The case of Iceland highlights some of the problems encountered by public officials on this issue. Under the terms of the Icelandic Act on a Health Sector Database, provisions are made that such a database may be linked for basic and applied research purposes to a database of genealogical data and to a genetic database, provided that the methods meet the standards of the Data Protection Commission to ensure personal privacy. Those three databases require different forms of consent. The database on genealogy is a demographic public database and requires no consent, the Health Sector Database is based on presumed consent, *i.e.* people can opt out (only) if they request to do so, the genetic database requires informed consent.

This case further highlights the importance of an open and realistic international debate on the information required for consent, particularly against the background of increased global public/private research alliances and thus the likelihood that data will be increasingly transferred across borders and used for secondary purposes.

Annex 1
PROTECTING THE MOST VULNERABLE

Alastair Kent
President of the European Alliance of
Genetic Support Groups

As the ultimate "end user" of the outputs from increased scientific understanding of the contribution made by genetic factors to their health and well-being, patients are also the only group unable to walk away from the consequences of living with the mutations that cause disease. Thus, the imperative need to invest in service development, professional education and training, collaboration between centres to ensure access to scarce knowledge (especially for very rare disorders), the creation of a regulatory regime that is flexible enough to respond to scientific advance while protecting vulnerable people from exploitation, the proper application of intellectual property to ensure the development of good products while encouraging research and development and the application of market forces in ways that promote access for all rather than restricting it to the wealthy. These are issues that should be at the heart of the development of frameworks to guide the application of genetic testing.

At the OECD Workshop in Vienna in February 2000, it is timely to send a message to governments of the OECD and beyond from those who have most to gain from the proper application of the science of genetics and most to fear from its abuse.

As our understanding of genetics increases, it becomes more and more apparent that, notwithstanding our superficial differences, we are all much more alike than we might think. To attempt to use genetics to categorise ethnic groups or individuals, to divide "us" from "them", is not only morally reprehensible, it is bad science. The Vienna Workshop has made this clear.

All of us share a common genetic heritage. The vast majority of our genes we hold in common with every other citizen of the planet. We all have the potential to be affected by genetic mutations that will have a major impact on our, or our children's lives. However, patient groups are concerned that there may be attempts to revive the flawed policies of the past.

Attempts to justify racist, eugenicist or discriminatory policies on the basis of claimed genetic “facts” are politically motivated and spurious. These are doomed to failure because there is no scientific justification for the social and political outcomes being sought. This was true in the past, and it was known to be true by scientists then. It is even clearer now.

This Conference, addressing scientific and ethical issues in the application of human genetics, endorses this message and asks that it is conveyed to the governments of the OECD, to ensure that they know that those who study and work in this field argue that there is no scientific justification for racist or eugenic policies. Such policies are totally without scientific or moral authority.

Annex 2

OECD WORKSHOP VIENNA 2000 ON GENETIC TESTING: POLICY ISSUES FOR THE NEW MILLENNIUM

PROGRAMME

Dates	23-25 February 2000
Venue	Festsaal – Federal Chancellery, Radetzkystrasse 2 A-1031 Vienna, Austria
Chair Session 1 *(Setting the Scene)* Rapporteur	Dr. D. Harper, *Chief Scientist, Department of Health, United Kingdom* Dr. P. Minor, *Division of Virology, National Institute for Biological Standards and Control, United Kingdom*
Chair Session 2 *(Access to Genetic Tests)* Rapporteur	Dr. J.-C. Galloux, *Professor, University of Versailles, France* Dr. N. Zacherl, *Forschungsinstitut für Molekulare Pathologie, Vienna, Austria*
Chair Session 3 *(Laboratory Quality Assurance)* Rapporteur	Dr. Margeret McGovern, *Associate Professor and Vice-Chair, Department of Human Genetics, Mount Sinai School of Medicine, United States* Ms. C. Netterfield, *Office for Policy and Co-ordination, Health Canada*

Chair Session 4 *(Impact of Free Market & Technological Developments)*	Dr. P. Propping, *Professor, Human Genetics Department, University of Bonn, Germany*
Rapporteur	Dr. H. Karlic, *L. Botzmann Institute, Austria*
Chairs Session 5 *(Ethical/Legal/Social Aspects Technological Developments)*	Dr. B. Knoppers, *Professor, Université de Montréal, Canada* and Dr. A. Pompidou, *Professor, Faculté de Médecine, Laboratoire d'Histologie, Hopital Cochin - Port-Royal, France*
Rapporteur	Dr. A. Daar, *Chairman Department of Surgery, College of Medicine, Oman*
Chair Session 6 *(International Policy Forum)*	Dr. A. Taylor, *Genetics Secretariat, Department of Health, United Kingdom*
Rapporteur	Dr. P. Minor, *Division of Virology, National Institute for Biological Standards and Control, United Kingdom*
Workshop Rapporteur	Dr. P. Minor, *Division of Virology, National Institute for Biological Standards and Control, United Kingdom*
Organisers/Sponsors	OECD, Directorate for Science, Technology and Industry (DSTI); Federal Chancellery, Austria; Department of Health, United Kingdom

First Day, Wednesday 23 February 2000

Opening Session: Official Welcome and Opening Speeches

Welcome
Mr. R. NEZU, Director, Directorate for Science, Technology and Industry, OECD

Conference Goals and Objectives

Dr. A. HASLBERGER (Austria)

Dr. D. HARPER (United Kingdom)

Session 1: Setting the Scene

(Chair: Dr. D. Harper; Rapporteur: Dr. P. Minor)

This session will review scientific/clinical developments in our understanding of the way in which genetic factors contribute to disease, and developments in technology which have the potential to revolutionise the way in which genetic testing services are delivered. The session will also review policy issues relevant to genetic testing, which are being considered in other international forums.

New Developments in Genetics for the New Millennium
Professor B. MODELL (United Kingdom)

Benefits and Costs of Genetic Testing: the Case of Breast Cancer
Dr. V. GRANN (United States)

International Issues:

World Health Organisation (WHO)
The Ethical Issues in Human Gene Testing and Community Screening
Dr. B. WILLIAMSON (Australia)

HUGO
International "Genomic" Ethics and HUGO
Professor B. KNOPPERS (Canada)

From Gene-specific Tests to Pharmacogenetics
Dr. L. MIDDLETON (United Kingdom/Glaxo)

Case Study
Dr. T. FRANK (United States/Myriad)

Prenatal Testing and Screening for Down's Syndrome: Lessons from Practices in Europe
Professor S. AYMÉ (France)

Discussion on the Scope and Objectives of Genetic Testing

Session 2: Access to Genetic Tests

(Chair: C. Galloux; Rapporteur: N. Zacherl)

This session will review how access to genetic tests is likely to change, and will include consideration of the limitations of testing and the "therapeutic gap", i.e. *testing for conditions for which there may be no satisfactory treatment. Public oversight and legal issues will also be considered.*

Access to Genetic Tests - Legal Aspects
Professor O. GUILLOD (Switzerland)

Forecasting Legal Scenarios
Justice F. ZWEIG (EINSHAC, United States)

Panel 1

Possible impacts of a free market and changing access. Public oversight, legal and regulatory issues.

Participants:
International Consumer's Associations and Patient Organisations:
Dr. A. KENT (United Kingdom); Dr. A. VAN BELLEN (Netherlands); Dr. N. ZACHERL (Austria)

Second Day, Thursday 24 February 2000

Session 3: Laboratory Quality Assurance

(Chair: Dr. M.M. McGovern; Rapporteur: C. Netterfield)

This session will consider the desirability of:
- Clients and clinicians referring genetic tests to accredited facilities.
- Mutual Recognition Agreements between regional bodies.
- Harmonization of regulatory regimes for the validation of genetic tests.
- Mutual recognition of EQA systems across OECD countries.

Validation of Genetic Tests
Dr. U. KRISTOFFERSSON (Sweden)

Laboratory Accreditation
Dr. M.M. MCGOVERN (United States)

External Laboratory Assessment Schemes
Dr. R. ELLES (United Kingdom)

Genetic Screening for Cancer: False Positives and Predictability
Dr. P. VINEIS (Italy)

The Development of "Best Practice" Guidelines for Molecular Genetic Testing
Dr. D. BARTON (Ireland)

Discussion on Session 3

Session 4: Impact of the Free Market and Technological Developments on Service Availability, Service Delivery and Genetic Support Services

(Chair: Professor P. Propping; Rapporteur: Dr. H. Karlic)

This session will examine goals of genetic counselling in relation to genetic testing. The effects of gene patent licensing arrangements and commercialisation on the delivery of genetic testing will also be covered.

Free Markets and New Diagnostic Technology
Dr. E. RONCHI (OECD)

Availability of Genetic Services (includes resource issues)
Dr. I. BLANCQUAERT (Canada)

Genetic Counselling: Evolution of Involution?
Professor M. FRONTALI (Italy)

Panel 2

The future role of counselling: education and training needs.
Participants:
Professor H. YOSHIKURA (Japan); Professor P. PROPPING (Germany); Dr. T. FRANK (Myriad, United States); Dr. E. KUBISTA (Austria)

Third Day, Friday 25 February 2000

Session 5: Ethical, Legal and Social Aspects

(Chairs: Professor B. Knoppers and Professor A. Pompidou; Rapporteur: Dr. A. Daar)

This session will review the wider ethical and legal issues raised by genetic testing and will include consideration of areas where further international co-operation could add value.

Icelandic Database
Dr. D. GUNNARSSON (Secretary-General, Ministry of Health, Iceland)

The Icelandic Healthcare Database: Risks and Benefits
Dr. K. STEFANSSON (Decode Genetic, Iceland)

Creation of the Estonian Human Genome Heredity
Dr. A. RANNAMÄE (Estonia)

Banking Biological Collections and Digitalizing DNA: Data Warehousing, Data, and Data Dilemmas in Molecular Medicine and Public Health Policy
Dr. R. BLATT (United States)

Privacy and Confidentiality of Genetic Data
Dr. B. LOWRANCE (United States)

Legal, Ethical and Social Issues
Professor S. RODOTA (Italy)

Genetic Testing and Life Insurance
Dr. B. BALDINGER (Swiss Reinsurance, Switzerland)

Panel 3

Questions and discussion on Session 5
Suggested Participants: Session speakers

Session 6: International Policy Forum and Final Policy Considerations

(Chair: Dr. T. Taylor; Rapporteur: Dr. P. Minor)

This session will draw together the views of participants and will identify areas where OECD could provide policy guidance. It may also identify areas where OECD may wish to consider further work.

Final Discussion Session

Rapporteur's Conclusions and Closing Remarks

Annex 3

STATEMENT OF OBJECTIVES AND SCOPE OF THE CONFERENCE

- To review the current situation in genetic testing and to explore the impact of new genetic technologies upon healthcare practice in the next few years.

- To consider the impact of commercialisation of new genetic technologies on healthcare economics and on the delivery of genetic testing.

- To consider best practice and make policy statements on:
    - The importance of genetic counselling.
    - Storage and confidentiality relating to samples and genetic data.
    - Facilitating access to genetic testing.
    - Appropriate involvement of patient/consumer groups in policy making, regulation and oversight.
    - Referring tests to accredited facilities.

- To consider the benefits of international harmonisation in the areas of:
    - Regulation of the validation of genetic tests.
    - International recognition of external quality assessment programmes.
    - Standards for recording of genetic data.
    - Evaluation of the efficacy of new genetic tests and technologies.
    - International recognition of laboratory accreditation.

QUESTIONS AND MAIN TOPICS ADDRESSED AT THE WORKSHOP

I. The likely consequences of a rapid expansion of genetic testing

- What are the issues that healthcare services and policy makers will have to face as priorities in developing guidelines for genetic testing for different conditions and for various types of patients?
- Would some genetic tests require greater oversight than current systems provide?
- What policy measures can facilitate fair exchange internationally of genetic services and products?
- How might policy makers best assess the impact of new genetic tests?

II. Safeguarding quality and equitable access

- How is demand likely to change? How will patients respond to the increasing availability of tests?
- Are genetic counselling centres adequately prepared to face the consequences of a rapid expansion of genetic testing? Are patients and physicians prepared for the increasing variety of tests which are expected on the market?
- How can policy makers encourage appropriate availability of and access to counselling services in association with genetic testing?
- How might changes in regulations affect access to tests and genetic services?
- What is the impact of offering tests for conditions for which currently no effective intervention exists?
- How can the OECD facilitate mutual recognition of guidelines and the establishment of any necessary international standards?

III. Incentives and barriers to the diffusion of novel genetic tests

- What policy measures can facilitate fair exchange internationally of genetic testing services and products, develop a “level playing field” for public and private service providers and offer a uniformly high standard to the public?
- What are the impacts of a free market and technological developments on service availability, service delivery and genetic support services?
- What policy issues should be considered a priority to encourage equitable transfer of genetic testing to developing countries?

IV. Ethical, legal and social aspects – banking DNA

- What is special about genetic data/medical data/personal data? What is the understanding about consent?
- What are the principles that are called upon to protect personal, medical and genetic data? Are they shared by OECD countries?
- What are the impacts of current regulations in OECD Member countries on data protection laws?
- What is the risk or benefit of storage and release of population genetic data?

Annex 4

AD HOC WORKING DEFINITION OF GENETIC TESTING

"Genetic testing is testing for variations in germline DNA sequences, or for products/effects arising from changes in heritable sequences, which are predictive of significant health effects."

1. This definition is a working definition, intended to draw a boundary around the issues to be discussed at the Workshop.
2. It is worded to enable wider issues to be discussed at the Workshop, in addition to the science and technology.
3. It specifically excludes identity testing and acquired changes in a person's DNA.
4. It covers genetic testing that is diagnostic of a particular disease or condition as well as predictive genetic testing that is carried out before there are any clinical signs of the disease or condition.
5. It refers to testing in the individual for germline changes.
6. It may have relevance both to the individuals being tested and their wider family and offspring.
7. Even when undertaken at the population level (population screening), genetic testing should be performed for the benefit of the individual.

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