

***OECD WORKSHOP VIENNA 2000 ON  
GENETIC TESTING  
POLICY ISSUES FOR THE NEW MILLENIUM***

***23-25 FEBRUARY 2000***

**ABSTRACTS**

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## **NEW DEVELOPMENTS IN GENETICS FOR THE NEW MILLENNIUM**

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A future in which there are no financial or technical barriers to large-scale genetic population screening will involve all parts of health systems. In particular, it will require active involvement of primary health care services.

The basic ethical principles of genetic counselling - autonomy, full information, confidentiality - mean that health workers must be willing and able to share genetic information fully with their patients. But how can health workers, particularly when working within the constraints of primary care, ever gain access to, and issue, correct information about hundreds of thousands of DNA variants, each with different health implications?

Screening for genetic reproductive risk of haemoglobin disorders has been widely practised for 20 years, and offers an excellent opportunity for studying the requirements for delivering genetic screening to populations. We propose that to meet the challenge of ubiquitous genetic testing, health workers require both ongoing updating in genetics, and ready access to mutation-specific information materials designed for themselves and for their patients.

Fortunately, the information revolution runs parallel with the genetics revolution, and makes it realistic to plan information systems that link mutation databases with clinical data, to produce standardised, clear, mutation-specific information materials for health professionals and the public. Integration with electronic health records could go further, and allow information to be personalised.

It is also important to gather information on the delivery of genetic services, and the uses people make of genetic information, when it is delivered. This data can be aggregated from individual patients' records. Aggregation by diagnosis and interpretation at a national level provides an efficient mechanism for gauging the effectiveness of service delivery, and the response of the community.

**BENEFITS AND COSTS OF GENETIC TESTING:  
THE CASE OF BREAST CANCER**

*Victor R. Grann, M.D., M.P.H.*

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Five to 10% of breast cancer may be caused by genetic mutations. In the United States alone in the year 2000, it is estimated 183,000 women will develop breast cancer and 41,000 will die from it. The economic burden may be greater than 10 billion dollars. We have performed two studies to understand the efficacy of genetic testing and preventive treatments for women who test positive for genetic mutations. The first is to determine the cost-effectiveness of screening Ashkenazi Jewish women for BRCA1/2 genetic mutations and the second, to compare the benefits and cost-effectiveness of preventing breast cancer with chemoprevention or prophylactic surgery in women who test positive for these mutations. The results of these studies show that in the Ashkenazi Jewish population, with a high prevalence of BRCA1/2 mutations, genetic screening may significantly increase average survival and, depending on costs and screening/treatment strategies, be cost-effective by the standards of accepted cancer screening tests (To be cost effective women tested need to be willing to have prophylactic surgery if they test positive.) These estimates require confirmation through prospective studies and clinical trials, but they have broad implications for policy makers. The second decision analysis model suggests that although surgery may yield more substantial survival and cost benefits, quality of life issues may make chemoprevention a more attractive option for young women at high genetic risk. The engines that drive the benefit and costs of genetic screening and prevention will be discussed.

## THE ETHICAL ISSUES IN HUMAN GENE TESTING AND COMMUNITY SCREENING

*Professor Bob Williamson  
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The following ethical framework within which medically relevant data from the human genome project is offered to individuals and the community is proposed: .

- The human genome project has the potential to deliver outcomes of great benefit for the health of all peoples, both by prediction and therapy.
- All uses of human genetic data, as for other clinical practices, must be based on respect for the individual, the commitment to do no harm, and principles of justice.
- There are no new ethical issues from the new genetics, but some issues are sharpened. .
- Organisations considering the ethical implications of genetic testing should join to propose a code of practice which is realistic and can be agreed internationally. .
- This code should recommend legal provisions to protect individuals from discrimination due to genetic data, by individuals, corporations or governments. .
- This code should provide clear recommendations on gene patenting. .
- This code should define certain procedures, such as human reproductive cloning, which are unethical and should not be attempted. .
- This code recognises that genetic screening has the potential to reduce the burden of handicap both in children and adults, but can be carried out only with informed consent and in accordance with the principles of equality of care and respect.

## INTERNATIONAL "GENOMIC" ETHICS AND HUGO

*Bartha Maria Knoppers  
Chair, HUGO Ethics Committee*

The majority of international or national guidelines, specific to human genetics concentrate on actual or potential clinical applications. In contrast, HUGO's Ethics Committee, attempts to provide guidance to the bench scientists engaged in fundamental research in genomics prior to any clinical applications. The major goals of the HGP, as cited by The National Center for Human Genome Research, are to:

- create a genetic map of the human genome;
- create a physical map of the human genome;
- sequence all 3 billion base pairs of human DNA;
- create research databases and computerised analysis tools;
- study ethical, legal, and social implications of human genome research; and
- train students and scientists.

Often confused as constituting the HGP (Human Genome Project) itself, HUGO's (Human Genome Organization) ultimate goal is to assist in the world-wide collaboration underpinning the HGP. It is an international organisation with 1,229 members in approximately 60 countries.

Essentially, there are three key features of HUGO. First, HUGO is an organisation for those with scholarly or research interests in the HGP. HUGO is not under the control or direct influence of governments, government agencies, or other (public or private) funding bodies. Second, HUGO is an international organisation that functions globally and is not restricted in outlook or activities to any one area of the world. Any concentration of activities in particular countries reflects the current size and state of development of nationally funded programs of genome research rather than an order of priority or preference. Finally, HUGO functions as an enabler. HUGO is not a body for funding research and so does not judge the work of the collaborators it serves, nor does it have any financial hold over them.

The Ethics Committee is one of HUGO's six international advisory committees. Composed of experts from a number of countries and disciplines, the HUGO Ethics Committee promotes discussion and understanding of social, legal, and ethical issues as they relate to the conduct of, and knowledge derived from, the Genome Initiative. Currently, it has 13 members from 11 different countries. It has produced statements on the conduct of genetic research, on cloning, and, will present its "Statement on Benefit-Sharing" at HGM 2000. The Intellectual Property Committee of HUGO has been active in the controversial area of patenting.

The issue of benefit-sharing is one that has its source in the mandate of both committees. How to avoid both commodification of the person through payment for access to DNA and biopiracy with no return of benefits to the families or community? While patents are a legitimate form of recognition for innovation,

there seems to be no therapeutic exception to some of its stringent rules and the "morality" exclusion has lain dormant. The Statements of the HUGO Ethics Committee are based on the following 4 principles:

- Recognition that the human genome is part of the common heritage of humanity:
- Adherence to international norms of human rights:
- Respect for the values, traditions, culture, and integrity of participants: and
- Acceptance and upholding of human dignity and freedom.

Its Statement on the Principled Conduct of Genetic Research maintains inter alia that:

"That undue inducement through compensation for individual participants, families, and populations should be prohibited. This prohibition, however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care or of information infrastructures, reimbursement of costs, or the possible use of a percentage of any royalties for humanitarian purposes".

The "Statement on Benefit-Sharing" then examines the issues of defining community, common heritage, distributive justice and solidarity before arriving at its conclusions in benefit-sharing. These will be presented at the meeting.

## FROM GENE SPECIFIC TESTS TO PHARMACOGENETICS

*Allen D. Roses*

*Vice President & World-wide Director, Genetics*

*Co-Chair, Exploratory Discovery Board*

*GlaxoWellcome Research and Development*

The terms “pharmacogenomics” and “pharmacogenetics” are often interchanged and used without clear definition. For the purpose of this meeting, I will use working definitions. Pharmacogenetics refers to people including gene identification and “right medicine for right patient.” Pharmacogenomics refers to the application of tools including, but not limited to, the functional genomics toolbox of differential gene expression (DGE), proteomics, yeast 2-hybrid (Y2H) analyses, tissue immuno- and histopathology, etc.

There are two applications of pharmacogenetics that may use similar techniques but are quite distinct: A] susceptibility gene identification; and B] “right medicine for right patient.”

### **A] Susceptibility gene identification**

For monogenic diseases current linkage methods are now extremely efficient in identifying mutant genes, depending mostly on the total amount of family structures and DNA samples available. For susceptibility genes, identifications of confirmed polymorphisms associated with the disease have been much more challenging. In general, a comparatively large linkage area with indistinct boundaries has been the best scientists can provide. Within these large linkage areas there may be hundreds of genes that are usually examined one at a time for candidate gene association. There are many candidates, each with a proposed relationship to the disease, but very few widely confirmed susceptibility gene identifications exist. The apolipoprotein E locus (APOE) association with common, late-onset Alzheimer disease (AD) was the first polymorphic susceptibility locus identified by linkage for a major disease. The association of the APOE4 allele with earlier age of onset distributions, and thus increased risk, was confirmed in over 150 populations with no non-confirmations in any group of more than thirty patients and controls. The association of the APOE2/3 genotype with a later age of onset and decreased risk is also widely confirmed. Thus common APOE genotypes carried by people can be interpreted in multiple populations in epidemiological models.

To test whether or not high-density single nucleotide polymorphism (SNP) mapping could detect a susceptibility locus within a large region, GW scientists constructed a SNP map of 2 megabases (mB) on either side of APOE.<sup>1</sup> We asked the question whether a SNP map analysis could detect the location of the APOE locus for AD, if we did not know it was there. The locus was narrowed to less than 100 kilobases (kB), which included the APOE locus, in a very short time frame. This process has since been employed within GW for other disease susceptibility gene searches through large linkage regions, including psoriasis,

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1. E. Lai, J. Riley, I. Purvis, A. Roses. A 4-Mb high-density single nucleotide polymorphism-based map around human APOE. *Genomics*. 54(1):31-8,1998.

diabetes mellitus, migraine, chromosome 12-linked AD, and others. These experiments will define the practical density of SNP maps useful for narrowing the large linkage areas to 50-200 kB, containing far fewer candidate genes that could then be tested for disease association.<sup>2</sup>

The construction of a whole genome high-density SNP map clearly focuses the next stage of susceptibility disease gene research on the availability of well-constructed, accurately phenotyped patient populations. In anticipation of The SNP Consortium (TSC) map, GW is generating useful patient collections from multiple diseases with large unmet medical need.

## **B] “Right medicine for right patient”**

Can we use genetic profiling to recognise patients who will respond positively to a particular medicine? Can we use profiling to identify those patients who will have an adverse event by taking a particular medicine? Can genetic profiling be performed at reasonable cost using a standardised genetic map? These were some of the questions that led to the formation of TSC.

Assuming that a whole genome SNP map with a density of 15-kb average were to be used, this would be approximately 200,000 SNPs. Each SNP genotype would require at least two reactions, one for each allele, or 400,000 genotypes per person. In a phase 2 trial with 500 people of whom 100 were drug responders, 200 million genotypes would be required. This one experiment, if based on \$0.01 each, would cost \$2 million. Clearly for these experiments to be affordable for development of early phase drugs the cost and speed of genotyping will need to be significantly different than current costs and methodologies allow. Our current data, and future experiments, would determine the practical SNP density that would be needed to profile patients. Although it is estimated that there may be several million SNPs that could be identified in the human genome, the practical significance of a commercial experiment must be a consideration. The current goal at GW is to be able to measure 200,000 SNPs in 500 people over a two-week period at a reasonable cost, since we perform in excess of 25 such clinical trials annually. We have developed a bead-based system at GW and beta tested in parallel with standard methods of SNP analyses.

For a SNP mapping system to be useful across the industry, particularly with regulatory authorities, it must be standardised, readily available, and amenable to GLP procedures. It is expected that profiles of SNP linkage disequilibrium maps could be abstracted down to several hundred to a few thousand SNPs and be analysed using conventional chip methodologies. If a SNP profile were to be useful linked to a medicine prescription, then hundreds of thousands of conventional chips would need to be distributed to diagnostic laboratories. It is important to note a critical ethical point: the abstracted SNP profile would give no information concerning any other genetic characteristic than the medicine response, and thus no collateral information to family members concerning any genetic disease. ([http://207.78.88.3/fda/transcripts/tran\\_roses.htm](http://207.78.88.3/fda/transcripts/tran_roses.htm))

The time frame for the SNP map is two years, with concurrent development of analytical methods and bioinformatic [data-mining] read-out methodologies. Application to medicines that are already registered and in the market place, but have significant adverse characteristics that limit their commercial value will no doubt be the first area studied over the next five years. These studies will also provide the proof of principle for parameters for registration of new medicines during the next five years.

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2. E.R. Martin, J.R. Gilbert, E. Lai, J. Riley; B.D. Slotterbeck, A.R. Rogala, C.A. Sipe, J. Grubber, I. Purvis, M.A. Pericak-Vance, A.D. Roses, J.M. Vance. Association mapping of APOE with Single Nucleotide Polymorphisms, submitted for publication.

## CASE STUDY

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The international collaboration to decode the human genome will provide information that will fundamentally change the practice of medicine. The discovery of genes responsible for hereditary cancer syndromes provides an illustration of how genetic research can result in improved patient care. *BRCA1* and *BRCA2*, the two genes responsible for most hereditary breast and ovarian cancer, were discovered in 1994 and 1995. By the end of 1996, applications of biotechnology enabled analysis of the more than 16,000 base pairs of these genes to be offered as a diagnostic test for evaluating hereditary cancer risk. The clinical availability of such tests is justified by the ability to identify appropriate patients for testing, the accuracy of laboratory analysis of these genes and the medical utility of the information. The progress of *BRCA1* and *BRCA2* from the laboratory bench to the patient bedside provides an illustration of the benefits and challenges of identifying the genes responsible of hereditary cancer risk. Knowledge of the hallmarks of hereditary risk, options for medical intervention and the interpretation of *BRCA1* and *BRCA2* laboratory analysis enables medical experts to effectively counsel and manage women concerned about the possibility of hereditary risk of breast and ovarian cancer.

**PRENATAL TESTING AND SCREENING FOR DOWN SYNDROME :  
LESSONS FROM PRACTICES IN EUROPE**

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Prenatal testing for Down syndrome started in the mid-seventies by an offer to high-risk couples well aware of their risk and of the disease. In the eighties, prenatal screening started with a more or less systematic approach of older women. Soon after ultrasound screening extended the possibility of detecting high risk women. In the nineties, serum marker screening became available at the general population level. Despite the availability of these technologies through Europe, practices and policies are different from one country to another. There are countries where prenatal screening is widely used without clear recommendations, others where there is a national policy, and some countries where there is no screening, only testing on request. As a consequence the detection rate ranges from 18% to 70% among regions of Europe. There are also variations in termination rates after prenatal diagnosis: for Down syndrome it ranged from 67% to 95%. The termination rate is statistically linked to the parity of the pregnancy, the highest the parity, the lowest the termination rate, and with the region. There is no link between the detection rate and the termination rate. Opinion polls show a very large consensus about prenatal screening for Down screening among professionals and among women in various countries but decision-makers are uncomfortable with prenatal screening. In the absence of clear policy, some questions remain unanswered like the questions of inequity in accessing the tests, quality of the information delivered, quality of the screening procedure, handling of screened positive women, management of anxiety raised by the tests, unnecessary diagnostic tests for too many women. The most appropriate way to counter-balance the trend toward systematic prenatal screening seems to develop social and medical services for the disabled, not to ignore the trend.

## ACCESS TO GENETIC TESTS – LEGAL ASPECTS

*Olivier Guillod*  
*Professor, Director of the Health Law Institute*  
*University of Neuchâtel (Switzerland)*

Access to medical services has always included two basic issues: the availability of the service itself and the coverage of the service through a social insurance scheme. In the case of access to genetic tests, a third issue comes into the picture: therapy has not kept pace with the increasingly rapid development of new genetic tests. As a result, we can today diagnose early, or even predict, an ever wider range of conditions for which there is no satisfactory treatment presently and for the near future. To further complicate matters, the present socio-economic context will lead to strong pressures for expanding genetic tests. On the one hand, genetic tests have become a booming market with perspectives of huge profits for the biotech firms. On the other hand, individuals (in our Western societies) long for a perfect health and their quest is fuelled by social representations and commercial advertisements stressing health and fitness as the ultimate goal. As a result, the health market easily induces new “health needs” within the population and therefore increases the demand for medical services, including genetic tests.

Such a context should not be ignored when dealing with problems of access to genetic tests. Given the sensitivity of the information gained through genetic tests and the resulting risk of unfair discrimination, the State has a responsibility to set up a regulatory framework for genetic tests that takes into account the protection of individual liberties, the promotion of public health and the guarantee of equal treatment. At the same time, national States tend to become minor regulatory players on the world scene, because it has become so easy to overcome national regulations through actual or virtual (Internet !) travelling. This makes the involvement of international and supranational organisations even more important.

The legal framework to be drawn should rely on three pillars. First, measures should be taken to empower patients to make free and informed choices. This includes wider and better information to the population on advantages and shortcomings of genetic tests as well as individual informed consent before any test. Secondly, programs of quality assurance should be set up in collaboration with the health professionals directly involved. Thirdly, the availability of genetic tests as well as the coverage of genetic tests through social security should be regulated. In the latter respect, the following issues will be briefly dealt with :

- limiting genetic tests to health-related purposes or medical research purposes ;
- making genetic tests conditional on a medical doctor’s prescription ;
- restricting the performance of genetic tests to licensed institutions ;
- outlawing the sale of genetic tests for public use (“ kits ”);
- forbidding genetic tests on incompetent patients when they cannot be followed by any positive therapeutic or prophylactic measure ;
- limiting social security coverage to genetic tests that provide accurate and reliable results and that can lead to therapeutic or preventive measures.

## FORECASTING LEGAL SCENARIOS

*Franklin M. Zweig, Ph.D., JD*

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Human genetic testing, and its next logical technological plateau, gene therapy, are largely unregulated in the United States and much of the world. Since the basic science and some of the technological know-how related to such tests and therapeutic regimes cross national boundaries with the flip of an internet switch, the disputes that follow in the wake of popular response to such technological advances could arise in virtually any court in the world. For much of the post-industrial world, this pits the unfettered processes of medical decision-making against standards of the rule of law enforced by independent courts of law. For a substantial portion of the developing world, courts are not independent and the rule of law is precariously standardised. There the proponents of unbounded genetic test development and experimentation have greatest opportunities for mischief that can create civil, criminal and military strife.

We will propose and discuss methods to forecast case scenarios. We will analyse their application in judicial science education of 1 300 American judges. We will emphasise the globalisation of civil and criminal conflicts that may be spurred by the use of genetic testing. We will assess the growth of extra-judicial dispute resolution and support an analysis of why it is likely to fail in the case of human genetic tests. We will propose an international means of judicial discourse that has potential to bring objectivity and even-handedness to the just resolution of issues spurred by engineered evolution. Perhaps the avoidance of eugenics as state policy is the most massive challenge faced by all peoples and all nations. The paper will discuss the American experience with eugenics in the era before genetic engineering, cloning and the faux genetic science of behavioural trait prediction and manipulation. The setting was different in a pre-biological era, but the moral considerations were similar to those we face today.

Testing for genetic predispositions and susceptibility to disease can propel targeting of molecular and chemical medicine, holding great benefits for customised treatment. Epidemics may be prevented, and life spans elongated. Genetic test technologies are the escalators needed to rise to genetic treatment platforms. While tests themselves have a dark side - false results, societal utility discrimination, and uncontrollable disclosure of deepest personal information among them - it is the road to gene therapy that holds greatest danger for the community of nations committed to the rule of law and opportunities to realise the fruits of life, liberty and property.

The issues generated by these scientific developments will be enumerated. Their resolution will require Einstein's insight and Solomon's wisdom.

**ACCESS TO GENETIC TESTS:  
ISSUES FROM THE PERSPECTIVE OF PATIENTS AND THEIR FAMILIES**

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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 who are unable to walk away from the consequences of living with the mutations that cause disease. For patients, the new knowledge brings hope. It can also create problems 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, whilst at the same time preventing abuse and unfair discrimination a number of new issues will need to be resolved. The major concern for patients is the question of what the information that results from being tested will mean for them? Will it be of sufficient quality and in a form that is understandable and comprehensive enough to enable them to use it to make significant decisions regarding their own health and welfare and possibly that of their children. Consequent on this is the issue of getting access to the services and support necessary to avail themselves of this information. For this to happen there needs to be investment 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 whilst protecting vulnerable people from exploitation, the proper application of intellectual property to ensure the development of good products whilst 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 can be developed in the panel discussion.

## VALIDATION OF GENETIC TESTS

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A genetic test is a procedure of information transfer in which the laboratory investigation is integrated. It consists of any analysis of family data, of human chromosomes, DNA, RNA, protein or certain metabolites to detect heritable or acquired disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include diagnostic, predictive, carrier, prenatal, preimplantation, or new-born testing, thus predicting risk of disease, identification of carriers, establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations based on the analyses of pedigree information, the proposita, or a relative.

Validation is the procedure in which the possible errors of the diagnostic process are identified, measured, and evaluated to minimise the risk of an erroneous outcome of the test procedure. For the testing in the different situations above, the specificity, sensitivity and robustness of the laboratory procedure, as well as of the design of the counselling process are different, producing different models for the cost-effectiveness of a certain genetic aberration.

In validating a genetic test special consideration must be taken to pre- and post test genetic counselling. The test itself is a part of the testing procedure and cannot be completely validated on its own. Parts of the validation process are the development of technical standards and counselling procedures in collaboration between the professionals and lay persons and state authorities.

## LABORATORY ACCREDITATION

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The regulation of clinical laboratories in the United States is mandated by the Clinical Laboratory Improvement Amendments of 1988 (CLIA). These regulations are based on a complexity model, with molecular genetic testing (MGT) considered high complexity. It has been suggested that specific regulation of MGT is required to ensure quality assurance (QA), and to protect patient's rights with regard to confidentiality and informed consent. Thus, a survey of MGT laboratory directors (n=245; response rate 75%) was conducted to collect information about the availability of MGT, personnel standards and clinical laboratory practices. The main study outcome was the assignment of a QA score. The mean QA score was 90% (range 44 to 100%) with 15% of laboratories scoring below 70%. Higher scores were associated with: test menu size > 4 tests (p=0.011), annual performance of more than 30 analyses (p=0.01), a director with a PhD degree compared to MDs (p=0.002), board certification of the director (p=0.028), independent and hospital laboratories compared to a research laboratory (p<0.001), participation in a proficiency testing program (p<0.001), and CLIA certification (p=.006). Seventy percent of laboratories provide access to genetic counselling, 69% have a policy about confidentiality and 45% require informed consent prior to testing. The identification of factors associated with QA score, suggests that both personnel qualification and laboratory practice standards may need to be mandated to ensure quality in MGT laboratories.

## EXTERNAL LABORATORY ASSESSMENT SCHEMES

*Rob Elles, Head of Genetics Laboratory,  
Regional Molecular Genetics Laboratory, St Mary's Hospital  
United Kingdom*

External Quality Assessment (EQA) or proficiency testing is an independent check on the performance of a laboratory measured against an external 'gold standard'. In Clinical Molecular Genetics some EQA systems have developed to enable the whole analytical process to be measured. These rely on a disease specific approach that tests the proficiency of the laboratory to *interpret* genotype results in their clinical context and issue clear reports. Testing interpretation and reporting also allows the development and application of Best Practice guidelines and encourages a convergence of methodology and practice. EQA can both measure and encourage an improvement in performance and forms an important part of 'total quality' laboratory management.

EQA is largely a voluntary system and there is no pressure for laboratories to participate in and pay for EQA. The introduction of accreditation for service will change this and will oblige laboratories to join a recognised EQA scheme and to pay for it - allowing the development of well-founded and administered schemes. At present proficiency testing is an entirely educational process and this is helpful when there is a variety of standards amongst centres. However accreditation will give EQA organisers the authority to address centres that perform poorly.

Many genetic diseases are relatively rare making a national approach to EQA difficult. This and the increasing trend for tests to cross national boundaries encourages an international approach to EQA and harmonisation and mutual recognition of national and regional schemes.

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## GENETIC SCREENING FOR CANCER: FALSE POSITIVES AND PREDICTABILITY

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Genetic screening is sensible if at least two conditions are met: that the identification of a mutation is followed by effective preventive/therapeutic measures, that prolong survival and improve the quality of life; and that the population examined shows a high concentration of mutants as to achieve a high *predictive value* of the screening test. If the prevalence of the mutation in the population is low - even in the case we have effective preventive/therapeutic means - a screening strategy is unrealistic, since we have to screen hundreds of thousands to find one true positive plus (usually) a large number of false positives. So, rare mutations can be reasonably sought in families (where they are concentrated), not in the general population.

Conversely, if the mutation is frequent (a polymorphism) its penetrance is likely to be low and its effects to depend on interaction with external exposures. 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)(Table). 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 6 per thousand in category A and to 15.5% in category B, with an absolute reduction of 8 per thousand and 21.5% respectively. The Number Needed to Treat is the inverse of such figures, i.e. 1250 in category A and 45 in category B. This means that we have to screen 1250 subjects to prevent one cancer in category A, while it is sufficient to screen 45 individuals in category B to achieve the same result.

|  | GENOTYPE       |                 |
|--|----------------|-----------------|
|  | LOW PENETRANCE | HIGH PENETRANCE |
|  | Category A     | Category B      |
| Risk of cancer without screening (U)   | 0.014          | 0.37            |
| Risk reduction due to screening(U-T)/U | 58%            | 58%             |
| Risk of cancer in the screenees (T)    | 0.006          | 0.155           |
| Absolute reduction of risk (U - T)     | 0.008          | 0.215           |
| NNT to prevent one cancer 1/ (U - T)   | 1/0.008=1250   | 1/0.215=45      |

## **THE DEVELOPMENT OF "BEST PRACTICE" GUIDELINES FOR MOLECULAR GENETIC TESTING**

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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. There will always be many different possible methods of detecting any genetic lesion, and potentially many different ways in which the laboratory findings might be reported. The harmonisation of approaches to molecular genetic testing is best achieved by developing a consensus amongst the professionals involved in testing. External quality assessment (EQA) schemes highlight differences in approaches to testing between laboratories. Scheme organisers and assessors, in particular, are in a good position to observe the different approaches in use and to assess which approaches yield the best results. In the UK, 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 ([www.cmgs.org](http://www.cmgs.org)). The Guidelines offer advice on appropriate reasons for referral, contain links to key references from the literature and links 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. These Guidelines have now been adopted as a starting point for the development of European Guidelines through the European Molecular Genetic Quality Network (EMQN). The Guidelines now act as a resource to which laboratories can refer when necessary, and which guides the EQA assessors in their work. The challenge for the future is to maintain the consensus behind the Guidelines in the context of a rapidly broadening base of users.

## FREE MARKETS AND NEW DIAGNOSTIC TECHNOLOGIES

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The Human Genome Project has engendered a new vision of a genetically-based, individualised preventive medicine, and with this new incentives for industry to develop genetic tests. 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.

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 how a significant proportion of these 50 biotechnology companies were developing or offering tests for three of the most common complex disorders (Alzheimer's disease, breast cancer, hereditary nonpolyposis colon cancer). The remaining were addressing frequent single-gene disorders (cystic fibrosis, fragile X, muscular dystrophy).

To date the majority of US companies market their 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/consumers. Based on the following arguments, this trend, however, is likely to increase.

In recent years, as a consequence of concerns over escalating public health care expenditure many OECD countries have encouraged some shift towards out-of-pocket payment for a selection of health care services and goods. This has affected, if only marginally in some cases, the private/public mix of responsibilities in the health care sector. A strategy commonly used has been to increase the level of cost sharing specified in insurance policies by raising co-payments or co-insurance rates. The assumption behind these measures is that an important element of cost containment is cost consciousness on the consumer's part. In addition there are other considerations to make. Patients are today much better informed and better educated. Also, the rate of growth of health expenditure has been contained in the last five years or so both in countries with public health insurance and in the US which has mainly private health insurance, in the latter by means of 'managed care'. As a consequence both of this new "empowerment" and of 'rationing' or 'management' of care by insurers, patients 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.

Concurrent with this expansion is the increase of direct-to-consumer marketing of generic drugs and diagnostic services over the web and mail-order tests. Further expansion of the medical diagnostic kit market to include genetic test kits will depend on several variables, e.g.: the extent of government intervention, trends in income, price, individual preference. However, uncertainty, risk, unequal information and the need for adequate counselling, imperfect competition, equity of access and clinical validity and utility, all might help explain why buying and selling genetic diagnostic kits over the counter could raise significant policy considerations.

## AVAILABILITY OF GENETIC SERVICES

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Data on availability of genetic services are relatively scarce and suffer from several limitations. However, emerging patterns of service delivery are observed in different countries. The nature of the test and of the disease being targeted determines the specialities involved in service delivery. Furthermore, the prior existence of a network of services dedicated to the particular condition facilitates the integration of the new tests into clinical practice. The analysis of these emerging patterns of organisation of services may help us understand which factors influence the availability of tests and services.

The ability of each health care system to respond to an increasing demand for genetic tests and services will depend not only on the type of health care system and on its financial resources, but also on the current organisation of its genetic services. In particular, the strengths and weaknesses with respect to both the laboratory infrastructure and the clinical and counselling services, the networking of clinical geneticists, and the respective responsibilities assumed by tertiary and primary care may determine the appropriate use of new diagnostics.

An overview of available data and their limitations will be presented, as well as examples of emerging patterns of service delivery for adult-onset diseases and cancer genetics. Considering these organisational issues is a necessary step towards planning the provision and funding of clinical and laboratory services. An additional concern in developing health policies for genetic services is the implementation of oversight mechanisms. These are necessary to ensure that the pressure of public demand is balanced by an adequate demonstration of test validity and a thorough evaluation of the utility, acceptability and feasibility of the proposed testing/screening strategies, taking resource issues into consideration.

## GENETIC COUNSELLING: EVOLUTION OR INVOLUTION?

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Genetic counselling is a complex process, born in opposition to eugenic principles, meant to help families in coping with the diagnosis of an inherited disorder, in facing its implications and in making meaningful decisions about their medical and non-medical options. As genetic testing is increasingly involved in the diagnosis of inherited disorders, counselling becomes an integral part of it, aimed at promoting autonomy of potential users and reducing adverse consequences of test results. The need for counselling derives from several factors such as: a) the peculiarities of genetic information, as compared to other biomedical tests, with particular reference to its predictive character; b) the existing gap between the ability to diagnose and treat an inherited disorder; c) the value attributed in western culture to heritable characters, and d) the psycho-social and ethical problems often arising in test situations. Counselling is traditionally performed by health-care professionals, specifically trained to use different procedures and attitudes from those of everyday clinical practice. The growing number of available tests (both for rare mendelian and common disorders), the development of easier and cheaper molecular techniques, as well as the increasing tendency of physicians to recur to such tests bypassing alternative diagnostic procedures are expanding the demand for genetic testing beyond the availability of counsellors. The growing commercial and/or monopolistic offer of genetic tests is further contributing to short-circuit genetic counselling, and may decrease the safeguards against testing promotion. In this context, a role might be played by computer-based genetic information and primary health-care professionals, but professional counselling remains necessary to handle the situations most problem-laden. Other solutions will be discussed, including promotion of studies on model genetic services, and surveillance programs on services actually offered by tests providers, as well as expanding training programs and positions for genetic counsellors.

## **GENE TESTING IN JAPAN - PRESENT STATUS AND FUTURE**

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According to a database (<http://www.kuhp.kyoto-u.ac.jp/idennet/idensoudan/02.html>), fourteen companies are doing genetic tests in Japan. The list includes both detection of monogenic disease, ex. Chromosomal trisomies, and genetic mutation or polymorphism that could be related to diseases which may appear late in life, e.g. diabetes. Tests for cancer-related genes are also available. Information as to how such tests are currently used is unclear.

It is widely recognised that counselling is necessary for gene testing. Ethical issues associated with the prenatal diagnosis are much debated in Japan but a consensus has not been obtained yet. Counselling on diseases that appear after interaction of the genetic trait and environment appears difficult because the question whether the mutation or polymorphism really predisposes the disease in humans is rarely answered in a direct way. This will be particularly true for SNPs, which are largely results of association studies.

## ICELANDIC DATABASE

*Dr. David Á. Gunnarsson, Permanent Secretary,  
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The paper will cover the following points:

- Historical background.
- The Health Sector Database.
- Act No. 139/1998 on a Health Sector Database.
- Regulation No. 32/2000 on a Health Sector Database.
- Operating Licence for the Creation and Operation of a Health Sector Database issued 22 January 2000.
- Security of information in the Health Sector Database.
- Genealogy in Iceland.
- How can genetic-related questions be directed towards the Health Sector Database ?

## THE ICELANDIC HEALTHCARE DATABASE: RISKS AND BENEFITS

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The expectation from the new genetics in medicine's future is that genetic information will lead to 1) earlier diagnosis leading to earlier treatment or change in lifestyle, 2) tailor-made treatments specific to disease-subtype and which avoid side-effects, 3) more informed, cost-effective disease management practices, and 4) the identification of more relevant drug targets leading to more specific drug therapies. That the new genetics can deliver is still a hypothesis and the demonstration of its effectiveness is a prerequisite for its application in medical care of the future. The Icelandic Healthcare Database that will be built by Decode Genetics will contain medical data generated within the Icelandic health system and could be linked to genealogy, environmental, and genetic data that is obtained through individual informed consent. The database bill proposed by the Icelandic Health Ministry and passed by the Icelandic parliament in December 1998 is consistent with EU directives and International law. Decode Genetics was recently awarded the license to create the database by the Health Ministry. Further group consent will be obtained through the ethics committee and collaborations with the hospitals and clinics before the database is constructed. The data would be coded in multiple steps, one irreversibly, and the use of the database monitored by the data protection and ethics committees in Iceland. The medical data would be brought in without informed consent but individuals may opt out of the database at anytime. No genetic data would be added to the database without informed consent by the individual. Icelandic physicians and the health ministry would have free access to the database as long as the information is not funnelled to a natural client of the database. Foreign scientists may also have access to the database through collaborations with Icelandic physicians or Decode Genetics. The population gains in high technology jobs that would help reverse the brain drain in Iceland. Decode Genetics pays a user fee in the form of upgrading the entire health care informatics systems and a portion of the profits. All of the operations of the company are in Iceland and the company is majority owned by Icelanders so that most value created accrues to Icelandic people and their government.

## **CREATION OF THE ESTONIAN HUMAN GENOME HEREDITY**

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Creation of a comprehensive health database for Estonia's population means the collection of unique genotype (high-density SNP map) and phenotype information about all volunteers and their current health status. The database may be viewed as a means of diagnosing diseases more efficiently and accurately, determining the risk of developing certain diseases and providing more efficient treatment in future. The database will be a source of information for discovering new disease genes using association studies, developing new medicines and favourable grounds for establishing new gene and information technology companies.

The creation of such a database undoubtedly raises very sensitive legal and ethical issues. To succeed, the project needs the community's agreement and the necessary political will, as well as regulations, which reflect international requirements and are based on good practice.

It is estimated that the Gene Heredity Programme (GHP) will be carried out over ten years (2001-10) and that the database will have 1 million entries. In 2000, activities will focus on the preparation of the GHP and the legal requirements for launching the project. The Estonian Government has clearly been supportive in the preparatory phase. The media and the public have been quite attentive and mostly positive. Estonia's advantages for proceeding successfully with the GHP include sufficient genetic homogeneity among the population, a well-developed medical network, the project's relatively low cost, etc.

**BANKING BIOLOGICAL COLLECTIONS AND DIGITALIZING DNA:  
DATA WAREHOUSING, DATA MINING, AND DATA DILEMMAS IN MOLECULAR  
MEDICINE AND PUBLIC HEALTH POLICY**

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Repositories of biological samples have existed for decades in public and private research laboratories, pathology departments, and clinical health care settings. Recently, however, the perceived value of stored genomic material 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 controversy about the ownership, research uses and regulatory requirements governing biological specimens.

While DNA databases may offer the opportunity to 1) assess population-based prevalence of specific genes and variants, 2) simplify the search for molecular markers, 3) improve targeted drug discovery and development for disease management, 4) refine strategies for disease prevention, and 5) provide the data necessary for evidence-based decision-makings, serious scientific and social questions remain. Whether samples are identified, coded, or anonymous, biological banking raises profound ethical and legal issues pertaining to access, informed consent, privacy and confidentiality of genomic information, civil liberties, patenting, and proprietary rights.

This presentation will provide an overview key policy issues and questions for consideration, with a focus on developments in public health and academic-industry alliances. Using a case study approach, it highlight the challenges posed by advances in genetics research and commercialisation, and propose alternative models for harmonising biological banking policies.

## PRIVACY AND CONFIDENTIALITY OF GENETIC DATA

*William W. Lowrance, Ph. D. (Switzerland)*

A variety of ethical and legal controls apply to genetic data: healthcare licensing and medical confidentiality laws; the Declaration of Helsinki, various WHO, CIOMS, and other guidelines, and medical experimentation laws; and the EU Directive 95/46 and related data-protection laws.

Benchmark principles are those of the OECD Data Protection Guidelines of 1980, which now form the conceptual armature of a great many laws and other instruments. The OECD Principles address: collection limitation, data quality, purpose specification, use limitation, security safeguards, openness, individual participation, and accountability. All of these are relevant for genomic data.

The main issues are: personal identifiability of data; consent by subjects; consent, in some instances, by populations; limiting use of data, especially unspecified future use; rights of data-subjects, their relatives, and other parties to know, suppress, control, or exploit genetic information; and obligations of data-holders.

Research on, and commercial use of, stored tissue samples present special issues. So does the protection of data (and the data-subjects) as data are transferred across national borders.

A problem is that genetic science has become so pervasive that it may be hard to distinguish "genetic test data" from genetic data generally (such as family histories, blood or metabolic analyses, or gene maps), and almost impossible to partition "genetic data" from other health data.

## LEGAL, ETHICAL AND SOCIAL ISSUES

*Stefano Rodotà, President,  
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The increasing availability of genetic tests is causing widespread concern; this concern has been a feature of genetic research ever since the start of the Genome Project. Discrimination is feared above all, in that it may lead to the establishment of a “caste society” - or anyhow a “classification society”. In order to prevent this risk, the general principle has been laid out that genetic tests are lawfully to be performed “only for health purposes or for scientific research linked to health purposes” (Convention on Human Rights and Biomedicine, article 12) and that genetic data “must be held confidential” (Universal Declaration on the Human Genome and Human Rights, article 7). However, these general declarations do not appear sufficient and are being increasingly supplemented by specific regulations – such as the recent (08.02.2000) Executive Order issued by President Clinton “To Prohibit Discrimination in Federal Employment Based on Genetic Information”.

Thus, it has become evident that the complex issues related to genetic testing warrant an analytical approach which must focus, inter alia, on the following items:

- conditions legitimating the performance of genetic tests as well as access to the resulting information; the concept under which genetic data is exclusively personal information is being abandoned by stressing its connection with a person’s “biological group”;
- the risk represented by genetic reductionism and the so-called “DNA mystique” with the resulting underestimation of social, cultural, environmental factors;
- predictive medicine and the possibility of building a “counter-destiny”;
- setting up of genetic data banks;
- use of genetic testing in sensitive areas such as employment contracts, insurance policies, judicial investigations;
- customisation of medical treatment;
- marketing of genetic tests, the risk of their trivialization, the impact of economic pressure and the changes in medical profession.

## GENETIC TESTING AND LIFE INSURANCE

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Genetic testing broadened the spectrum of diagnostic possibilities. Interpretation of test results and genetic counselling are very complex and require specific knowledge. The individual should have the free will to decide whether to undergo a test or not and should have access to specialists in clinical genetics. Under this aspect, the Swiss life insurers have proposed a moratorium with respect to genetic testing. The new federal law on genetic testing contains the prohibition to require a genetic test. The Swiss Insurance Association is supporting this view. In a majority of applications the family history is sufficient to estimate the statistical risk of future disease. However, to respect the basic principle of private insurance, the applicants should disclose existing genetic test results. This obligation for information should only include tests that are approved for their technical reliability and clinical use. With the fast pace of development in genetic technology it will, however, become possible to test asymptomatic individuals for frequent multifactorial diseases. This development will most likely allow detection of a genetic constellation related to certain diseases. In that case, the predictive value of genetic test results will probably become superior to information gained from family history. If used in asymptomatic individuals, the results might have a strong influence on people with a high-risk constellation to buy insurance cover. Given this long-term perspective, the life insurers are interested to maintain the applicant's obligation to disclose information on the current health status. This includes information about previously performed genetic tests and their results.