

# **ETHICAL, LEGAL, SOCIAL AND POLICY ISSUES IN MEDICAL GENETIC TESTING OF RELEVANCE TO SINGAPORE: PERSONAL PERSPECTIVES**

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## **Introduction**

The field of modern medical genetic testing is advancing rapidly, in the scope of available tests, technologies and availability/cost. Instead of considering how individual genetic tests available today are offered and taken up, it is perhaps more enduring to consider some general features of genetic testing, describe some challenges that their application poses in the socio-cultural and legal realms, and propose some bioethical principles from which practical solutions could be drawn. A small body of published literature and public policy statements around these topics has recently grown, and the reader is directed to a selection of these, which review the current thinking on these issues (see bibliography and footnotes).

In this paper, I describe my views on these topics, with an emphasis on those that relate particularly to diseases, research, medical services and social contexts of Singapore. While no attempt is made to be comprehensive about diseases or tests, a few examples are provided as points of illustration, as are some tentative suggestions. As this paper covers many areas of genetic testing, it is not possible to discuss these in the depth that might be required for formulation of public policy. I anticipate that this is part of an ongoing discussion and review of this evolving field and hope that this paper helps to generate issues for discussion.

## **Principal Considerations**

### ***Rapid Scientific Progress and Unique Opportunity to Improve Human Health***

The formal completion of the Human Genome Project was announced several months ago<sup>1</sup>. It is a major milestone in science and marks the fifty years of research and discovery into the structure, sequence and function of DNA. This achievement outstrips any previous biological knowledge base by orders of magnitude, and genetic/genomic information is still accumulating at an exponential rate. While there have been major

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<sup>1</sup> In April 2003. <http://www.genome.gov/10001772>

advances in the understanding of causes and mechanisms by which human diseases develop, the expectation is that these will be translated into improvements in human health, and indices of longevity, disability and disease incidence. Genomic (or gene-based) medicine seeks to bring about this translation.

Indeed the estimated 30,000-40,000 genes in the human genome have been identified and are being characterized, and the genes causing some 1,351 Mendelian (single-gene) disorders have been mapped and cloned.<sup>2</sup> Molecular tests to detect mutations in these genes are therefore available in research laboratories, and many are now offered by clinical genetic service laboratories.<sup>3</sup> While specific treatments for these generally rare diseases are not routinely available, approaches such as gene therapy and stem cell therapy for some of these conditions are undergoing clinical trial.

The majority of human morbidity is attributable to multifactorial “complex” diseases involving the interaction of many genes and environmental factors. Identifying their specific predisposing factors is scientifically more challenging. However progress has been made in determining the factors involved in cardiovascular disease and diabetes, cancer, autoimmune diseases and allergies, neuro-psychiatric illnesses and in biological response to drugs.<sup>4</sup> An era is anticipated when an individual’s vulnerability to heritable and environmental disease-inducing risk factors could be determined by lab tests so that steps could be taken to ameliorate the condition or even prevent its occurrence.

In fact, a vision for the next stage of human genomics has been enunciated.<sup>5</sup> This genomic era, of which we are at the threshold, will see the application of the DNA sequence information to a deeper understanding of the biology of cells and organisms, of understanding disease and improving health, and of maximizing benefits to society (Table 1).

**Table 1: A Blueprint for the Genomic Era**

- I. Genomics to Biology: elucidating the structure and function of genomes
  - a. Comprehensively identify structural and functional components encoded in human genome
  - b. Elucidate organization of genetic networks and protein pathways and establish how they contribute to cellular and organismal phenotypes
  - c. Develop a detailed understanding of the heritable variation in the human genome
  - d. Understand evolutionary variation across species and the mechanisms underlying it
  - e. Develop policy options that facilitate the widespread use of genome information in both research and clinical settings
- II. Genomics to Health: translating genome-based knowledge into health benefits
  - a. Develop robust strategies for identifying the genetic contributions to disease and drug response

<sup>2</sup> Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), Accessed 31 July 2003. <http://www.ncbi.nlm.nih.gov/omim/>

<sup>3</sup> Editorial. (2003) Getting a grip on genetic testing. *Nature Medicine* 9:147.

<sup>4</sup> Glazier AM, Nadeau JH, Aitman TJ. (2002) Finding genes that underlie complex traits. *Science* 298:2345-9.

<sup>5</sup> Collins FS, Green ED, Guttmacher AE, Guyer MS. (2003) A vision for the future of genomics research. *Nature* 422:835-847.

- b. Develop strategies to identify gene variants that contribute to good health and resistance to disease
  - c. Develop genome-based approaches to prediction of diseases susceptibility and drug response, early detection of illness, and molecular taxonomy of disease states
  - d. Use new understanding of genes and pathways to develop powerful new therapeutic approaches to disease
  - e. Investigate how genetic risk information is conveyed in clinical settings, how that information influences health strategies and behaviours, and how these affect health outcomes and costs
  - f. Develop genome-based tools that improve the health of all
- III. Genomics to Society: promoting the use of genomics to maximize benefits and minimize harms
- a. Develop policy options for the uses of genomics in medical and non-medical settings
  - b. Understand the relationships between genomics, race and ethnicity, and the consequences of uncovering these relationships
  - c. Understand the consequences of uncovering the genomic contributions to human traits and behaviours
  - d. Assess how to define the ethical boundaries for uses of genomics

We are now presented with exciting new opportunities, perhaps unprecedented in scientific and human history, to improve health and wellbeing. Various governments are taking steps to draft and adopt policies to systematically incorporate genetics into medical systems to improve national health.<sup>6</sup>

This has not escaped the attention of commercial concerns, as private industry funds a significant part of applied biomedical research. There are increasing numbers of biotechnology companies marketing products and services not just for the R&D sector, but also the healthcare sector and to the public directly. Singapore has identified the biotechnology and life sciences sector as an important industry and it aspires to be a major player. Genetic testing and diagnosis, being one of the first medical areas in which genomics has been applied, is already a developed field in many western countries. In Singapore, the field is just emerging. It is therefore timely to consider the ethical, legal and social aspects of genetic testing so that necessary professional, educational and regulatory measures can be implemented.

We are faced with a conundrum of new and sophisticated technologies, new scenarios for their application, increased private commercial participation and an evolving global health market.

### ***Human Genetic Tests as Medical Information***

The intention of genetic testing is to provide information that can help improve an individual's medical or health status through diagnosis and treatment. It shares the same goals as the delivery of healthcare, which are to prevent illness and promote wellbeing.<sup>7</sup> Medical genetic testing can therefore be considered a form of medical

<sup>6</sup> Department of Health UK (2003) Our inheritance, our future: realizing the potential of genetics in the NHS. *Government White Paper 24 Jun 2003*. <http://www.doh.gov.uk/genetics/whitepaper.htm>

<sup>7</sup> One form of human genetic testing that is non-medical is personal identification for forensic, legal or security purposes. Genetic profiling ("DNA fingerprinting") services are now offered directly to the public for evaluation of paternity or genealogy, for instance. The availability and quality of such services, often commercial, is outside the scope of this report. Mandated large scale DNA banking and DNA profiling of those convicted of serious crimes has been started in several countries – these have

investigation and should be considered in the context of contemporaneous standards in clinical care and the current implementation of the healthcare system. The evolution of genetics testing services is influenced by practices of and challenges faced by the health care profession.<sup>8</sup>

Listed below are several examples of how genetic testing could be considered within the larger context of healthcare delivery:

- i. Genetic tests need to be incorporated into the larger scheme of clinical practice plans and guidelines for effective interpretation and medical follow-up, constituting part of overall information required for diagnosis or prognosis.
- ii. The lack of nurses, clinician-scientists, and nurse educators is likely to adversely affect the availability of genetic counsellors and medical scientists.
- iii. Deregulation and commercialization of health care provision with the increasing role of private for-profit medical institutions as well as personal medical insurance will affect how genetic services are provided.
- iv. Medical malpractice and liability insurance trends will impact the role and regulation of professionals and the operation of laboratories involved in genetic testing.
- v. Needs for genetic tests could parallel demographic and disease incidence trends.

Placing genetic testing in a healthcare context provides a foundation for discussing the practical and bioethical aspects of this new field. It also refocuses discussion on the purpose of the tests, rather than on the technology.<sup>9</sup> Hence conventional methods such as antenatal ultrasonography, biochemical blood tests, and chromosomal analysis (karyotyping), when used for diagnosing inheritable diseases, fall under the definition of genetic tests.<sup>10</sup> These tests have been used widely for many decades in Singapore and in many other countries. Genetic testing, therefore, is not new and there is experience among medical, obstetric and nursing professions, health and public policy makers as well as the general public in providing and using genetic testing.

*In Singapore, screening of male newborns for G6PD deficiency is routinely carried out to reduce risks of neonatal jaundice and its complications. Similarly ultrasound scans are routinely performed in the first trimester of life to detect, among other things, presence of congenital malformations and/or genetic disorders. The routine typing of*

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been implemented usually after due governmental processes, including enactment of enabling legislation.

<sup>8</sup> Bloom F.E. (2003) Science as a way of life: perplexities of a physician-scientist. *Science* 300:1680

<sup>9</sup> For the purpose of this paper, genetic testing is defined as the analysis of biological samples in order to detect heritable disease-causing or disease-predisposing conditions. Hence “genetic” applies primarily to the condition or trait that is being tested for, and only secondarily to the biological sample being used.

<sup>10</sup> From a technical point of view, somatic mutations are non-genetic in that they are not heritable, while germ-line mutations, including those arising spontaneously *de novo*, are. However, as many conditions (e.g. cancer) involve an interplay of both types of mutations, testing for either type of mutation can broadly be regarded as genetic.

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*blood group is done on a nation-wide scale, and while there are no disease predispositions associated with blood groups, it is a genetic trait which has implications for the establishment of non-paternity. In fact, in as much as gender being a genetically defined trait, sex determination of foetuses is a form of genetic test.*

Modern gene-based laboratory assays for heritable conditions often serve the same overall purpose as pre-molecular era methods of clinical observation and biochemical assays (i.e. to provide as definitive diagnosis as possible for subsequent intervention by treatment, palliation, lifestyle modification or reproductive counselling). However, these gene-based tests have particular unique characteristics that pose potential and real ethical challenges, for which theoretical concepts and practical solutions need to be sought.

In considering human genetic data as a subset of personal medical information, several ethical principles have been elucidated and are generally widely accepted in western societies. These established principles include the necessity that the individual benefits from the procedure or information obtained (beneficence), the requirement of free and informed consent for obtaining and disclosing personal medical data (autonomy) and respect for the patient's privacy (confidentiality). These principles, also relevant in the conduct of human research, could form the basis from which issues specific to genetic testing could be developed.

Another type of “genetic” test of medical relevance of non-human targets involves the use of human samples<sup>11</sup>. This includes diagnosis of communicable and infectious diseases, where tests seek to determine the presence or quantities of DNA/RNA of pathogens (viruses, bacteria, fungi and parasites). Such gene-based tests are becoming widely used for a variety of infections including those prevalent in the tropics and Asia (e.g. hepatitis B, tuberculosis, malaria and HIV). Issues pertinent to human genetic testing also apply to this group: costs, quality assurance and regulation.

A third category of gene-based tests of relevance to human health are performed on non-human material. These include the testing of food, water and environmental air samples for naturally occurring pathogens or for agents of bioterrorism. Testing of agricultural products (including genetically modified organisms) as well as detection of vectors of disease (e.g. mosquitoes) also have major impacts on human health. Issues such as test quality, patenting, allocation of resources and health disparities are also relevant to this area.

While medical ethics could be a useful framework, particularly at the onset, for the considering ethical, legal and social aspects of genetic testing, the implications of such tests in a wider societal context also eventually need to be looked into. Genetic information on behavioural traits such as personality, or intrinsic traits such as intelligence or ancestral origins such as race and ethnicity do have social and

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<sup>11</sup> These are more appropriately termed “molecular” or “gene-based” tests as the conditions they detect are generally not regarded as heritable, but the methods used could involve “genetics”.

psychological implications to both individual and community. There would be a need to identify issues of relevance to Singapore's communities and institutions (e.g. military/security, education, ethnic/dialect associations, insurance, welfare/disability groups) and to critically predict, analyze and monitor their impact from a multidisciplinary viewpoint. Eventually, this understanding could be translated into appropriate means of communication, education and public policy formulation, tailored to Singapore's unique socio-cultural and economic landscape. The Bioethics Advisory Committee is one example of such an endeavour.

### **Unique Aspects of Genetic Testing**

In considering human genetic testing as a form of a medical *in vitro* diagnostic (IVD) test, there are several features of the genetic sample analyzed, the molecular genetic technology used and the genetic diseases or conditions tested for, which require particular consideration.

#### ***Permanence of Genetic Information***

Most genetic tests seek to determine the genetic status (clinical phenotype, chromosome, genotype, mutation or allele) of an individual, which remains relatively stable throughout the individual's life.<sup>12</sup> Therefore, the duration of impact of a test result could be much longer than other medical tests.

The results of genetic tests conducted before birth, or during infancy and childhood at the request of parents will be available later in life, whether or not the person wishes to know the outcome. This is of particular concern for diseases which manifest only during adulthood, and for which no effective preventive steps could be taken earlier. Examples of these include heritable blindness *retinitis pigmentosa* and the neurodegenerative disease *Huntington's chorea*. In such cases, unless the information is necessary to enable diagnosis of another family member, it is advisable that testing not be performed until the individual is able to make his own informed decision.

Similarly, a current social obligation (e.g. suitability for military service, employment or insurability) motivating the need for a genetic test may be far outlived by the result of the genetic test. Where such genetic tests are of social or medical significance, the individual should retain the ultimate decision in whether to be tested. He/she should not be unduly pressured to be tested, or the confidentiality of its results should be statutorily ensured.

Errors of testing, whether technical or clerical, will also have a long-term impact, and individuals should be aware of this possibility, so that opportunities for review or

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<sup>12</sup> Examples of exceptions include quantifying levels of microbes for prognosis or to monitor anti-infective treatment, quantifying the "take" of a bone marrow transplant, or determining the molecular status of a tumour to assist choice and monitoring of treatment.

retesting are made available. A means of high fidelity, long term storage of the test results and documentation beyond that required medico-legally and which the individual can transfer to subsequent health care providers, would be of benefit. Safeguarding the content, quality and confidentiality of such genetic databases needs to be considered.

### ***Pre-symptomatic and Predictive Testing***

For most single gene disorders there are few environmental factors or other genetic modifiers involved. Hence genetic tests could be highly predictive. Where they are performed routinely in a healthy population as part of a genetic screening program, or offered to healthy individuals who are at risk due to affected family members, this constitutes pre-symptomatic testing.

Pre-symptomatic predictive testing is offered on the premise that there is some benefit, usually medical, that can be derived from knowing early of the likelihood (or not) of developing disease. This may take the form of more intensive screening (e.g. regular colonoscopies for *familial adenomatous polyposis* or FAP carriers), lifestyle changes (e.g. avoiding particular anti-malarial or antibiotic drugs in *G6PD deficient*s) or medical treatment (whether surgical, pharmacological or gene-based therapies).

As the biological functions of many of these disease-causing genes are not yet known, no effective measures can be taken to prevent the onset of some diseases. In these cases, the benefits of testing are largely psychological or social (to allow personal future planning, relief from uncertainty or fulfilment of a patient's wishes). These are important reasons and adequate indications to perform the test. Genetic tests should not be withheld because no effective treatment is currently available. Furthermore, genetic test results would be useful for future gene-based treatments, many undergoing development now. However, there are possible social repercussions such as genetic discrimination or psychological effects of fear, anxiety and depression. Pre-test genetic counselling which is non-directed is particularly necessary for these diseases to avoid misguided expectations on medical intervention, to reduce psychological harm and to inform patients about non-therapeutic choices.<sup>13</sup>

*Huntington's disease is one notable example. Its onset is during the third to fifth decades of life and it is both seriously disabling and progressive. A highly predictive test has been available for the past ten years, and this serves as a model for understanding attitudes about predictive testing. Eighty percent of individuals from families with a history of HD refuse the offer to be tested. They cite as reasons, lack of treatment and fears of insurance discrimination. For those who take the test, there is lessening of anxiety and depression, even among those who tested positive for the disease.*

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<sup>13</sup> Burgess MM. (2001) Beyond consent: ethical and social issues in genetic testing. *Nature Reviews Genetics* 2:147.

The utility of personal genetic information is not as clear for multifactorial diseases, caused by a variable array of interacting genetic and environmental factors.<sup>14</sup> There are multiple genes and alleles that cause risks, some of which are specific to particular populations. A positive test for one allele will only result in a small change in the relative risk, and is of limited clinical usefulness. The validity of these tests and recommended follow-up intervention needs to be established through epidemiological and clinical studies. While such genetic information could direct lifestyle and behavioural modifications such as diet, the limitations of interpreting such tests need to be communicated to the public, especially when such tests are performed outside medical supervision and associated with marketing of health products such as “nutriceuticals” and health supplements.

Hence standards of genetic tests should include not only the accuracy of the test, but where applicable, the validity as it relates to predicting clinical outcome.

### ***Information Affecting Others in the Family and Community***

When the gene is not fully identified or when heritability needs to be established, samples from relatives of the patient may be required to establish a diagnosis. In such instances, the patient is motivated to help obtain samples and consent from these relatives.

Uniquely, a person’s genetic information can also provide, directly or by association, information on other family members, and those who share, or who are perceived to share a common genetic heritage. A person’s test for a mutation can reveal from which parent the mutation was inherited, whether the siblings are likely to inherit it, and whether his/her children could inherit it. Hence harms and benefits are not isolated to the person being tested. Those most affected need to be contacted but this is not always feasible, especially with families that are separated, or when some members insist on their “right not to know”.

The effects of genetic testing could extend beyond the family to whole communities that are small, homogeneous and which share a common genetic heritage. Inbred populations (such as native indigenous people groups) are useful for research in that they allow easier elucidation of risk alleles and genes. There is a potential risk that the entire ethnic group may be stigmatized as being genetically defective. Some form of collective authorization (by leaders or community representatives) in addition to individual consent is usually sought, and some benefits of research are returned to the community.

In fact, individualized ideas about autonomy and informed consent are part of the culture of bioethics in western societies. Resorting to the individual to assess net benefit in the face of ambiguity is a feature of liberal political philosophy. For genetic tests

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<sup>14</sup> International Congress of Genetics Report. (2003) The limits of predictive medicine. *BioMedNet* <http://www.biomednet.com>

where the technical and social issues are complex, it may be inappropriate to place the bulk of responsibility on the individual consumer (“caveat emptor”). There may be other models, such as an obligation on the government, scientific community and commercial producers to share information, decisions and collective responsibility. These may be worthy of consideration in Singapore’s cultural, demographic and historical contexts. Additionally, there may be a spectrum of models needed to account for our pluralistic multicultural background. Social research is needed to explicitly determine what these alternative models are.<sup>15</sup>

### ***Medical Interventions or Lack Thereof***

For most genetic disorders, an effective permanent treatment is the exception rather than the rule. As many of the single gene disorders which are tested for are rare, specific treatments are still undergoing development (such as gene therapy), or is only available in an experimental setting or is costly.

There may be some lifestyle changes that may help in delaying the onset of disease or retarding its progression, but their effectiveness may not have been scientifically established. This is particularly so for complex disorders attributable to a multitude of risk factors that vary between populations, families and individuals. The effect of a single factor (e.g. allele) is likely to be small in most people. However, as these disorders are common and constitute a potentially large consumer market, there is a danger that commercial interests could exploit fears and desires of the public in offering alternative or over-the-counter tests and “therapies” whose efficacy has not been adequately demonstrated. Genetic testing services coupled with dietary supplement products are already being marketed (see below).

For many severe genetic disorders, preventing the birth of an affected baby is the main approach used, through pre-conception counselling and family planning, *in vitro* fertilization and pre-implantation diagnosis, or antenatal testing and abortion of pregnancy. In the settings of pre-implantation and antenatal diagnosis, the clinical procedures are tightly linked to the genetic testing, and hence the ethical considerations cannot be easily separated. The bioethical considerations of genetic testing should therefore be expanded to include the interventions that its results will direct.

*For instance while determining the gender of a foetus can be regarded as a right to personal information and abortion on demand is a legal right in Singapore, aborting a foetus because of its sex is widely regarded as unethical medical practice. The future availability of new non-invasive and low risk methods of antenatal testing (such as using maternal blood or samples) may increase the risk of such abuse. It would be technically feasible to test for cosmetic and behavioural traits such as hair/eye colour in future. There may be a need to review existing legislation on procedures related to genetic testing.*

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<sup>15</sup> Burgess MM. (2001) Beyond consent: ethical and social issues in genetic testing. *Nature Reviews Genetics* 2:147.

Protocols and standards for genetic tests should not target merely the provision of accurate genetic information, but should ensure that it is properly interpreted, often with other non-genetic lab findings or clinical assessments, and followed up by the appropriate intervention.

### ***Rapid Development and Multitude of Tests, Formats and Technologies***

Genetic tests for almost 1000 diseases are currently available<sup>16</sup>. This number is expected to grow rapidly, with the large scale identification of common genetic variants which could account for inter-individual differences in disease susceptibility, innate traits and behaviour, or ancestral background.<sup>17</sup> Genetic tests of the future could involve testing for panels of these variants for a range of traits and disease predispositions. The types and combinations of tests, as well as the reasons for which they are requested will increase.

The technology for analyzing genetic mutations and variants is also varied and is evolving rapidly. Many genetic tests have been developed in research laboratories specifically interested in a particular disease and with specialist expertise, and who offer it on a limited “for research purposes only” status. Consequently, a wide range of in-house instrumentation and “home brews” are used for assays. Many of these are provided to labs as “analyte specific reagents” for which manufacturers have less responsibility to the patient, and such reagents are less tightly regulated than whole kits or services. Current methods (e.g. DNA chips) allow largely automated analysis of large numbers of variants and samples simultaneously. Samples for genetic analysis can now be easily collected (e.g. mouth swabs) and transported by mail, so genetic test service providers are not restricted geographically.

Despite such heterogeneity in assays, technologies and lab settings, there have been some attempts at quality assurance.<sup>18</sup> So far, other countries (e.g. USA, UK) and regions (e.g. Europe) have approached this with voluntary regulation and, to a lesser extent, legislation. A variety of lab accreditation schemes assess the staff expertise, management and operational procedures of labs. Individual genetic assays are evaluated through voluntary participation in performing tests on samples circulated between labs. The types of assays and scope of assessment, however, vary between countries due to differences in diseases/mutations and referral systems.

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<sup>16</sup> Genetic tests for 997 diseases have been listed, of which 644 were offered clinically and 353 were research only. University of Washington (2003) GeneTests website accessed on 31 Jul 03. <http://www.geneclinics.org/>

<sup>17</sup> Single nucleotide polymorphisms (SNP) are a form of variant, common in the genome, differing from individual to individual. They may be responsible for susceptibility or resistance to disease, and also for variation in human traits such as height, skin colour, etc. More than 3 million of such human SNP have been identified.

<sup>18</sup> Dequeker E, Ramsden S, Grody WW, Stenzel TT, Barton DE. (2001) Quality control in molecular genetic testing. *Nature Reviews Genetics* 2:717-23.

It is also increasingly being recognized that ensuring that the lab test is performed accurately is insufficient. Due emphasis is now being placed on how referrals are administratively handled (as clerical mistakes are a major source of error) and, importantly, how the results are interpreted and communicated. Similarly the development process through which a new assay is validated, approved and introduced is important given the large numbers of new tests that will enter the market. As the clinical utility of a test will grow when more test results and outcomes are available, it is also useful to monitor periodically the uptake, cumulative results and experience of genetic tests after they have been introduced (akin to the post-release surveillance for drugs).

With the large numbers of tests made available only recently, it is difficult for non-genetic specialists in the health care professions to keep apace with developments in genetics relevant to their clinical disciplines and the impact of these discoveries on patient management. One survey had shown that many medical practitioners were unable to provide proper genetic counselling or to interpret results correctly.<sup>19</sup> There is a need to propagate an understanding of gene-based medicine to the nursing and medical professions.

### ***Genetic Discrimination - Insurability and Employability***

Discrimination of access to employment and insurance is a real threat of genetic testing, and has been discussed extensively. These aspects are well summarized in the following three paragraphs quoted from the World Health's Organization 2002 report.<sup>20</sup>

Medical Insurance: "Rating health insurance by health risks, whether based on genetic or other factors, has the intended, though from the standpoint of the social purpose of health insurance, perverse effect of making it more difficult, or even impossible, for individuals to obtain health insurance who may need it the most".

Life Insurance: "While individuals who learn that they have a serious genetic health risk should not be deprived of health insurance, they should not be able to amass large amounts of life insurance on the basis of serious health risks of which they, but not their life insurer, are aware."

*In 2000, the UK government permitted the use of genetic test data for insurance purposes, for a single-gene disease for which a highly predictive pre-symptomatic test was available. Policy holders were not required to take the test for Huntington's Disease, but were required to disclose the result if they had been tested before.*<sup>21</sup>

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<sup>19</sup> In a survey of 177 patients tested for the colon cancer gene APC, 32% of physicians misinterpreted the test results. Giardiello FM. (1997) The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *N Engl J Med.* 20;336(12):823-7.

<sup>20</sup> World Health Organization. (2002) Genomics and world health. *Report of the Advisory Committee on Health Research.* [http://www3.who.int/whosis/genomics/genomics\\_report.cfm](http://www3.who.int/whosis/genomics/genomics_report.cfm)

<sup>21</sup> Dickson D. (2000) UK insurers allowed to use genetic tests. *Nature Medicine* 6:1199.

Employment: “Current health problems that would prevent a person from carrying out the duties of employment, even when employers have made reasonable accommodations for illness or disabilities, can justifiably be used in employment decisions. But genetic conditions that constitute risks for future health problems should not be used to bar otherwise qualified people from employment.”

There is an ongoing need to monitor and investigate instances of genetic discrimination involving conditions for which genetic tests are available.<sup>22</sup>

## **Particular Aspects of Relevance to Singapore**

### ***Genetic Diseases, Traits and Environmental Factors***

Not surprisingly, the single-gene disorders prevalent in Singapore differ from those in other non-Asian populations. Thalassaemias, other inherited blood disorders and G6PD deficiency are more common here, while cystic fibrosis, haemophilia and colour blindness are more common in Caucasian populations. The specific mutations involved also differ in frequency between populations and ethnic groups, and there is an added possibility that the same mutation may present different risks due to other modifier genes that are not tested for.

The list of important causes of death in Singapore is generally similar to those in other developed societies, with common complex diseases prevailing: heart disease, strokes, cancers. However, the role of specific genetic factors varies between our Asian populations and those of predominant Caucasian western societies, both in terms of relative contributions and risk genotypes. Furthermore, gene-environment interactions serve to complicate the relationship between genotype and phenotype (disease or trait), making prediction imprecise at this time. For instance, how the body’s ability to handle drugs affects cancer risk is confounded by exposure to dietary factors and smoking. Molecular epidemiological studies and clinical trials need to be performed in our population (or one similar to it) to validate genetic tests for susceptibility to these common diseases.

Susceptibility and immunity to infections is of public health importance here because of, firstly, our geographical location in a tropical region endemic with vectors and animal hosts, and secondly, our exposure to international human traffic, and thirdly, recently heightened risks of urban societies to bioterrorism. The recent Nipah and SARS outbreaks were largely confined to our Malaysia-Singapore and Asia, respectively, while hepatitis B, dengue, malaria and melioidosis continue to be endemic regionally. Such diseases attract proportionately less research and commercial interest than other diseases such as AIDS.

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<sup>22</sup> Otlowski MF, Taylor SD, Barlow-Stewart KK. (2003) Genetic discrimination: too few data. *European J Hum Genet.* 11:1-2.

These population-based differences have several consequences for genetic testing:

- i. There may be less scientific understanding of diseases common here. Clinical and laboratory expertise for these diseases may be more limited. Reagents, standardized protocols or kits may not be available, or at relatively high cost.
- ii. Accreditation and external quality assurance schemes in US and Europe may not cover these tests.<sup>23</sup> The type of mutations tested for could also differ.
- iii. Predictability and clinical utility for these tests may not have been established adequately in the local context.
- iv. Tests for diseases common in Caucasian populations may also not be available here because the low test volumes may not justify setting up of tests.

### ***Provision of Genetic Services***

There is substantial basic genetics/genomics research performed in local institutes, and some genetic services are provided in clinical departments primarily in the restructured hospitals. However, Singapore currently lacks a university or academic department of human genetics, and there are no local training schemes for medical geneticists, genetic counsellors or genetic nurses. The number of experienced or professionally qualified clinical geneticists or clinical scientists is also few. Many labs offering genetic tests are R&D labs with specialist expertise and interests in specific diseases, and have developed a patient/test referral base in the region and beyond. By and large, they are few in number. Overall, it is estimated that a small proportion of all genetic tests are available locally.

In view of the current state of development of medical genetics in Singapore, it is suggested that:

- i. Current levels of manpower training and locally residing expertise prevents sufficient specialization or scope required for provision of high quality genetic services, and therefore need to be improved.
- ii. Some form of quality assurance of tests, labs and services is required both as an impetus to improve standards as well as to ensure good medical care. There are currently insufficient labs and experts to allow a locally developed and administered accreditation system. Standards could be adopted from a variety of overseas accreditation systems of comparable merit, bearing in mind differences in training, diseases and legislation.
- iii. The continued scarcity of local genetic services could drive local patients and referring physicians to use overseas services or could drive foreign

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<sup>23</sup> Guidelines have been developed for most diseases prevalent in Caucasian populations. As an example the most common severe single gene disorder there is cystic fibrosis and many countries including UK, Europe and US have technical guidelines: American College of Medical Geneticists. (2001) Laboratory Standards and Guidelines for Population-based Cystic Fibrosis Carrier Screening *Genetics in Medicine*, March/April 2001 3: 149-154.

companies to market directly to the Singapore consumer. Regulation of access to such offshore services needs to be considered.

*The UK Human Genetics Commission is proposing statutory regulation of genetic tests such that tests for serious illnesses such as Huntington's disease will be available only by "prescription only". Other tests for paternity or genealogy may be less stringently regulated and could be available over the counter.<sup>24</sup>*

### ***Economic Issues***

The Singapore government is involved in a drive to establish a biotechnology and life science industry. While the local market is small, products have a potentially large worldwide market. Hence the local healthcare environment is seen as a possible test bed for validating new ideas and products. From the industry point of view, this environment should be similar to that of the major markets, such as US and European Union. It is useful to homogenize our business and health care environments and regulations with that of the Western economies. The establishment and regulation of ethical and technical standards should therefore not be seen as inhibitory to enterprise.

Outpatient medical costs, including laboratory investigations, are most often directly borne by individuals. As reimbursement for genetic tests is not made by commercial bodies such as medical insurance companies and healthcare management organizations, the consumer lacks the technical competence to decide whether a genetic test/treatment is warranted and whether it is performed satisfactorily. There is therefore a greater need to regulate and oversee the service provider (i.e. either referring physician or genetic laboratory). This can be done through a combination of voluntary self-regulation (peer review, accreditation and quality control by professional bodies) and statutory regulation (governmental certification and licensing).

The role of genetic testing is primarily preventive health – to avoid births of individuals of high genetic risk (through family planning), to prevent or delay development of disease (prophylaxis), or to prevent disease progression or complications. Conventional healthcare providers, particularly commercial enterprises, are therefore seldom motivated to participate in such efforts unless the genetic services are themselves profitable or if products can subsequently be sold (neither of which as we have seen is desirable without careful regulation). It therefore rests with governmental agencies with an interest in promoting overall health to spearhead development of such services or facilitate their growth.

From a public health perspective, ensuring fair and uniform access to genetic services is a means to prevent large disparities in health. The cost of a genetic test needs to be limited to an affordable level, or the means to meet those costs needs to be provided. This applies not only to the genetic test and counselling, but also to therapies and associated social implications such as medical insurance premiums (see below). While

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<sup>24</sup> Mitchell P. (2003) UK to regulate 'serious' genetic tests. *Nature Medicine* 9:250.

a deregulated free market approach to genetic testing could be the best way to bring about cost-effective services, certain aspects such as cost/access, standards and ethics need oversight. It should be apparent that one has little say in what comprises one's own genetic constitution and can therefore hardly be held responsible for the effects of his genes.<sup>25</sup>

One area where the goals of public health and industry appear to have competing goals is the patenting of gene sequences and their assays. The protection of intellectual property is a cornerstone in high technological industries. It has been argued that enforcing the rights of holders and licensees of gene test patents will result in more private sector funds for identifying disease genes, developing assay methods and making them commercially available. However, it has also been shown that patenting delays publication of discoveries, inhibits further research into improved methods or clinical interpretation, and increases overall costs.<sup>26</sup> The refinement of patent requirements for gene sequences to more explicitly include evidence of inventiveness and utility will help prevent restrictive licensing and monopolization of clinical testing services.

### ***Local Attitudes and Knowledge of Genetic Medicine***

Unlike Europe or the USA, Singapore was not exposed to the persuasive arguments of the eugenics movement of the 1920s to 1930s, which were extrapolated by Nazi Germany to justify its genocidal atrocities of the Second World War. The Singaporean population at large is therefore not likely to be aware or conversant with the history and ethical issues relating to testing for genetic diseases and condition. The Abortion Act of 1975 mandates a woman's right for abortion on demand, and a utilitarian approach might best describe public attitudes towards the prevention of congenital abnormalities and serious disease.

This is coupled with a general lack of knowledge or education in the biomedical sciences. Recently the mass media's portrayal of major scientific advances relating to genes, genetics and the human genome have increased awareness of the career and medical opportunities in the life sciences, but not necessarily public knowledge. As genetics is complex subject even in the medical profession, there is potential for misinformation (whether intended or not), for over-expectation and for exploitation. Pre-test genetic counselling and education for the patient becomes all the more important, especially if patients are required to be informed before they give consent for testing. Genetic counsellors will need to explain the reason and results of a test, the options available, and the implications of the results. This has to be performed in

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<sup>25</sup> This is not intended to spark a debate on genetic or biological determinism. There has been excessive misinformation in the media on attributing a genetic basis to many human behaviours and failings. Scientific research has currently little to say on such matters. However the clear role of genetic factors in single-gene disorders is beyond contention. The argument that society should reduce the stakes of "genetic lottery" applies primarily to serious genetic conditions.

<sup>26</sup> Merz JF, Kriss AG, Leonard DGB, Cho MK. (2002) Diagnostic testing fails the test. *Nature* 415:577-579.

various languages, in various social and religious contexts, and at varying educational levels. This therefore makes direct-to-consumer marketing in the absence of face-to-face professional advice hard to justify.

### ***International Availability of Tests***

As the biotechnology sector seeks to productize and realize investments, some tests are being marketed directly to consumers, with or without medical oversight or consultation. Tests for non-disabling and common diseases are particularly being sold by mail, through the media or internet. Advertisements for genetic tests are appearing in the print media.<sup>27</sup> The web in particular presents a global marketplace for healthcare services such as genetic testing that are not equally accessible due to regulations or availability.<sup>28</sup> As genetic testing conveys complex information, does not undergo premarket review, and is of variable clinical utility, direct advertising to the consumer is likely to mis-communicate or even manipulate consumer behaviour.

**Table 2 Some genetic tests marketed direct-to-consumer on the internet<sup>29</sup>**

Country	Name	Website	Tests/Remarks
UK	Sciona	<a href="http://www.sciona.com">http://www.sciona.com</a>	Nutrition, Drug, Alcohol
US	Great Smokies	<a href="http://www.gsdl.com">http://www.gsdl.com</a>	CVS disease, Osteoporosis, Immunity, Detoxification
US	NuGenix, GeneLink	<a href="http://www.bankdna.com">http://www.bankdna.com</a> <a href="http://www.nugenix.com">http://www.nugenix.com</a>	Nutrition, CVS, various
Canada, US	Seryx	<a href="http://www.signaturegenetics.com">http://www.signaturegenetics.com</a>	Drug, Nutrition, Lifestyle
US	DocBlum	<a href="http://www.docbluminc.com">http://www.docbluminc.com</a>	"Reward deficiency syndrome"

That such poorly scrutinized tests of doubtful public health value are easily available has been argued as suggesting the voluntary regulation in countries as the UK is inadequate and that statutory regulation is needed. There is also a wide range of regulatory environments, health care services and genetic testing practices between countries, and homogenization of standards is realistically unlikely.<sup>30</sup>

*The case of a couple, who underwent pre-implantation diagnosis to give birth to a child selected to be tissue-compatible with an older sibling, was widely reported recently.<sup>31</sup> The older sibling was suffering from a rare genetic disease treatable by stem cell therapy. The couple lived in the UK, where such genetic selection was banned, but had their procedure performed in the US.*

<sup>27</sup> Gollust SE, Hull SC, Wilfond BSW. (2002) Limitations of Direct-to-Consumer Advertising for Clinical Genetic Testing. *JAMA*. 288:1762-1767.

<sup>28</sup> Williams-Jones, B. 2003. Where There's a Web, There's a Way: Commercial Genetic Testing and the Internet. *Community Genetics* 6(1) 46-57.

<sup>29</sup> Barrett S, Hall H. (2003) Dubious genetic testing. *Quackwatch website accessed on 30 Jul 03* <http://www.quackwatch.org/01QuackeryRelatedTopics/Tests/genomics.html>  
A longer list compiled in 2000/1 can be found in the preceding reference.

<sup>30</sup> Cox SM, Faucett WA, Chen B, Dequeker E, Boone DJ, McGovern MM, and Lubin IM (2003) International Genetic Testing. *Genetics in Medicine* 5(3):176-182.

<sup>31</sup> BBC. (2003) Designer baby born to UK couple. *BBC News 19 June 2003* <http://news.bbc.co.uk/1/hi/uk/3002610.stm>

Enforceable guidelines and regulations, given the worldwide market of suppliers as well as heterogeneous regulatory environments, are needed.

## **Suggestions and Recommendations**

### ***General***

Human genetic testing is a component of medical diagnosis and treatment. Like other medical technologies, it is a new and sophisticated science in which there are still gaps in knowledge that prevent widespread application. Indeed, many aspects of the mechanisms, diagnosis and treatment for genetic diseases are being scientifically researched or clinically trialled. Understanding of the wider societal and ethical implications lags behind further. The risks of premature or inappropriate use of genetics to both the individual and to community (epitomized by the eugenics movement) are well documented. On the other hand, there are models in related areas of medical ethics and bioethics (such as medical technology, human experimentation) that can be used to frame and discuss issues. There are also existing regulatory frameworks (professional and legislative) that could be extended to include issues surrounding genetic medicine.

However, recent reports on purported human cloning and genetic selection of newborn suggest that some people will not wait for important gaps in scientific knowledge and ethical understanding to be filled. In addition, the involvement of private funding and commercial interests, the general lack of public knowledge and the availability of genetic services across borders will make the problem urgent and difficult to control. There will be, in particular, commercial pressure to move genetics from the laboratory to the shop shelf at a pace that may compromise quality and safety standards, and hence consumer interests.

Ethical, social and policy considerations cannot be divorced from the scientific and technological ones. The provision of safe and responsible genetic testing to the public is ensured as much by control regulations and competent professional training as by locally relevant epidemiological data and psychosocial insights. Therefore a range of suggestions are listed below:

### ***Local Research and Data***

- There are some aspects of genetic testing unique to Singapore's local population, health care setting and socio-cultural context, for which information is needed. While some emphasis and resources are being committed to scientific research, scholarly consideration of the larger ethical and social issues is lacking.
- Research is needed in these areas, among others:
  - Laboratory analysis of mutations/polymorphisms prevalent in local population
  - Molecular epidemiology of genetic variants in Asian populations, environmental interactions and disease outcomes

- Clinical trials to establish clinical utility and incorporate genetic tests into clinical guidelines of practice
  - Health economic and policy analysis of preventive genetic testing, community genetic services, commercial providers
  - Cost-benefit analysis of specific genetic tests for population screening and high risk individuals
  - Psychological and sociological research – attitudes towards heritable diseases, healthcare costs and regulation of medical care
  - Genetic determinants of ethnicity and race, and of other traits ascribed to racial differences
- There are insufficient local scientists and academics addressing the above issues. A network of local researchers in universities, research institutes, and think-tanks should be formed, facilitated by funding of good quality research projects of local relevance and opportunities at local conferences/meetings hosted to discuss these. This could take the form of a professional society for human genetics, as it does in many other countries.
  - The establishment of a human genetics department with clinical, academic and research roles will help provide a nucleus for future multidisciplinary analyses and applications of genetics. Institutions currently involved in genetics research (e.g. GIS, NUS), teaching (e.g. NUS) and clinical services (e.g. hospitals) could benefit from such synergy and cross-fertilization.
  - The field of genetic testing is dynamic, not only due to advancing technology but also evolving public perceptions and professional attitudes. There is a need for ongoing research to monitor, for instance, uptake and performance of genetic tests once they have been introduced, psychological outcomes of those tested, and newer technologies.

### ***Professional Training and Public Education***

- The field of human genetics is expanding at such a rapid pace that new specialisation is required, including those in clinical genetics, genetic counselling and clinical science laboratorians. Training schemes need to be developed and professional recognition needs to be accorded.
- As healthcare professionals are the interface between patient and genetics service providers, undergraduate, specialist and continuing medical education in the genetic sciences need to keep up with scientific developments applicable to their field. The role of informing and educating patients, their families and patient support/interest groups will fall on the wider scope of healthcare professionals and not just those in genetic departments.
- There is a realization that involving the public early on in discussing ethical and social implications is important in framing relevant and effective strategies to incorporate genetics and biotechnology into daily life. The public understanding

of genetic medicine needs to be developed beyond current mass media depictions of popular science (which are often superficial or misleading). While the life sciences are already being introduced at various levels of the education system, adults with or planning to have families need to be targeted. Preventive genetics will form part of primary health care and therefore could be provided as basic health education.

### ***Genetic Counselling***

- The provision of information in a clear and non-directed manner will enable a patient to decide whether and when to undergo a genetic test, and also how to deal with the results and implications. This will help him and his healthcarers to gain the maximum benefit from genetics. Genetic counselling is particularly important in Singapore where there educational levels, languages and cultures vary widely. The genetic counsellor will require an understanding of patient attitudes and the skills of communicating risks and science. His/her role will expand when genetic tests for common preventable conditions become available.<sup>32</sup>
- There is an urgent need to train more doctors, nurses and counsellors in genetics, to provide the referral and follow-up base of genetic testing. The setting up of one or more genetics departments in Singapore will help provide career advancements and training for a corps of genetics specialists.

### ***Regulation and Legislation***

- A combination of voluntary and statutory regulations is needed. The former is useful in the early stages of development of the field, as principles, issues and solutions are defined. Eventually however, with commercialization, consumerization and globalization of genetic testing, clear and effective legislation will be essential.
- Professional guidelines and quality standards, and accreditation are useful at this initial stage of development. These should cover:
  - Accreditation of professional qualifications, training and experience
  - External quality assurance of genetic tests
  - Clinical practice guidelines for genetic testing and interpretation
  - Standards of ethical conduct of genetics research and practice
  - Consumer interests – ombudsman for over-the-counter testing, consumer evaluations and comparisons
  - Clear and explicit delineation of out of boundary markers for improper use of genetics and testing, such as reproductive human cloning, genetic

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<sup>32</sup> Biesecker BB, Marteau TM. (1999) The future of genetic counselling: an international perspective. *Nature Genetics* 22:133-7.

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selection and enhancement of traits and permanently heritable (germline) genetic modifications.

- Local professional bodies should be encouraged to play this role, as they have the expertise to best perform functions of peer review and over-the-horizon assessment. They are also the ones primarily involved in educating and informing scientists, clinicians and nurses. These include the academy of medicine and its specialist chapters (e.g. Chapter of Pathologists), professional societies (e.g. Biomedical Research & Experimental Therapeutics Society of Singapore) and regulatory organs (e.g. Singapore Medical Council).
- Legislation is required in several areas (especially where there are significant commercial interests) that cannot be voluntarily regulated effectively. Clear and prescriptive regulation will help commercial development and provision of tests that pose little potential harm, and ensure the safety and quality of genetic tests and counselling for severe diseases. These areas require:
  - Overall regulation of genetic testing for non-research purposes, including tests, services and reagents/kits. A categorization scheme similar to that of pharmaceutical products could be explored, based on severity and impact of genetic condition (e.g. over-the-counter *vs* prescription-only *vs* restricted use). Different degrees of scrutiny would apply to these classes.<sup>33</sup>
  - Ethical advertisement and labelling of such direct-to-consumer tests (e.g. paternity testing) to prevent inaccuracy or lack of information, or manipulation of fear or distress.<sup>34</sup>
  - Accreditation and licensing of laboratories offering genetic services
  - Confidentiality of genetic information and data protection, including the requirement for informed consent for obtaining a sample or testing it
  - Appropriate and fair use of genetic information by insurers and employers to prevent genetic discrimination
- Prospective legislation controlling genetic testing would need to be harmonized with existing laws on abortion and reproduction, and on racial harmony, and other proposed regulations, such as that on human reproductive cloning.

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<sup>33</sup> There are however fundamental differences between pharmaceutical products and genetic testing services. In the latter, the pretest counselling, interpretation and follow-up intervention are particularly important for optimum benefit to the individual.

<sup>34</sup> This may be covered under general codes of advertising, such as: UK Advertising Standards Authority (2003) *The British Code of Advertising, Sales Promotion and Direct Marketing 4 Mar 2003*. [http://www.asa.org.uk/the\\_codes/index.asp](http://www.asa.org.uk/the_codes/index.asp)

## **Final Comments**

The potential impact of genomics and life sciences on the future of our economy and personal health is widely recognized. It would be negligent not to seize the opportunities that science and technology offer to explore new services and products for biomedicine and beyond. At the same time, there is a need to appreciate and an attempt to predict the wider implications of genetics, now primarily diagnostics, in our families and communities. Some of the ethical, legal, social and policy aspects have been raised and briefly discussed in the framework of established bioethical principles of autonomy, beneficence and informed consent.

It is my opinion that scientific and ethical oversight of research, development and trials of genetic testing in Singapore is largely adequate, and here the main challenges are to extend the pool of experts and expertise in healthcare, and to widen the scope of genetics research to include social and community aspects. However, considering the rapid development and globalized nature of genetic sciences, the provision of commercial genetic testing services potentially presents a challenge to current policies and frameworks of regulation. This area needs urgent and regular monitoring. Ongoing developments in the science and industry of genetic testing and evolving perceptions will require that this topic is revisited and public discussion warranted.

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