

# GENETIC TESTING AND GENETIC RESEARCH

A REPORT BY  
THE BIOETHICS ADVISORY COMMITTEE  
SINGAPORE

November 2005

## **FOREWORD**

Recent scientific advances in human genetics have greatly increased our understanding of genes and their role in maintaining health and causing disease. The application of this knowledge has led to the development of new and better techniques of diagnosing and treating diseases. Presently, a wide range of genetic tests is available clinically and research into developing novel tests for various diseases is taking place worldwide.

Owing to the sensitive and predictive nature of genetic information derived from genetic testing and the impact it can have on the individual and the family, it is important that such testing be conducted responsibly and ethically. As genetic testing is often an integral part of human genetic research, the BAC has considered the issues from both clinical and research perspectives.

The Human Genetics Subcommittee started considering ethical, legal and social issues of genetic testing and genetic research about two years ago. The recommendations in this Report were made after examining policies and guidelines from various international and national ethics and professional bodies, and after considering the views of international and local experts, as well as those of professional, religious and civic groups and members of the public. The BAC is much indebted to the various parties and individuals who participated in the three-month long public consultation process, which began in early April this year, as well as to the international and local experts who have contributed their views and comments.

It is hoped that these recommendations, which have been accepted by the Life Sciences Steering Committee, would not only provide ethical guidance to clinicians and researchers when carrying out genetic testing and genetic research, but also a useful reference for ethics committees reviewing such research.

I would like to thank members of the Human Genetics Subcommittee, chaired by Associate Professor Terry Kaan, for their dedication and commitment in the preparation of this Report.

Professor Lim Pin  
Chairman  
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### **About the Bioethics Advisory Committee**

*The Bioethics Advisory Committee (BAC) was established by the Singapore Cabinet in December 2000. The BAC was directed to “examine the legal, ethical and social issues arising from research on human biology and behaviour and its applications” and to “develop and recommend policies ... on legal, ethical and social issues, with the aim to protect the rights and welfare of individuals, while allowing the Life Sciences to develop and realise their full potential for the benefit of mankind.”*

*The BAC reports to the Life Sciences Steering Committee (formerly Life Sciences Ministerial Committee).*

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## LIST OF ABBREVIATIONS

AHEC	Australian Health Ethics Committee
ALRC	Australian Law Reform Commission
BAC	Bioethics Advisory Committee (Singapore)
CAP	College of American Pathologists
DNA	Deoxyribonucleic acid
ESHG	European Society of Human Genetics
ESHRE	European Society of Human Reproduction and Embryology
HFEA	Human Fertilisation and Embryology Authority (UK)
HGC	Human Genetics Commission (UK)
HGS	Human Genetics Subcommittee (BAC)
HGSA	Human Genetics Society of Australasia
IRB	Institutional Review Board
IVF	<i>In vitro</i> fertilisation
MOH	Ministry of Health (Singapore)
NHMRC	National Health and Medical Research Council (Australia)
NMEC	National Medical Ethics Committee (Singapore)
PGD	Preimplantation genetic diagnosis
PGS	Preimplantation genetic screening
PNGD	Prenatal genetic diagnosis
PTT	Preimplantation tissue typing
RNA	Ribonucleic acid
SAC	Singapore Accreditation Council
SINGLAS	Singapore Laboratory Accreditation Scheme
WHO	World Health Organisation

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# GENETIC TESTING AND GENETIC RESEARCH

## EXECUTIVE SUMMARY

### **Introduction**

1. As part of its remit to examine and recommend on issues arising from research in biomedical sciences in Singapore, the Bioethics Advisory Committee (BAC) has prepared this report on genetic testing and genetic research.
2. Genetic testing is often an integral part of human genetic research. Our intention is to provide a broad treatment of the subject, taking into account the current status of genetic testing and ethical principles observed in major jurisdictions.
3. Issues of confidentiality of test results, counselling and the conduct of research arise in consequence. Accordingly, this report considers:
  - (a) genetic testing for the detection of specific heritable genetic conditions or susceptibilities;
  - (b) the genetic information thereby derived; and
  - (c) human genetic research.
4. Issues relating to third party use of genetic information, such as by insurers or from linked medical registries, are far reaching and important. They will be addressed in more detail in a future report. We have also not considered genetic

- testing for forensic purposes or solely as a means to ascertain parentage or kinship, and research that involves only history taking such as in the construction of family trees where direct genetic testing is not performed.
5. Issues of consent for research have already been mentioned in our IRB Guidelines Report.<sup>1</sup> In the present report, these issues are elaborated as they apply to human genetic research.
  6. Genetic tests are a valuable aid to diagnosis and prevention of genetic disorders, but the conduct of such tests and the use of the information they yield are of concern. Test results may affect aspects of life, such as the job or marriage prospects of the individual tested, may have repercussions for family members who are genetically related, and may also impact family members, such as spouses, who are not genetically related.
  7. In preparing the report, the BAC examined policies and guidelines from various international and national ethics and professional bodies. The views of the National Medical Ethics Committee (NMEC) were sought, and considered. Views and comments from the public and 30 professional, religious and civic groups were also considered, in addition to the views of our international advisors. The BAC is grateful for all these inputs.
  8. Part I introduces the report. Parts II and III are concerned with definitions of genetic testing and genetic information respectively. Part IV, the main part of the report, considers general and specific ethical issues in genetic testing. Part V considers the direct supply of genetic tests to the public. Part VI deals with human genetic research.

### **Genetic Testing**

9. Genetic testing is the analysis of human DNA, RNA, genes and/or chromosomes, or the analysis of human proteins or certain metabolites, with the primary purpose of detecting a heritable genotype, mutation, phenotype or karyotype.
10. Genetic testing can be for research or for clinical purposes. Research genetic testing is done when the primary aim is to generate new information or test a research hypothesis. There are over 800 laboratory-based genetic tests already available for clinical use.
11. Clinical genetic testing subsumes the following:
  - (a) Confirmatory diagnosis for specific genetic disorders;
  - (b) Carrier testing for recessive disorders;

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<sup>1</sup> BAC, *Research Involving Human Subjects: Guidelines for IRBs* (November 2004).

- (c) Preimplantation genetic testing on embryos created by *in vitro* fertilisation (IVF), for the purpose of selecting or excluding embryos for implantation into the uterus;
  - (d) Prenatal genetic diagnosis (PNGD) to identify a specific genetic disorder in a foetus;
  - (e) Predictive testing of asymptomatic individuals; and
  - (f) Genetic screening of healthy individuals.
12. This report highlights concerns that can arise from the predictive and sensitive nature of genetic information deliberately obtained from genetic testing. Genetic information may be uncovered in the course of standard clinical tests for diagnosis or treatment and the conduct of such clinical tests should be in accordance with accepted medical guidelines. In the clinical context, our recommendations relating to consent and counselling for genetic testing do not apply, except when analysis of human DNA, RNA, genes and/or chromosomes is involved.

### **Genetic Information**

13. The nature of genetic information, as determined in the major jurisdictions, is reviewed. The most distinctive feature of genetic information is its predictive power for individuals and for their close relatives. It has to be interpreted with care as it is generally probabilistic in nature. In consequence, clinical genetic testing has been done in Singapore through registered physicians, who bear ultimate responsibility with regard to the use of tests and the interpretation of their results.

### **General Ethical Considerations in Genetic Testing**

14. When conducting genetic testing, it is important to observe the welfare, safety, religious and cultural perspectives and traditions of individuals.
15. The principle of informed consent should apply to genetic testing as with other medical procedures. For consent to be informed, the individual will need to be given appropriate counselling.
16. It is possible to conduct genetic testing on tissue samples obtained through deception or taken without the consent of the individual, and the resulting information could be used in ways that are not in the interests of the person tested. We are of the view that the non-consensual or deceitful taking of human tissues for the purpose of genetic testing should be prohibited.

17. Vulnerable persons require special safeguards. We consider three categories of vulnerable person:
  - (a) children and adolescents;
  - (b) the mentally impaired; and
  - (c) other persons in dependent relationships.
18. In the case of children and adolescents, legal issues regarding consent and the management of their best interests arise. Subject to limitations in law, we are of the view that if a child or adolescent is capable of understanding the purpose and implication of genetic testing, they may be regarded as mature enough to give the necessary consent.
19. We are of the view that carrier testing of children should generally be deferred till the child is sufficiently mature, or until he or she has to make reproductive decisions. We recognise exceptions in certain cases where it may benefit family members, or may reflect public policy in the eradication of diseases. We do not encourage predictive testing on children unless there are preventive measures available in childhood.
20. Additional safeguards are appropriate for persons lacking the mental competence to decide on genetic testing. In clinical testing, the best interest of the person tested is the important consideration, qualified only by the possibility that an imperative need may exist for the confirmatory diagnosis of genetic disease in related family members. The legal guardian in such cases is the appropriate person to give consent.
21. For persons in dependent situations (such as prisoners or students) it is especially important to ensure that consent is given freely, and in particular, that no benefits currently provided or in prospect would be jeopardised by a refusal.
22. Healthcare professionals and researchers have an obligation to protect the confidentiality of genetic information. Genetic test results should therefore not be released without consent to third parties.
23. In the event that nondisclosure of the test result may endanger the life of a third party, however, we concur with the NMEC's position that a physician's duty of confidentiality may be overridden if certain conditions are met.
24. Generally, individuals would want to know the results of genetic tests taken by them or their genetic relatives. However, there may be cases where the individual does not wish to know if he or she is at risk of a genetic disorder or to share this information with family members. Notwithstanding this, the individual's wish should be respected, but with appropriate counselling.

### **Specific Ethical Considerations in Genetic Testing**

25. The report reviews ethical concerns arising from the use of specific types of genetic testing.
26. Preimplantation genetic diagnosis (PGD) is of value in allowing an option for some couples to conceive a child without certain genetic diseases, because candidate embryos obtained by IVF can be tested and only unaffected embryos implanted. However, it is ethically debatable.
27. The ethical issues raised by preimplantation genetic testing include religious concerns about the sanctity of life and assisted reproductive technologies generally. There are also wider concerns about whether such testing could in principle be used to select favourable traits, rather than just the exclusion of genetic diseases. In addition, it is an expensive and therefore restricted technology. This raises equity issues of public concern.
28. As the experience of other jurisdictions suggests that effective regulation is possible, preimplantation genetic testing should be allowed to prevent the transmission of a serious disease in genetically at-risk couples to the next generation. We are further of the view that a provision for conscientious objection should be included in the regulatory framework.
29. We do not think preimplantation genetic testing should be allowed for purposes of eugenic enhancement, even if feasible, nor to accommodate individual parents who might actually prefer an affected embryo (for example, to have a deaf child) for reasons of family compatibility. It seems to us that children should not be born having to meet expectations derived from decisions made by parents about desired genetic makeup.
30. We are of the view that sex selection for non-medical reasons is generally unacceptable, as it may promote or reinforce gender stereotyping and discrimination. It may also promote gender imbalance in the population structure, which in turn may have undesirable social implications.
31. Preimplantation tissue typing (PTT) can be used in combination with PGD to allow couples to have a healthy child who is also immunogenetically compatible, as a potential stem cell donor, to a sick sibling. While this does raise an ethical issue of whether a child should to this extent be created as a means to an end, we give some weight to the argument that parents willing to go to such lengths are unlikely to deny equal affection to a child conceived by way of PTT. We therefore think that with appropriate regulation, such cases may be allowed.
32. Germline genetic modification is a type of gene technology, currently still in experimental stage, which involves the alteration of a person's genetic makeup in a manner that is permanent and can be transmitted to his or her offspring. As

- such, its effects in future are incalculable, and we do not think it should be allowed in clinical practice at this time.
33. Routine prenatal care may include PNGD. Couples can be counselled on the basis of results and helped to make a decision as to whether or not to continue the pregnancy, if appropriate.
  34. For reasons as given in paragraphs 29 and 30, we do not think that PNGD should be employed for trait or gender selection without medical justification.
  35. Predictive genetic testing identifies healthy individuals who have inherited a gene or genes for a late-onset disease, that is, a disease that normally becomes symptomatic only in adulthood.
  36. The predictive information may be almost certain, as in late-onset dominant diseases such as Huntington's disease; more commonly it may reflect an increased risk but not a certainty, as in cases where there are interactions of multiple genes and environmental factors. Alzheimer's disease, diabetes, and certain cancers and heart diseases fall into this latter category.
  37. Predictive genetic information can be burdensome or traumatic, given the uncertainties of the risk, and this reinforces the need for voluntary informed consent and counselling pre- and post-test.
  38. Genetic screening involves tests offered to healthy individuals with an increased risk of developing a particular genetic condition. It aims to prevent a disease or minimise morbidity and mortality through early diagnosis and treatment. In genetic screening programmes, a confirmatory diagnostic test should be performed as soon as possible after a positive screening test, so as to minimise unnecessary anxiety or to enable measures for the prevention or treatment of the condition to be instituted without delay.

### **Quality Control Issues in Clinical Genetic Testing**

39. The welfare of tested individuals depends on the integrity of the diagnostic process and the test methodology. These aspects should be carefully monitored, keeping in mind the increasing tendency for direct approaches to be made by clients to laboratories, or for tests to be available directly to the public, bypassing medical practitioners, as in internet-based services.

### **Genetic Counselling**

40. Genetic counselling is needed to achieve two objectives:
  - (a) to provide sufficient and unbiased information to enable full and informed choices to be exercised; and

- (b) to provide appropriate support to the patient and his or her family members.
- 41. Counselling should be provided in a timely manner by appropriately qualified healthcare professionals. It should be done in a manner appropriate to the needs and comprehension of the patient, in a face-to-face meeting wherever possible. Counselling requires an empathic manner and should generally be non-directive in character, though with regard to possible legitimate third-party interest in the patient's genetic information.
- 42. It may not be practicable for genetic counselling to be restricted to physicians. Others such as medical geneticists or nurses may be involved, even though the clinical responsibility for a case rests ultimately with the physician in charge.

### **Direct Supply of Genetic Tests to the Public**

- 43. The commercialisation of genetic testing kits and services direct to the public increases access to genetic tests without a medical consultation. This situation is causing concern in a number of countries. This concern is mainly focussed on the twin problems of potential misinformation and risk of testing without consent. We share this concern and recommend steps, as far as practicable, to ensure that genetic testing is done by qualified healthcare professionals, and to limit the availability of tests that provide predictive health information directly to the public.

### **Ethical Considerations in Human Genetic Research**

- 44. A general ethical framework for human biomedical research has been set out in our previous reports, and the comments here respect this framework.
- 45. All research participation must be voluntary and informed, and researchers must obtain consent from potential research participants, with suitable allowance in the case of vulnerable or dependent populations. The information given to potential participants must include the nature of any risks, whether or not any genetic information derived from the study will be disclosed to them if requested, and the procedures for protection, anonymisation, or disposal of information or biological materials on withdrawal from or completion of the research.
- 46. Human genetic research is not conducted with the aim of providing research participants with specific information about their genetic status or health. However, if there is a possibility that the research may yield individual data of clinical significance, the research participant should be informed of this possibility and whether he or she would receive such information if so desired, prior to participation in the research.

47. Researchers have an obligation to protect the privacy of research participants and their family members, and to ensure confidentiality of all genetic information derived from the research, including information about the participant's relatives, who may not be part of the research project.
48. Research considerations should not compromise or prejudice the clinical purpose of genetic testing where such testing is also providing information for research.
48. All human genetic research requires the approval of a research ethics committee or an institutional review board and in addition, if the research involves human embryos for reproductive purposes, written approval from the Ministry of Health.



## LIST OF RECOMMENDATIONS

### *Genetic Information*

#### **Recommendation 1:**

Genetic information derived from clinical genetic testing should be regarded as medical information and the usual standards in medical ethics apply in its derivation, management and use.

### *General Ethical Considerations*

#### **Recommendation 2:**

Genetic testing should be conducted in a manner that is respectful of the welfare, safety, religious and cultural perspectives and traditions of individuals.

#### **Recommendation 3:**

Genetic testing should be voluntary. The individual should be given sufficient time and information to ensure informed consent before testing. Consent should also be obtained for the future use of tissue specimens.

#### **Recommendation 4:**

The non-consensual or deceitful taking of human tissues for the purpose of genetic testing should be prohibited.

### *Genetic Testing of Vulnerable Persons*

#### **Recommendation 5:**

We do not recommend the broad use of genetic testing on children and adolescents. Confirmatory testing and predictive testing for genetic conditions where preventive intervention or treatment is available and beneficial in childhood are recommended. Carrier testing should generally be deferred until the child is mature or when required to make reproductive decisions, but where compelling interests of other family members or public health interests exist, the physician should be able to decide, together with the parents, whether or not to determine the carrier status of the child. Predictive testing where there is no preventive intervention or treatment, or where intervention or treatment is only available and beneficial during adulthood, should be discouraged.

#### **Recommendation 6:**

Clinical genetic testing involving vulnerable persons should only be conducted if it is medically beneficial to the vulnerable persons and after informed consent has been obtained. In the case of persons in dependent relationships, extra care should be taken to ensure that such persons clearly understand that refusal to consent will not prejudice any current or prospective benefit.

### *Confidentiality and Privacy*

#### **Recommendation 7:**

Results from clinical genetic testing should only be used to advantage or empower an individual or family and for the management or prevention of disease. Such information should not be disclosed to third parties without the informed consent of the individual unless in exceptional circumstances when the information is required to avert serious harm.

#### **Recommendation 8:**

An individual should be informed of the result of a clinical genetic test without undue delay unless he or she has clearly indicated a wish not to know.

### *Preimplantation Genetic Testing*

#### **Recommendation 9:**

Preimplantation genetic screening and diagnosis are permissible, subject to licensing and monitoring by a relevant authority and should be limited to preventing serious genetic conditions. Provision should also be made so that no one shall be under any duty to be involved in preimplantation genetic testing to which he or she has a conscientious objection.

#### **Recommendation 10:**

The use of preimplantation genetic testing for the selection of desired traits or gender for non-medical reasons should not be allowed.

#### **Recommendation 11:**

Preimplantation tissue typing, whether as the sole objective or in conjunction with preimplantation genetic diagnosis to avoid a serious genetic disorder, is permissible but should be licensed and evaluated on a case-by-case basis.

### *Germline Genetic Modification*

#### **Recommendation 12:**

The clinical practice of germline genetic modification should not be allowed at this time.

### *Prenatal Genetic Diagnosis*

#### **Recommendation 13:**

Prenatal genetic diagnosis should be limited to serious medical disorders. The use of prenatal genetic diagnosis for the selection of desired traits or gender for non-medical reasons should not be allowed.

### *Predictive Testing*

#### **Recommendation 14:**

Presymptomatic testing should be available for adults at risk who request it, even in the absence of treatment, after proper counselling and informed consent.

#### **Recommendation 15:**

Susceptibility testing should not be applied clinically unless there is significant empirical evidence of validity and utility.

### *Genetic Screening*

#### **Recommendation 16:**

In genetic screening programmes, a confirmatory diagnostic test should be performed as soon as possible after a positive screening test, so as to minimise unnecessary anxiety or to enable measures for the prevention or treatment of the condition to be instituted without delay.

### *Standards of Genetic Test Providers*

#### **Recommendation 17:**

All laboratories conducting clinical genetic tests should be accredited by a body designated by the relevant authority, based on standards it considers appropriate.

### *Results Interpretation*

#### **Recommendation 18:**

Interpretation of clinical genetic test results should only be performed by healthcare professionals who are appropriately qualified or have sufficient experience. As far as is practicable, genetic counselling should immediately follow the disclosure of the test result, particularly if the test result is not favourable.

### *Genetic Counselling*

#### **Recommendation 19:**

Genetic counselling should be offered to all individuals before and after they undergo clinical genetic testing.

#### **Recommendation 20:**

Genetic counselling should generally be conducted in a non-directive manner and should provide sufficient information and appropriate support to the individual and his or her family members.

*Professional Diversification and Development*

**Recommendation 21:**

The relevant authority should provide professional training and accreditation in medical genetics and counselling to healthcare professionals.

*Direct Supply of Genetic Tests to the Public*

**Recommendation 22:**

Genetic testing should generally be conducted through a qualified healthcare professional. Tests that provide predictive health information should not be offered directly to the public. The advertising of direct genetic tests to the public should be strongly discouraged. The relevant authority should develop an oversight framework for the supply of genetic tests, services and information direct to the public.

## **GENETIC TESTING AND GENETIC RESEARCH**

### **I. Introduction**

- 1.1 Human welfare can be elevated through the responsible development and application of biomedical science. One such application arises from advances in mapping the human genome. Such mapping has contributed to a better understanding of the role of genetics in many common diseases such as cancer, heart diseases and diabetes. This has in turn fuelled the hope that new and more effective means of diagnosis and treatment of diseases may be developed through the increasing application of gene technology in medicine. Currently, this principally entails the development and use of genetic tests. New treatments and gene therapy may become more prominent in future.
- 1.2 Genetic tests can help in the diagnosis, prevention and treatment of serious genetic disorders but they also present ethical, legal and social concerns to individuals and society. These issues are varied and complex, with long-term ramifications. Many countries and international organisations are beginning to attend to these issues, some of which may have imminent ethical, legal or social impact.
- 1.3 The demand for genetic information in the healthcare and health-related sectors of many scientifically advanced countries has been rising steadily and has in turn fuelled the application of genetic testing for a diverse range of diseases. Consequently, more than 800 different genetic tests may now be conducted by clinical and research laboratories.
- 1.4 Genetic information derived from genetic testing may disclose far greater details about an individual's health than medical information derived from a doctor's medical examination and interview alone. It provides information that has broader implications extending to genetically related family members, spouses, and future generations. Occasionally, unexpected or potentially sensitive information may be revealed, for instance, information about parentage or about the likelihood that an apparently healthy individual may develop a serious genetic condition later in life. The result of a genetic test, especially one that is positive for a serious genetic disorder for which there is no treatment, may have significant psychological impact on an individual and possibly on his or her family.<sup>2</sup> Due to the shared nature of genes and the predictive nature of genetic information, family members and third parties such

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<sup>2</sup> For the purposes of this report, the terms "family" or "family members" can refer not only to persons who are genetically related to the individual concerned but also to those whom the individual regards as family members in the broader sense of the family as a social unit. The context will make clear when genetic relatedness is the relevant concern.

as insurers and employers may have an interest in a person's genetic information, and there is a need to ensure that genetic testing is conducted with due consideration and protection of the individual's interests and rights.

## Objectives

- 1.5 This report is prepared with the following objectives:
- (a) to consider the ethical, legal and social issues arising from the conduct of genetic testing and research; and
  - (b) to provide guidance for the ethical conduct of genetic testing and research.

## Scope

- 1.6 In this report, we focus on three main aspects of human genetics:
- (a) genetic testing for the detection of specific heritable genetic conditions and susceptibilities;
  - (b) the quality of genetic information thereby derived; and
  - (c) research in human genetics.
- 1.7 The use of genetic testing and genetic information can have social and economic implications. As genetic information may be misinterpreted or misused, it carries the potential of causing harm if suitable measures of information control are lacking. In this report, we provide broad ethical guidelines for the derivation and use of genetic information derived from genetic tests.
- 1.8 This report does not cover in detail the ethical, legal and social issues relating to third party access of personal genetic information, such as access by insurers or employers and similar issues relating to the use of genetic information from linked medical registries and genetic databases for research purposes. Such issues are manifold and likely to have long-term implications for all levels of society. We intend to address these issues in a future report.
- 1.9 Ethical issues arising from genetic testing in Singapore were considered by the National Medical Ethics Committee (NMEC)<sup>3</sup> in its *Ethical Guidelines for Gene Technology* (NMEC Gene Technology Guidelines) published in February 2001. The Guidelines defined "gene technology" as "the use of techniques for

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<sup>3</sup> The NMEC was established in January 1994 to assist the Ministry of Health (MOH) in addressing ethical issues in medical practice and to ensure a high standard of ethical practice in Singapore.

the analysis and/or manipulation of DNA (deoxyribonucleic acid), RNA (ribonucleic acid) and/or chromosomes”<sup>4</sup> and focussed on gene technology in the context of medical practice and doctor-patient relationship.

- 1.10 In this report, we build on some of the NMEC Gene Technology Guidelines, and provide specific recommendations relating to the ethical conduct of genetic testing, the quality of clinical genetic tests and the interpretation of test results. We have placed particular emphasis on the importance of sound and effective counselling, which we regard as indispensable to the ethical conduct of clinical genetic testing. Genetic testing is often an integral part of human genetic research, for which we also set out the ethical considerations.
- 1.11 The recommendations in this report were made after examination of the policies and guidelines from various international and national ethics and professional bodies, and consideration of views from our international advisors and local experts and public feedback on a Consultation Paper entitled *Ethical, Legal and Social Issues in Genetic Testing and Genetics Research*. Position papers written by these local experts are at Annex C and the Consultation Paper prepared by the Human Genetics Subcommittee, is at Annex D. The Consultation Paper was publicly released on 5 April 2005 and 107 healthcare and governmental institutions, including the NMEC, and professional, religious and patient support organisations, were invited to provide comments. A list of these organisations is provided in Annex E. Thirty-one written responses were received and are set out in Annex F. In addition, the BAC held dialogue sessions with religious representatives and healthcare professionals to gain in-depth understanding of any concerns related to the issues discussed and the recommendations made in the Consultation Paper. To facilitate further discussion and to obtain views from members of the general public, 14 focus group discussions were conducted over the period of 14 May to 9 July 2005. Reports on the dialogue sessions and focus group discussions are provided in Annex G.

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<sup>4</sup> NMEC, *Ethical Guidelines for Gene Technology* (2001), Section 1.1.

## II. Genetic Testing

- 2.1 Genetic testing is the analysis of human DNA, RNA, genes and/or chromosomes, or the analysis of human proteins or certain metabolites, with the primary purpose of detecting a heritable genotype, mutation, phenotype or karyotype.
- 2.2 In the clinical context of patient care, our recommendations for counselling and consent are intended only for genetic tests entailing the analysis of DNA, RNA, genes and/or chromosomes. In this context where genetic tests entail the analysis of human proteins and metabolites, only the requirements of established medical ethics apply. We discuss issues related to counselling and consent in greater detail in Part IV.
- 2.3 Though many human diseases have a genetic basis in the sense that they are caused by mutations (alterations) in genes, most such mutations or alterations are not capable of being passed on to the next generation, and so affect only the patient. Such mutations are known as somatic mutations. In contrast, other mutations can be transmitted to the next and subsequent generations, so that a child may inherit a mutation from a parent. This kind of heritable mutation is known as a germline mutation.<sup>5</sup> We therefore restrict our definition to those tests involving germline mutations that define heritable conditions. Tests for somatic mutations that carry no implication of heritability are excluded.
- 2.4 Clinical genetic testing is the use of validated genetic tests for purposes which may include but are not limited to the following:
- (a) *Confirmatory diagnosis* performed to confirm the diagnosis of a specific genetic disorder in an individual who already has signs or symptoms of that disorder. A positive test result identifies the genetic basis of the disorder;
  - (b) *Carrier testing* for recessive disorders conducted to identify individuals with a genetic or chromosomal abnormality that generally does not

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<sup>5</sup> Many human diseases involve alterations in genes. If these genes only affect somatic cells, they are called somatic mutations and they are not heritable. Somatic DNA/tissue analysis from tumor specimens examines the genetic changes in the tumor that occur during the conversion to cancer. Amplification of HER-2/neu in breast cancers and the BCR-ABL gene translocation, also in breast cancers, are examples of somatic genetic alterations profoundly affecting the behaviour of the tumor, and which are used in standard diagnostics, but which are not inherited. This information does not have implications for heredity and therefore is limited to the patient and his/her condition. By contrast, mutations that affect the sperm and eggs of individuals can be passed on to subsequent generations and are called germline mutations, for example, in Huntington's disease, thalassaemia, or haemophilia. Mutations in BRCA1 associated with susceptibility to breast and ovarian cancers are further examples of germline aberrations. Germline DNA analysis has potential impact not only in predicting the future health of the individual, but also that of his or her relatives.



affect the person's health but puts him or her at higher risk of having a child with a specific genetic disorder;

- (c) *Preimplantation genetic testing* conducted on early embryos created by *in vitro* fertilisation (IVF), to determine the presence or absence of one or more genetic conditions, or a certain immunogenetic make-up, before selecting a suitable embryo for implantation into the uterus;
- (d) *Prenatal genetic diagnosis (PNGD)* conducted on a foetus or a pregnant woman so as to identify a specific genetic disorder;
- (e) *Predictive testing* conducted on asymptomatic individuals to determine if they are at risk of developing a genetic disorder in the future; and
- (f) *Genetic screening* conducted on healthy individuals to determine their status with regards to a specific genetic disorder.

2.5 Genetic testing can also be done for other purposes such as:

- (a) Identity testing or forensic testing, e.g. to exclude or identify a suspect in a crime, to search for missing persons or to identify deceased persons; and
- (b) Parentage or kinship testing, e.g. to determine if two persons are biologically related to each other.

The use of genetic testing for these two purposes will not be covered in this report.

2.6 Research genetic testing is the use of genetic tests with the primary aim of generating new information or to test a research hypothesis. It is a clearly circumscribed activity which should take place within a framework for the regulation of research involving human subjects. This would include scrutiny of the ethical aspects of the proposed research by an institutional review board (IRB) and monitoring of approved projects for compliance with ethical requirements. Information from genetic testing in research is research data, which although subject to strict rules of confidentiality, should not be included as part of the subject's medical record. An earlier BAC report entitled *Research Involving Human Subjects*<sup>6</sup> covers the fundamentals of ethical requirements for all biomedical research; their application to genetic research is discussed in Part VI of this report.

2.7 In the case of clinical genetic testing, the situation is less clear cut. Patients or members of the public may consult a physician for a specific medical complaint. In the course of the consultation, diagnostic investigations which do not entail

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<sup>6</sup> BAC, *Research Involving Human Subjects: Guidelines for IRBs* (November 2004).

the analysis of the patients' DNA, RNA, genes or chromosomes, may nonetheless detect disorders which have a genetic basis. The biochemical investigation of anaemia, for example, could lead to a diagnosis of thalassaemia, a genetically inherited disorder. In such situations, we are of the view that the biochemical testing is covered by the standard and usual medical consent procedures for diagnostic tests assuming the patient has sought a consultation. But if, for example, the physician decides to further include a genetic test to determine a particular mutation for thalassaemia, specific consent would be required. Physicians and healthcare institutions are bound by medical confidentiality, and the disclosure of such information to third parties not involved in the patient's healthcare, would generally require the patient's consent.

- 2.8 In routine public health screening procedures, such as for neonates or other defined populations, the relevant public institutions have given consideration to the societal impact of early detection of such genetic disorders. However, the usual confidentiality obligations will apply to the genetic information thereby derived.
- 2.9 We emphasise that there are situations, even within the patient-physician relationship, where specific informed consent for clinical genetic testing would be essential. These situations include:
- (a) the analysis of patients' DNA, RNA, genes or chromosomes to detect a specific heritable disease or condition, particularly if the disease is likely to be serious and without effective medical treatment, e.g. Huntington's disease; or
  - (b) genetic testing to follow up findings uncovered in the course of standard clinical procedures for diagnosis or treatment.
- 2.10 In any event, there are legitimate concerns when managing genetic information from genetic tests, because of its perceived sensitivity. Clinical tests (other than genetic tests, and whether or not directed at somatic genetic mutations) may also reveal sensitive genetic information about the patient, such as information about paternity or about the presence of a heritable genetic condition. Physicians and researchers should be aware of these perceived or actual sensitivities in managing such information.
- 2.11 In sum, the intention of this report is to highlight concerns that can arise from the peculiar predictive nature of heritable personal genetic information obtained from genetic testing. These concerns arise when the acquisition of genetic information is the primary purpose, whether in research or in clinical practice, and should be taken into account in the management of research participants or patients. Genetic information may be uncovered in the course of standard clinical tests for diagnosis or treatment and the conduct of such clinical tests

should be in accordance with accepted medical guidelines. In the clinical context, our recommendations relating to consent and counselling for genetic testing are not intended to apply, except when analysis of human DNA, RNA, genes and/or chromosomes is involved.

### III. Genetic Information

- 3.1 Genetic information broadly refers to any information about the genetic makeup of an individual. It can be derived from genetic testing as defined in paragraph 2.1 in either clinical or research settings or from any other sources, including details of an individual's family history of genetic diseases. This report is concerned with information about heritable conditions obtained by genetic tests, whether it is for clinical purposes or for research.
- 3.2 The practice of genetic testing in Singapore has largely addressed medical concerns. Hence, genetic testing is generally conducted through a physician and in the context of a physician-patient relationship. Genetic test results, or the genetic information that is derived from such clinical genetic testing, are thus filed together with the medical record of the patient. Generally, the law and medical ethics require that medical records be treated as strictly confidential. Information provided or derived during the course of patient management should only be used for the treatment of the patient concerned unless important public interest (such as an immediate or imminent danger to the life of a third party) requires its disclosure regardless of the consent of the patient. As such, genetic information from clinical genetic tests is treated as a part of the patient's medical record and enjoys corresponding confidentiality.
- 3.3 The ethical and legal status of genetic information relative to other medical information is perceived differently by various authorities and ethics bodies. On the one hand, the US Task Force on Genetic Testing<sup>7</sup> and the European Commission's Expert Group on the ethical, legal and social implications of genetic testing have argued that both genetic information and other medical information should be accorded the highest level of ethical and legal safeguards.<sup>8</sup> On the other hand, certain characteristics of genetic information require that it be set apart from medical information in some circumstances. Some of these distinctive features have been articulated by the UK Human Genetics Commission (HGC) and the joint proposal of the Australian Law Reform Commission (ALRC) and the Australian Health Ethics Committee (AHEC) of the Australian National Health and Medical Research Council (NHMRC).
- 3.4 In its report *Inside Information: Balancing interests in the use of personal genetic data* (2002), the HGC identifies four overlapping categories of personal genetic information. These are observable genetic information (such as eye colour), private (or non-observable) genetic information (such as carrier status

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<sup>7</sup> US Task Force on Genetic Testing, *Promoting Safe and Effective Genetic Testing in the United States* (1997). The Task Force was established by the National Institutes of Health-Department of Energy Joint Working Group on the Ethical, Legal and Social Implications of Human Genome Research.

<sup>8</sup> European Commission Expert Group, *Ethical, legal and social aspects of genetic testing: research, development and clinical applications* (May 2004), pages 46-47.

for a genetic condition, for example thalassaemia), sensitive genetic information and non-sensitive genetic information. The HGC observed that it is the predictive feature and significance for individuals and their family members, future reproductive choices and subsequent generations that render genetic information sensitive in the healthcare context. It further sets out the following features of personal genetic information that distinguish it from other forms of information:

- (a) It is almost uniquely identifying and capable of confirming, denying or revealing family relationships;
- (b) It may be obtained from a very small amount of material, possibly without consent of the person;
- (c) It has predictive power, predicting heritable disorders that develop later in life;
- (d) It may be used for purposes other than those for which it was originally collected;
- (e) It may be of interest to others, including relatives who may be affected, insurers and employers;
- (f) It may be important for establishing both susceptibility to rare inherited disease and the likely effectiveness of some treatments; and
- (g) It can be derived from DNA recovered from stored specimens or even archaeological material after many years.

3.5 The ALRC and the AHEC adopted a similar analysis and crystallised these features of genetic information into essentially three unique characteristics in their report *Essentially Yours: The Protection of Human Genetic Information in Australia* (2003):

- (a) It is ubiquitous in its availability from tissues (such as hair or fingernail) usable for genetic testing by sundry parties;
- (b) It is important not only to the individual but also to the individual's family due to the possible hereditary implications; and
- (c) It is predictive of the individual's future health.

While the ALRC and the AHEC stopped short of categorising genetic information as distinct from medical information, they did propose that a commensurate level of legal protection may be required where there is a likelihood of special threat to privacy or discrimination. On this subject, both

the Council of Europe<sup>9</sup> and the Bioethics Committee of Japan's Council for Science and Technology<sup>10</sup> have stated similar positions.

- 3.6 The most distinctive feature of genetic information is perhaps its predictive power. We note that other information such as a smoking habit, which is related to the carcinogenic effect of tobacco and exposure to certain toxic substances, also provides predictive health information. Nevertheless, potential difficulty in the use of genetic information may arise if the limitations on the certainty of prediction are not recognised and accurately conveyed to the recipient. Some conditions, such as Huntington's disease, are virtually certain to occur within the normal average lifetime if the disease gene is present. For many other diseases, however, genetic mutations only confer an increased likelihood of developing the condition. Even when it is virtually certain that a disease will occur, the age of onset and the severity of the condition is unpredictable. Unless the limits of certainty are carefully explained and understood, the burden of uncertainty of the economic and social implications that may be imposed on the carrier or the carrier's family may be unnecessarily heavy.
- 3.7 The current practice of clinical genetic testing in Singapore is through physicians qualified to practise under the Medical Registration Act. Such a "physician-based" system is also found in many leading jurisdictions. Under such a system, it is incumbent on physicians and other healthcare professionals working with or under the supervision of physicians to ensure that the conduct of genetic testing is in line with the ethics of clinical practice. In any case, the physician in charge of the patient has ultimate responsibility with regard to the use of a test and the interpretation of the test result.
- 3.8 Given the current practice of clinical genetic testing in Singapore, and the current use of genetic information derived from it, we are of the view that genetic information should not be treated differently from medical information. In saying this, we refer to genetic information as accessed and managed by or under a physician for a healthcare or health-related purpose.

**Recommendation 1: Genetic information derived from clinical genetic testing should be regarded as medical information and the usual standards in medical ethics apply in its derivation, management and use.**

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<sup>9</sup> Council of Europe, *Recommendation No. R(92)3 on Genetic Testing and Screening for Health Care Purposes* (1992), Part III.

<sup>10</sup> Bioethics Committee, Council for Science and Technology (Japan), *Fundamental Principles of Research on the Human Genome* (2000), Principle 11.

## IV. Ethical Considerations in Genetic Testing

### Section A: General Ethical Considerations

- 4.1 As with many other types of technology, genetic testing not only presents healthcare benefits, but also possible harms if misused. In the conduct of genetic testing, the following ethical principles articulated in our earlier reports should continue to apply:
- (a) respect for the welfare, safety, religious and cultural perspectives and traditions of individuals;
  - (b) informed consent;
  - (c) respect for vulnerable persons; and
  - (d) privacy and confidentiality.

#### *Respect for Welfare, Safety, Religious and Cultural Perspectives and Traditions*

- 4.2 In a multi-cultural and multi-religious society, researchers and healthcare professionals must be sensitive to the religious and cultural perspectives and traditions of individuals. For instance, certain cultures may be particularly sensitive to the presence of a hereditary disorder in a member of the family. Any communication of this nature, in the context of genetic counselling or disclosure of genetic test results, should be carefully managed. Similarly, in selecting a group to be screened, it is important to avoid stigmatisation of the entire group.
- 4.3 In both clinical and research settings, the health, welfare and safety of individuals undergoing genetic testing should be of paramount consideration. When genetic testing is conducted primarily for a clinical purpose, research considerations should not compromise or prejudice this purpose.

**Recommendation 2: Genetic testing should be conducted in a manner that is respectful of the welfare, safety, religious and cultural perspectives and traditions of individuals.**

#### *Informed Consent*

- 4.4 A requirement of informed consent for genetic testing arises from the broader societal value of respect for persons. It is generally accepted that the individual is free to decide whether to undergo any genetic testing, regardless of whether done in the context of screening, diagnosis or research. When the tissue samples provided for clinical use are intended also for research, informed consent for the

research is required in addition to the consent for taking the tissue for clinical use. Consent is also required if there is an intention to store the tissue for future use.

- 4.5 Consent is effective only if the person giving the consent is aware of the circumstances, conditions and consequences for which it was given. How an individual may be appropriately informed prior to giving consent to testing depends on the person, the situation in which consent is sought and the level of communication between the parties. In addition, the individual should be given sufficient time to understand the information provided and to decide whether or not to undergo genetic testing.
- 4.6 The individual should be given appropriate genetic counselling and informed about the nature of the test and risks of the procedure (if any) before giving consent. Pre-test counselling is thus intrinsic to the process of consent-taking. We discuss genetic counselling for clinical testing in Section D.

**Recommendation 3: Genetic testing should be voluntary. The individual should be given sufficient time and information to ensure informed consent before testing. Consent should also be obtained for the future use of tissue specimens.**

- 4.7 Obtaining consent and maintaining confidentiality are fundamental tenets of trust in the physician-patient relationship. They are also fundamental to the conduct of research. Third parties, however, may have a vested interest in knowing the genetic status of an individual, owing to the predictive power and hereditary nature of genetic information. It is easy to think of ways in which tissues can be taken from individuals without their knowledge, let alone their consent. The use of genetic information derived from tissues obtained without proper consent may result in harm not only to the individual, but possibly to his or her family members. We are strongly against the taking of an individual's tissues without consent or by deceit. We note the HGC's recommendation that "consideration be given to the creation of a criminal offence of the non-consensual or deceitful obtaining and/or analysis of personal genetic information for non-medical purposes."<sup>11</sup> This recommendation has since been accepted by the UK legislature and was enacted as law in November 2004.<sup>12</sup> We regard it as timely for Singapore to consider similar action.

**Recommendation 4: The non-consensual or deceitful taking of human tissues for the purpose of genetic testing should be prohibited.**

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<sup>11</sup> UK HGC, *Inside Information: Balancing interests in the use of personal genetic data* (2002), paragraph 3.60.

<sup>12</sup> *Human Tissue Act 2004*, Section 45.



### ***Respect for Vulnerable Persons***

- 4.8 There are certain categories of persons who are particularly vulnerable to circumstances that can compromise their volition and safety when undergoing genetic testing. Special procedures ought to be in place to safeguard their welfare. We consider three categories of vulnerable person in particular: children and adolescents, the mentally impaired and other persons in dependent relationships.

#### *Children and Adolescents*

- 4.9 Genetic testing of children and adolescents raises a number of difficult ethical and legal issues. Children and adolescents are dependent on their parents and guardians for survival and are limited in their ability to protect their own interests. As a result, it is generally recognised that persons responsible for the care of children or adolescents should only act in the best interest of the latter.
- 4.10 We appreciate that “best interest” is dependent on the specific circumstances and conditions of a child or adolescent. Physicians should always consider, together with the parents or legal guardians, the best interests of the child or adolescent and any possible harm before recommending genetic testing. In this regard, we note the recommendation of the European Society of Human Genetics (ESHG), that diagnostic genetic testing be permitted where it is necessary for the child’s or the adolescent’s own health, or where the information would be imperative to diagnose the existence of genetic disease in family members.<sup>13</sup> Similar recommendations have been made by the Council of Europe<sup>14</sup> and the UK HGC.<sup>15</sup>
- 4.11 Genetic testing is recommended in cases where preventive intervention or treatment is available and beneficial in childhood or adolescence. However, the informed consent of the parent or legal guardian of the child or adolescent should be obtained. In addition, the child or adolescent should be involved in the consent process as comprehensively as possible.
- 4.12 The ability of a child or an adolescent to comprehend the purpose and implications of genetic testing will differ from one child or adolescent to another. Therefore, the extent of involvement of a child or adolescent should be considered on a case-by-case basis, through the process of genetic counselling. An older child or adolescent who is sufficiently mature, should be involved in the consent process and his or her wish to undergo or to refuse a test should be respected. In Singapore, the law concerning the age at which a child is to be

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<sup>13</sup> ESHG, Provision of Genetic Services in Europe: Current Practices and Issues, *European Journal of Human Genetics*, Volume 11, Supplement 2, S2-S4, Recommendation 14 (2003).

<sup>14</sup> Council of Europe, *Recommendation No. R(92)3 on Genetic Testing and Screening for Health Care Purposes* (1992).

<sup>15</sup> HGC, *Inside Information: Balancing interests in the use of personal genetic data* (2002).

regarded as having the capacity to make medical decisions for himself or herself follows the English common law principles. However, as these principles have not been tested or expressly adopted by the Singapore courts, we think that clarifying legislation may be helpful in this context.<sup>16</sup> From an ethical perspective, we recommend that the capacity of a child or an adolescent to participate in the consent process be assessed according to his or her level of maturity rather than some arbitrary age.

- 4.13 We recognise that as a matter of principle, carrier testing in asymptomatic children should generally be deferred until the child is mature or required to make reproductive decisions. This is because to do otherwise is to risk pre-empting a later decision by the child, when adult, not to know his or her own genetic status or have it made known to others (paragraph 4.21 refers). However, the defence of this right must be weighed against the interests of other family members, the proper medical care of whom may depend on full and accurate information about a genetic condition in the family, as well as the wider public health interests of a given community. In Singapore, genetic screening programmes for at-risk groups aimed at lowering the incidence of lethal or disabling genetic conditions common in the local population, such as thalassaemia, are widely supported by both the medical profession and the public. Considerable success has been achieved over the years in reducing the incidence of affected children, born to parents who would not have been aware that they carried the risk, had they not been tested when children themselves. Where compelling interests of other family members or public health interests exist, we are of the view that the physician should be able to decide, together with the parents, whether or not to determine the carrier status of the child. In cases where the child shows symptoms, confirmatory testing is in any case appropriate.
- 4.14 Great caution has to be observed in predictive testing of children where there is no available preventive intervention or treatment, or where the intervention or treatment is only available during adulthood. It is generally discouraged because of potential harms that can arise. The potential harms include family and community stigmatisation, discrimination and adverse psychological reactions. Such predictive testing of children is best deferred until adulthood when they can make their own decisions.

**Recommendation 5: We do not recommend the broad use of genetic testing on children and adolescents. Confirmatory testing and predictive testing for genetic conditions where preventive intervention or treatment is available and beneficial in childhood are recommended. Carrier testing should generally be deferred until the child is mature or when required to make reproductive decisions, but where compelling interests of other family members or public health interests exist, the**

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<sup>16</sup> See Singapore Academy of Law, *Civil Inquiries into Mental Incapacity: The Report of the Sub-Committee of the Law Reform Committee of the Singapore Academy of Law for the Review of Proceedings under the Mental Disorders and Treatment Act (Cap 178) (1999)*.

**physician should be able to decide, together with the parents, whether or not to determine the carrier status of the child. Predictive testing where there is no preventive intervention or treatment, or where intervention or treatment is only available and beneficial during adulthood, should be discouraged.**

*The Mentally Impaired*

- 4.15 Additional safeguards should also be considered to protect the best interests of persons lacking the competence to agree to genetic testing. The ESHG identifies such persons as those suffering from mental disorders and adults placed under limited guardianship. Clinical genetic testing should only be permitted where it is necessary for their own health or where the information would be imperative to diagnose the existence of genetic disease in family members.<sup>17</sup>
- 4.16 In Singapore, the High Court has the power to appoint a legal guardian who may provide consent on behalf of a person lacking mental competence where it is appropriate to do so.<sup>18</sup> We also note the recommendation in the NMEC Gene Technology Guidelines that, in the case of an individual 21 years or older but mentally incapable of making a decision, a parent or guardian may consent on his or her behalf. In the main, we are of the view that genetic testing should not be conducted on a person who is mentally impaired unless consent has been obtained from a person who is legally authorised to decide on behalf of the mentally impaired.<sup>19</sup>

*Persons in Dependent Relationships*

- 4.17 Persons in dependent relationships require special consideration in the consent process. For example, prisoners who have been incarcerated may be under duress or some form of undue influence to give consent to those with authority over them, or they may hold some perception, which may or may not be real, that they have 'no choice' but to consent. Similarly, students or employees may be under duress or feel that they are under duress to agree to genetic testing. This category of dependent persons further includes poorly educated individuals, who are unable to fully understand what they are consenting to (due to language barriers for instance).
- 4.18 In cases of dependent relationships, it is important to ensure that consent is both informed and genuine. The Nuffield Council on Bioethics stated that special care is necessary when seeking consent from prisoners, student volunteers and individuals who do not speak English.<sup>20</sup> Similarly, the Human Genetics Society

<sup>17</sup> ESHG, Provision of Genetic Services in Europe: Current Practices and Issues, *European Journal of Human Genetics*, Volume 11, Supplement 2, S2-S4, Recommendation 14 (2003).

<sup>18</sup> *Supreme Court of Judicature Act (Cap 322)*, Section 17(e).

<sup>19</sup> Singapore Academy of Law, *Civil Inquiries into Mental Incapacity: The Report of the Sub-Committee of the Law Reform Committee of the Singapore Academy of Law for the Review of Proceedings under the Mental Disorders and Treatment Act (Cap 178)* (1999).

<sup>20</sup> Nuffield Council on Bioethics, *Genetic Screening: Ethical Issues* (1993), paragraph 4.27.

of Australasia (HGSA) stated that it would be unacceptable for those in positions of power to engage in actions that either coerce individuals into taking genetic tests or inhibit individuals from taking them for fear of social or economic disadvantage.<sup>21</sup> We agree with these statements. Where there are reasons to believe that a person agrees to genetic testing for fear of losing healthcare benefits, this misconception should be corrected. One way to do this is to expressly indicate when obtaining consent that however a person decides, no healthcare, employment, welfare, or other benefits that are currently provided or in prospect, will be jeopardised.

**Recommendation 6: Clinical genetic testing involving vulnerable persons should only be conducted if it is medically beneficial to the vulnerable persons and after informed consent has been obtained. In the case of persons in dependent relationships, extra care should be taken to ensure that such persons clearly understand that refusal to consent will not prejudice any current or prospective benefit.**

#### *Confidentiality and Privacy*

- 4.19 Healthcare professionals and researchers alike have an obligation to protect the confidentiality of genetic information. Article 7 of the 1997 *Universal Declaration on the Human Genome and Human Rights* of the United Nations Educational, Scientific and Cultural Organisation, states that: “Genetic data associated with an identifiable person and stored or processed for the purposes of research or any other purpose must be held confidential in the conditions set by law.” The WHO has similarly commented on the need for confidentiality and on the importance of ensuring that genetic data is only used to advantage and empower an individual or family, and for better treatment or prevention of disease.<sup>22</sup> We agree with these opinions. We further agree with the position of the HGC that: “Private genetic information should generally not be obtained, held or communicated without the free and informed consent of the individual.”<sup>23</sup>
- 4.20 We are of the view that genetic test results should not be disclosed to third parties without the informed consent of the individual. Individuals should be told how their privacy will be protected, before they consent to genetic testing.
- 4.21 Certain individuals may be unwilling to share or divulge their genetic test results with family members, other healthcare professionals or researchers. A difficult situation may arise when an individual refuses to disclose a test result which may be medically beneficial to a genetic relative, such as a high risk of

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<sup>21</sup> HGSA Policies, *Predictive Genetic Testing and Insurance* (1999).

<sup>22</sup> WHO, *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetics Services* (1998), Executive Summary.

<sup>23</sup> HGC, *Inside Information: Balancing interests in the use of personal genetic data* (2002), page 42.

developing colon cancer. The genetic relative could adopt preventive health measures if he or she knew the test result. However, disregarding the wish of the patient would contravene confidentiality and breach the requirement of informed consent to disclose the test result to a third party. Generally, an individual's request for the confidentiality of his or her test result to be maintained should be respected, and the test result should not be disclosed without the individual's consent. It is nevertheless important that healthcare professionals point out clearly the important positive and negative consequences of not disclosing the test result, although the final decision must rest with the tested individual in most cases.

4.22 There may be exceptional circumstances when genetic information may be disclosed despite the individual's right to confidentiality. A situation may arise where harm to a third person could be averted if the relevant genetic information is disclosed. There is therefore a need to balance the risks of breaching confidentiality against the risks of non-disclosure. In this connection, we note and agree with NMEC's position<sup>24</sup> whereby a physician's ethical duty of confidentiality to a patient can be overridden if the following conditions are satisfied concurrently:

- “(a) Separate efforts by two physicians to elicit voluntary consent to disclosure have failed, despite the patient or client fully understanding the implications of such refusal;
- (b) there is a high probability both that harm will occur to identifiable individuals or society at large if the information is withheld and that the disclosed information can actually be used to avert harm;
- (c) the harm that identifiable individuals (if any) would suffer would be serious; and
- (d) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed.”

4.23 In the event that the above conditions are met, the patient concerned should be made aware that such a disclosure would take place and that only relevant information would be disclosed to individuals or entities that need to know in order to avert serious harm. A judgement of seriousness evidently has to be made by the physician in the light of the circumstances of the case.

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<sup>24</sup> NMEC, *Ethical Guidelines for Gene Technology*, Section 2.4.1. A similar position was recommended by the US President's Commission for the Study of Ethical Problems in Medicine and Medical and Behavioral Research (1983) and supported by the WHO (1998), the American Society of Human Genetics (1998) and the Institute of Medicine (1994).

**Recommendation 7: Results from clinical genetic testing should only be used to advantage or empower an individual or family and for the management or prevention of disease. Such information should not be disclosed to third parties without the informed consent of the individual unless in exceptional circumstances when the information is required to avert serious harm.**

*The Right Not To Know*

- 4.24 Generally, individuals would be interested to know the results of genetic tests that they have taken or the results of tests taken by their genetic relatives. Unless an individual has clearly indicated a wish not to know his or her genetic status after a test has been performed, and to address the individual's anxiety, the test result should be disclosed to the individual without undue delay.
- 4.25 However, there may be situations where an individual does not wish to know the test results of his or her genetic relatives or even his or her own genetic status and hence, decides not to take any genetic test. There may also be situations where an individual changes his or her mind about knowing the test result after the test has been conducted. In such situations, the individual's wish not to know should be respected.
- 4.26 An individual tested positive for a predisposition to developing a specific genetic condition has to decide whether this risk should be disclosed to other family members who may also be at risk of developing the same condition. The individual may be additionally burdened with considerations for the family members who may or may not be affected by the condition and their wish to know or not to know. Family members who are not affected by the genetic condition may nevertheless be affected psychologically (such as the condition of "survivor guilt"). In view of these considerations, we emphasise the importance of pre- and post-test genetic counselling.

**Recommendation 8: An individual should be informed of the result of a clinical genetic test without undue delay unless he or she has clearly indicated a wish not to know.**

**Section B: Specific Ethical Considerations**

- 4.27 Clinical genetic testing is usually carried out as part of the health management or treatment of an individual. Hence, the ethical management of such clinical genetic testing should not differ significantly from that of conventional medical service. We note and agree with the NMEC that the "introduction of a genetic test into routine clinical use must be based on evidence that the gene(s) being examined is associated with the disease in question, that the test itself has analytical and clinical validity, and that the test results will be useful to the

people being tested.”<sup>25</sup> In this section, we discuss ethical issues related to specific types of validated genetic tests.

### ***Carrier Testing***

- 4.28 Carrier testing identifies an individual who carries a genetic abnormality that generally does not affect the person’s health but puts him or her at a higher risk of having a child with a specific serious genetic disorder. Individuals who are identified as a carrier of a disorder such as thalassaemia or muscular dystrophy, can then be counselled about these risks and the options available to them when making reproductive decisions.
- 4.29 We emphasise the importance of genetic counselling both prior to and after the test. Proper counselling can prevent confusion over the difference between being an asymptomatic carrier for a genetic disorder and being affected with the disorder. Furthermore, the risk of stigmatisation, discrimination and adverse psychological reactions may also be minimised. Genetic counselling is considered in Section D below and issues concerning carrier testing in children have been discussed in paragraph 4.13.

### ***Preimplantation Genetic Testing***

- 4.30 Preimplantation genetic testing is the testing of early embryos created by IVF before they are implanted into the uterus. Preimplantation genetic diagnosis (PGD) is a procedure whereby early embryos created by IVF are evaluated to determine the presence or absence of one or more genetic conditions, of which the embryos are at risk due to a known family history. Unaffected embryos are then selected and implanted into the uterus. PGD was developed following the availability of IVF and new genetic testing techniques, primarily to help couples at risk of having a child with a genetic disorder have healthy children. Before this procedure was developed, PNGD and selective termination of an affected pregnancy were used to enable couples at risk to have healthy children. With PGD, these couples now have the option of starting out with unaffected pregnancies, thus avoiding the need to consider selective termination of an affected pregnancy subsequently.
- 4.31 Preimplantation genetic screening (PGS) differs from PGD in that the genetic tests are performed on embryos from patients who are considered to have a higher than average risk of conceiving abnormal embryos. These patients may have unexplained recurrent miscarriages or are in advanced maternal age. Unlike PGD, the tested embryos do not have a known family history of a specific genetic condition.
- 4.32 Preimplantation tissue typing (PTT) is a procedure whereby early embryos created by IVF are tested to determine if they have the same immunogenetic

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<sup>25</sup> NMEC, *Ethical Guidelines for Gene Technology*, Section 3.1.1.

status as an existing sick sibling. It can be performed with the sole objective of providing cord blood or bone marrow to a sick sibling with a compatible immunogenetic status, or in conjunction with PGD to avoid the risk of a serious genetic condition in a child.

*Preimplantation Genetic Screening and Diagnosis*

- 4.33 Since 1992, when PGD was successfully applied to avoid a specific genetic defect leading to cystic fibrosis, many clinics throughout the world have begun offering preimplantation genetic testing services. At present such testing can be used to screen for more than 100 genetic conditions, such as Down's syndrome, sickle-cell anaemia, thalassaemia and Huntington's disease. It has been estimated that about 2,000 embryo-screened babies have been born throughout the world.
- 4.34 Although preimplantation genetic testing is currently not available in Singapore as a clinical service, it is available in more than 100 clinics in many other countries including the US, the UK, Belgium, Australia, India, Israel, Japan and South Korea. In Cyprus and Greece, PNGD and PGD have been applied for the prevention of haemoglobin disorders and the number of children born with  $\beta$ -thalassaemia major has since been drastically reduced.
- 4.35 Preimplantation genetic testing can be used by fertile couples as well as those with fertility problems. It has been most commonly recommended for patients:
- (a) who have a child confirmed to have a genetic disease and with an increased risk of having another child with the same disease;
  - (b) of confirmed carrier status (in one or both partners) for a serious genetic condition; or
  - (c) of advanced maternal age.
- 4.36 Preimplantation genetic testing is a technically demanding procedure. While it presents an option for some couples to conceive a child without a specific genetic disease, its effectiveness is limited and success rates, in terms of "take home" babies, are not high. Current PGD pregnancy rates are estimated at about 20%, which is similar to the rates for IVF alone. Although there are some concerns relating to the safety and long-term health consequences of PGD, there have been no reports of increased foetal malformations or other identifiable problems arising from pregnancies involving PGD-tested embryos. A recent study of the past 12 years of data from the world's three largest PGD centres, comprising 4,748 PGD attempts and 754 successful pregnancies, led to the conclusion that PGD is safe.<sup>26</sup>

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<sup>26</sup> Verlinsky Y *et al*, Over a Decade of Experience with Preimplantation Genetic Diagnosis: A Multicenter Report, *Fertility and Sterility*, Volume 82, Issue 2, pages 292-294 (August 2004).



- 4.37 The possible compromise of the sanctity of life represented in an embryo touches one of the central moral and religious concerns of these assisted reproductive technologies. Other ethical concerns relate to the possible use of PGD for trait selection and the implied danger of leading society closer to positive eugenics. It is feared that PGD may be used to select certain desired traits (for example, intelligence, colour of hair, sports ability or musical talent) for the “enhancement” of children, which thereby devalue and alter the way in which society views those who do not possess the desirable traits. Ethical concerns regarding the use of PGD for trait selection is aggravated by the prospect that, even if such use becomes widely and ethically acceptable, only the rich can afford to have offspring with the desirable traits in view of the high cost of PGD. As a result, society could be further stratified into the economically rich and genetically desirable in the top layer, and the economically poor and genetically unaltered at the bottom.
- 4.38 We acknowledge these concerns and attempt to address them by drawing on the two broad guiding principles of ‘justness’ and ‘sustainability’, which were adopted in our Human Stem Cell Report.<sup>27</sup> In the first principle of ‘justness’ is the obligation to respect the common good and the fair sharing of social costs and benefits. The second principle of ‘sustainability’ reflects an obligation to respect the needs of generations yet unborn. Together, these two principles are compatible with the concepts of beneficence and non-maleficence. They encourage the pursuit of social benefits alongside efforts to avoid or ameliorate potential harm.
- 4.39 The UK is one of a few countries that have resolved the ethical debate in relation to human embryo research. The establishment of the Human Fertilisation and Embryology Authority (HFEA) under the Human Fertilisation and Embryology Act of 1990 (the 1990 Act) is a result of several years of discussion and deliberation on this subject. The HFEA licenses and monitors IVF clinics and the creation and handling of human embryos for research. At the time the 1990 Act was passed, PGD was only an experimental procedure. By the turn of this century, PGD has become an acceptable method employed to avoid the births of children with genetic disorders.
- 4.40 From the experiences of countries where preimplantation genetic testing is practised, there are indications that this technology is helpful in addressing the reproductive needs of couples who have a known family history of a genetic disorder, are carriers of a genetic disorder, or have unexplained infertility. For instance, doctors in the US have recently succeeded in using PGD to enable a woman to bear a child free of the gene mutation linked to an early-onset Alzheimer’s disease that she carries. The presence of this gene mutation in an individual confers an almost 100% probability of manifesting symptoms of the disease by the age of 40 years. The experiences of countries that allow the

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<sup>27</sup> BAC, *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning* (June 2002), Chapter 7, paragraph 3.

practice of preimplantation genetic testing also suggest that it is possible to guard against serious violations of moral and ethical standards through careful and effective regulation.

- 4.41 As preimplantation genetic testing is a special form of genetic testing connected with IVF, it should be viewed as a technology to help “at-risk” couples to have healthy children. We are of the view that PGS and PGD should be allowed, provided that they are subject to control by a relevant authority and limited to preventing serious genetic conditions. Generally, a disease is considered to be serious if it is life-threatening, incurable and/or severely debilitating. However, a judgement of the “seriousness” of a condition is subjective. It will vary with the individual and family circumstances, the nature of the condition and the degree of associated disability. Thus, the decision regarding the seriousness of a condition is best left to the parents and the medical team, with the parents being provided with sufficient information to help them decide.
- 4.42 In the multi-cultural and multi-religious society of Singapore, views on the ethics of preimplantation genetic testing are diverse. A segment of the medical community and the public may not wish to be involved in such activities because of religious or personal moral beliefs. Such conscientious objection should be respected and protected so that no one should be under a duty to be involved in preimplantation genetic testing. However, it should be equally open to other members of the medical community and the wider public to participate in or have recourse to preimplantation genetic testing in ways that are not harmful to the moral and social fabric of Singapore as a whole.
- 4.43 The relevant authority should license, monitor and assess preimplantation genetic testing to ensure that all activities are conducted by appropriately qualified personnel in accredited laboratories, and that individuals requesting such services receive sufficient counselling. As such, the authority should issue clear guidelines for the conduct of these activities, including acceptable uses for preimplantation genetic testing and the procedure for the disposal of unselected embryos. Acceptable uses for preimplantation genetic testing should be consistent with the current practice of prenatal genetic diagnosis. Provision should also be made so that no one shall be under any duty to be involved in preimplantation genetic testing to which he or she has a conscientious objection.

**Recommendation 9: Preimplantation genetic screening and diagnosis are permissible, subject to licensing and monitoring by a relevant authority and should be limited to preventing serious genetic conditions. Provision should also be made so that no one shall be under any duty to be involved in preimplantation genetic testing to which he or she has a conscientious objection.**

- 4.44 We do not consider it acceptable to use preimplantation genetic testing for the selection of certain desired traits on non-medical grounds. A child who is selected for a particular trait such as greater mental or physical potential may

experience increased pressure to fulfil the expectation of this genetic potential. The situation is worsened if the child fails to reveal the superior mental and/or physical qualities for which he or she was genetically selected. In both situations, the proper relationship between parent and child is undermined, that is, the ideal that parental love should not be dependent on a child having characteristics that the parents hoped for, but rather as individuals in their own right. Allowing parents to exercise their preference in making such a selection may introduce an element of control over the result of conception, thus making the “experience of parenthood very different from the present situation in which... parents are happy just to take their child as they find them.”<sup>28</sup> We note that some have argued that such concerns are unjustified. In their opinion, expanding control over human reproduction may be thought of as merely an extension of parental responsibility to care for offspring. The reasons behind a couple’s choice to have children are often personal and should not be open to public scrutiny. We do not agree with this view. Personal interest must always be balanced against public interest in any kind of society. In this case, there is public interest in maintaining a stable and harmonious relationship between parents and their children, and this interest far outweighs the right of parents to select certain traits in their children for non-medical reasons.

- 4.45 There may also be situations where a couple may wish to implant an affected embryo for what could be called “lifestyle” reasons. For example, a deaf couple with inherited deafness may wish to have a deaf child because they do not consider deafness as a disability and wish for a compatible family. We agree with the Ethics Task Force of the European Society of Human Reproduction and Embryology (ESHRE) that the implantation of affected embryos “can only be defended if the welfare of the child is strictly considered within the familial boundaries or subculture. However, the functioning of this child within society at large would be severely impaired due to the imposed disability. Therefore, such deliberate restriction of the autonomy of the child is not considered justifiable.”<sup>29</sup> Hence, we consider such a practice unacceptable and recommend it be prohibited.
- 4.46 It is technically possible to use preimplantation genetic testing for sex selection. Couples may desire this for medical reasons, since certain genetic disorders are sex-linked and only affect persons of a particular gender, for example, Duchenne muscular dystrophy is X-linked and affects only males. Sex selection may also be desired for non-medical reasons, such as balancing the gender ratio in the family, personal preference, or due to certain social, cultural, religious or economic motivations. We are of the view that sex selection for non-medical reasons is unacceptable, as it may promote or reinforce gender stereotyping and

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<sup>28</sup> Nuffield Council on Bioethics, *Genetics and Human Behaviour: The Ethical Context* (2002), page 154.

<sup>29</sup> Shenfield F *et al* (ESHRE Ethics Task Force), Taskforce 5: preimplantation genetic diagnosis, *Human Reproduction*, Volume 18, Issue 3, pages 649-651 (March 2003).

discrimination. It may also promote gender imbalance in the population structure, which in turn may have undesirable social implications.

**Recommendation 10: The use of preimplantation genetic testing for the selection of desired traits or gender for non-medical reasons should not be allowed.**

*Preimplantation Tissue Typing*

4.47 In recent years, PGD has been used in combination with tissue typing, which not only allows couples to have a healthy child, but also enables the selection of an immunogenetically compatible stem cell donor for a sick sibling. We find the experience of the HFEA with PTT to be instructive. In 2001, the HFEA adopted a cautious approach and permitted PTT on a case-by-case basis under the following conditions:<sup>30</sup>

- (a) the affected child's condition is severe or life-threatening and of sufficient seriousness to justify the use of PGD;
- (b) the embryos created for PTT are themselves at risk from the condition affecting the existing child;
- (c) all other possibilities of treatment and sources of tissue for the affected child have been explored;
- (d) parents are not the intended tissue recipient;
- (e) the intention is to obtain only cord blood for the purposes of treatment and not other tissues or organs;
- (f) couples receive appropriate counselling;
- (g) families encouraged to participate in follow-up studies and PGD clinics are to provide detailed information regarding treatment cycles and outcomes; and
- (h) the created embryos are not genetically modified to provide a tissue match.

4.48 However, in July 2004, the HFEA extended the rules to allow embryos not at risk of a genetic disorder to be tested for their compatibility as stem cell donors for a seriously ill sibling. The HFEA requires that such cases demonstrate "a genuine need for potentially life-saving tissue and a likelihood of therapeutic benefit for an affected child."<sup>31</sup> This extension was made after careful consideration of the medical, psychological and emotional implications for

<sup>30</sup> HFEA Report: *Preimplantation Tissue Typing* (July 2004), page 2.

<sup>31</sup> HFEA Report: *Preimplantation Tissue Typing* (July 2004), page 10.

children and their families, and the safety of the technique performed in the past three years.

- 4.49 Ethical concerns have been expressed over this use of PTT in that children may be used as a means to an end. However, it has been argued that parents who conceive a child to save a life may be on higher moral ground than those who procreate as an incidental consequence of sex or for some selfish purpose. Others have also argued that parents who would go to such length to save the life of their child would also afford equal affection for the child conceived through PTT.
- 4.50 We have earlier expressed our view that preimplantation genetic testing should be allowed in Singapore provided that proper and effective safeguards are in place. In light of the UK's experience with PTT, we consider PTT to be also acceptable provided that it is subject to regulation by a relevant authority and evaluated on a case-by-case basis. We want to emphasise that PTT should be a measure of last resort. The relevant authority should provide clear guidelines on the eligibility of families for PTT. In this connection, we are of the view that such families must have the capabilities to ensure that the welfare of both the child conceived by way of PTT and the sick child are not compromised. In addition, we agree with the HFEA that follow-up studies on the psychological, social and other longer-term implications in these families should be encouraged.

**Recommendation 11: Preimplantation tissue typing, whether as the sole objective or in conjunction with preimplantation genetic diagnosis to avoid a serious genetic disorder, is permissible but should be licensed and evaluated on a case-by-case basis.**

#### *Germline Genetic Modification*

- 4.51 Germline genetic modification is a type of gene technology that involves the alteration of a person's genetic makeup in a manner that is permanent and can be transmitted to his or her offspring. It is one of the rising gene technologies applicable at the preimplantation stage of an embryo. We note that germline genetic modification may also be brought about inadvertently in gene therapy or through other experimental techniques.
- 4.52 We are of the view that the clinical practice of germline genetic modification should not be allowed at this time. Germline genetic modification is at present still experimental and will require substantial research to establish its feasibility and safety in clinical application. In addition, the potentially great impact on future generations presents serious ethical concerns. We will monitor progress in germline genetic modification and reassess its clinical applicability at an appropriate time in the future.

**Recommendation 12: The clinical practice of germline genetic modification should not be allowed at this time.**

*Prenatal Genetic Diagnosis*

- 4.53 PNGD provides important information to couples who are at increased risk of having a baby with a genetic disorder. This information may help them decide whether or not to terminate the pregnancy and if they decide not to, the information may help them prepare for the birth of a child with a disability. The information may also be useful for the professional team to prepare for a difficult delivery. The risk factors for having a baby with a genetic disorder include:
- (a) advanced maternal age;
  - (b) a family history of a serious heritable medical condition;
  - (c) one or both parents are “carriers” of mutation(s) in the same gene;
  - (d) abnormal screening test results such as ultrasound or first and second trimester screening tests; and
  - (e) a history of a previous child affected by a serious growth, developmental or health problem.
- 4.54 Prenatal screening precedes PNGD and provides prospective parents and healthcare professionals with information regarding the health of the developing foetus. Prenatal screening procedures include:
- (a) determining whether there is a history of infertility, miscarriages, abnormal children, or a family history of genetic diseases;
  - (b) maternal serum screening tests, which are done either in the first or second trimester. These tests measure circulating levels of certain blood proteins or other metabolites where abnormal levels may indicate possible genetic and/or structural defects in the baby; and
  - (c) ultrasound scans of the foetus, usually between 12 and 22 weeks of pregnancy to detect structural abnormalities, which may indicate possible genetic defects in the baby.
- 4.55 In Singapore, prenatal screening in conjunction with pre- and post-test counselling is part of routine prenatal care and specific diagnostic tests are performed when indicated. PNGD can be carried out for various genetic conditions, including Down’s syndrome, thalassaemia and haemophilia. If the results of prenatal screening tests indicate that the foetus is likely to be affected

- with a medical disorder, PNGD will be offered to verify the presence or absence of the disorder.
- 4.56 The range of available prenatal genetic tests is increasing as more knowledge is gained about genetic disorders through research. PNGD may require obtaining tissue specimens from the foetus. Acquiring these specimens involves an invasive procedure and hence poses a risk of miscarriage. It is therefore important that patients are fully informed of the risks, and their consent obtained prior to the tests being carried out.
- 4.57 If PNGD indicates that the foetus is or will likely be affected with a genetic disorder, the couple should be counselled about the disorder, its implications and the available options, to help them decide whether or not to continue the pregnancy.
- 4.58 It is possible to employ PNGD for trait or gender selection for non-medical purposes. For reasons similar to those that we have proffered in relation to preimplantation genetic testing, we are of the opinion that PNGD for gender or trait selection (whether physical, social or psychological characteristics or normal physical variations) should not be allowed. The current acceptable practice for PNGD is essentially confined to serious genetic disorders and we consider this to be appropriate. We note that the relevant professional bodies have guidelines on the practice of PNGD for their members.

**Recommendation 13: Prenatal genetic diagnosis should be limited to serious medical disorders. The use of prenatal genetic diagnosis for the selection of desired traits or gender for non-medical reasons should not be allowed.**

*Predictive Testing*

- 4.59 Predictive testing identifies healthy individuals who have inherited a gene for a late-onset disease, which is a disease that normally manifests in adulthood, although there may be cases where symptoms arise during late childhood.
- 4.60 Predictive tests can be classified into two categories based on the predictive certainty of the information derived from the tests:
- (a) *Presymptomatic tests* identify healthy individuals who have inherited a defect in a specific gene for a late-onset disease which confers on the individual an almost 100% risk of developing the disease at a later stage in life. However, these tests do not provide information on the severity and onset of the disease. Examples of such diseases include Huntington's disease and familial adenomatous polyposis coli, which are due to defects in single genes.

- (b) *Susceptibility tests (or predisposition tests)* identify individuals who have inherited a genetic variant or variants which may increase their risk of developing a multi-factorial disease some time in the future. Such disorders are often the result of the interaction of multiple genes and environmental factors. Alzheimer's disease, diabetes and certain cancers and heart disease fall into this category. While their genetic predisposition indicates that these individuals have an increased risk of developing the disease, some individuals may ultimately not develop the disease.
- 4.61 Healthy individuals requesting for predictive testing often do so to determine their risk of developing a genetic disease or passing on the disease to their children. Hence, presymptomatic tests are usually performed on individuals with a family history of a specific genetic disease, while susceptibility tests may be performed because of a family history or as part of population screening. As our knowledge in medical genetics increases, it is likely that the number of susceptibility tests will also increase.
- 4.62 Testing for a late-onset disease before an individual develops any symptoms allows the individual in some cases to make life-style changes to either prevent the disease from developing or assist him or her in making reproductive choices to prevent transmitting the disease to the next generation. It may also allow affected individuals to take preventive measures or undergo regular examinations to achieve early diagnosis and treatment of the disease.
- 4.63 Presymptomatic testing is generally well established, both technically and in its clinical application. It should be available for adults at risk who request it, even in the absence of treatment, after proper counselling and informed consent.
- 4.64 Generally, susceptibility testing has not been sufficiently developed and validated to be used extensively in current clinical practice. Therefore, it should not be applied clinically until there is significant empirical evidence of validity and utility. However, when validated tests are available, such as for breast cancer genes, susceptibility testing may be considered.
- 4.65 Predictive genetic information may be burdensome or psychologically traumatic given the uncertainty of the disease. We reiterate the importance of pre- and post-test counselling and informed consent in genetic screening and testing. We further note the NMEC's recommendation that: "Testing must be voluntary and patients and/or families must not be coerced into undergoing predictive testing. Regardless of the decision made, the care of the patient should not be compromised."<sup>32</sup>

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<sup>32</sup> NMEC, *Ethical Guidelines for Gene Technology* (2001), Section 2.2.1 (b).



**Recommendation 14: Presymptomatic testing should be available for adults at risk who request it, even in the absence of treatment, after proper counselling and informed consent.**

**Recommendation 15: Susceptibility testing should not be applied clinically unless there is significant empirical evidence of validity and utility.**

### *Genetic Screening*

- 4.66 The WHO defined genetic screening as “tests offered to a population group to identify asymptomatic people at an increased risk from a particular adverse outcome.”<sup>33</sup> The main purpose of genetic screening is to prevent a disease or minimise morbidity and mortality through early diagnosis and treatment.
- 4.67 Screening tests are not definitive as they are designed to identify those at risk. A confirmatory diagnostic test should be performed as soon as possible after a positive screening test, so as to minimise unnecessary anxiety or to enable measures for the prevention or treatment of the condition to be instituted without delay.
- 4.68 Generally, population genetic screening programmes are offered only when there are proven methods of treatment or prevention. Such programmes are different from other types of medical screening, as there may be risk implications for family members of the person screened.
- 4.69 In Singapore, there are several prenatal and newborn screening programmes. Many pregnant women are screened prenatally for foetuses with Down’s syndrome. All newborn babies are screened for Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency to reduce the risk of neonatal jaundice and its complications. They are also screened for congenital hypothyroidism and for hearing defects, half the cases of which are likely to be genetic in origin. These routine newborn and prenatal screening programmes, which serve a public health function and provide information useful to patients and their physicians, have become socially acceptable and even expected in Singapore.

**Recommendation 16: In genetic screening programmes, a confirmatory diagnostic test should be performed as soon as possible after a positive screening test, so as to minimise unnecessary anxiety or to enable measures for the prevention or treatment of the condition to be instituted without delay.**

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<sup>33</sup> WHO, *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetics Services* (1998), Section 6.

**Section C: Quality Control Issues in Clinical Genetic Testing**

- 4.70 In this section, our primary concern is the proper derivation and interpretation of genetic information in clinical genetic testing. This essentially rests on the quality of the genetic information, which in turn is dependent on the integrity of the diagnostic chain (this includes ensuring no sample switch or sample contamination) and the test methodology. As such, the sound practices of medical laboratories are directly relevant to the quality of the genetic information they provide and are a pre-requisite for accurate interpretation.
- 4.71 Accurate interpretation of genetic information presents one of the greatest challenges in clinical genetic testing. Another challenge is the presentation of genetic information in a comprehensible and empathetic manner. We address this latter challenge in the section on genetic counselling. Interpretation of genetic information, like other medical information, is as much an art as it is a science. Skill at interpretation depends on experience as well as up-to-date knowledge of the field.
- 4.72 As with other medical information, genetic information is likely to have psychological and social impact, or affect the reproductive choices of individuals. Given these concerns, we are particularly mindful of the care that is required in the accurate derivation and interpretation of genetic information.

***Standards and Quality of Genetic Test Providers***

- 4.73 As genetic information has far reaching implications, it is important to ensure its accuracy. The accuracy of a test is dependent on the integrity of the diagnostic chain and the test methodology. These aspects should be carefully monitored to ensure an acceptable level of confidence in the technical accuracy of test results. Generally, genetic tests are performed at laboratories selected by healthcare professionals. However, an individual may approach laboratories directly for testing to be done. We note in passing that such direct access may not be in the best interest of the individual as there is no assurance of the credibility of medical advice provided, if any, or of the quality of the test result.
- 4.74 Medical laboratories in Singapore are required to obtain a license from the MOH. Apart from minimum operational standards that the MOH prescribes, there are no binding standards for clinical genetic testing conducted by medical laboratories. There is however a system of voluntary accreditation for medical laboratories. Accreditation is often very helpful in providing greater assurance as to the overall competence of the testing laboratory, and thus the accuracy of the genetic information thereby derived.
- 4.75 In the US, the Clinical Laboratory Improvement Amendments establish quality standards for all clinical testing laboratories to ensure the accuracy, reliability and timeliness of the test result. In addition, professionals directing genetic

testing laboratories may be qualified under various mechanisms based on Federal laws and depending upon State laws. These mechanisms include holding licensure as a doctor of a particular field with laboratory experience, achieving board certification (from the American Board of Medical Genetics, etc.) and demonstrated specific experience as director of a clinical laboratory. Similarly in the UK, all laboratories providing genetic testing services need to be appropriately accredited and they take part in internal and external quality assurance programmes. Furthermore, it has been recommended that genetic testing be undertaken only by laboratories closely linked with other genetic services.<sup>34</sup> The Australian NHMRC stated that clinical genetic testing should be performed only by accredited laboratories.<sup>35</sup> Laboratories are required to be particularly sensitive to the possibility of error in the performance of genetic test.

- 4.76 Currently, the Singapore Accreditation Council (SAC) conducts general accreditation of medical laboratories. Although accreditation is not mandatory, the SAC actively encourages medical laboratories to be accredited. The SAC accredits medical laboratories as part of the Singapore Laboratory Accreditation Scheme (SINGLAS), which is essentially based on standards that are internationally accepted. SAC-SINGLAS is internationally recognised via mutual recognition arrangements such as the Asia-Pacific Laboratory Accreditation Cooperation, the International Laboratory Accreditation Cooperation and European Cooperation for Accreditation. It establishes best practices and standards for laboratories, including qualification requirements for the laboratory director and other technical personnel. In addition, SINGLAS also has specific criteria for accreditation in specialty areas such as molecular pathology and cytogenetics. Other than the SAC, accreditation of medical laboratories in Singapore has also been conducted by the College of American Pathologists (CAP), and jointly by the SAC and the CAP under the SAC-CAP Laboratory Accreditation Programme.
- 4.77 We propose that all laboratories conducting clinical genetic tests should be accredited by a body designated by the relevant authority, based on standards it considers appropriate. This is necessary to safeguard a high quality of genetic information derived from tests, which is in turn fundamental in safeguarding the welfare of tested individuals.

**Recommendation 17: All laboratories conducting clinical genetic tests should be accredited by a body designated by the relevant authority, based on standards it considers appropriate.**

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<sup>34</sup> UK Advisory Committee on Genetic Testing, *Report on Genetic Testing for Late-onset Disorders* (1998), pages 19 and 20.

<sup>35</sup> NHMRC, *Ethical Aspects of Human Genetic Testing: an Information Paper* (2000), section 2.5, page 23.

***Interpretation of Clinical Genetic Test Results***

- 4.78 There are several factors that affect the accurate interpretation of clinical genetic test results. These include:
- (a) the integrity of the diagnostic chain;
  - (b) the reliability of test methods;
  - (c) the technical competence of laboratory technicians;
  - (d) the ability of the individual to understand; and
  - (e) up-to-date knowledge, experience and competence of the genetic counsellor to interpret and communicate the test result and its implications effectively to the patient.

We believe that proper accreditation of medical laboratories should address factors (a) to (c). However, factors (d) and (e) will depend to a larger extent on the genetic counsellor conveying the test result to the patient.

- 4.79 The interpretation of clinical genetic test results is complex and dependent on many factors including the nature of the disease, the modality of testing, and the health status of the patient. Healthcare professionals have to ensure that sound interpretation is provided to patients, and so should be appropriately qualified and sufficiently experienced. Misinterpretation of results or misdiagnosis may lead to stress and unnecessary or inappropriate therapeutic interventions or changes to lifestyle for the patient and his or her family.

- 4.80 Genetic counselling should be provided in a timely manner. As far as is practicable, there should be no delay in counselling following the disclosure of a test result to a patient, to help the patient cope with any resultant psychological impact or emotional stress and the myriad medical, psychological, social, financial and legal implications that may arise. Sound and effective pre- and post-test counselling is thus particularly critical and should always be timely and integral to the practice of clinical genetic testing.

**Recommendation 18: Interpretation of clinical genetic test results should only be performed by healthcare professionals who are appropriately qualified or have sufficient experience. As far as is practicable, genetic counselling should immediately follow the disclosure of the test result, particularly if the test result is not favourable.**

**Section D: Genetic Counselling**

- 4.81 We have emphasised at various points in this report the importance of genetic counselling in the conduct of clinical genetic testing. Genetic counselling should seek to achieve the following objectives:
- (a) to provide sufficient and unbiased information to enable full and informed choices to be exercised; and
  - (b) to provide appropriate support to the patient and his or her family members.
- 4.82 In genetic counselling, the information provided should be adequate and comprehensible to the recipient, who will usually be a patient. It should be commensurate with the real and anticipated risks of the test, and the implications of the information it may yield. The patient should always be given sufficient time to consider the available options and have the opportunity to clarify doubts. Whenever practicable, counselling should be done in a face-to-face meeting. In addition, counselling should be conducted in an empathic manner and should be non-directive, especially if the condition is one where treatment is presently not available.
- 4.83 We have indicated that informed consent is dependent on the information that is provided to patients before genetic testing, and the manner in which such information is conveyed. For this reason, consent should be obtained after appropriate counselling. Taking into account the recommendations provided by the NMEC on this matter, we recommend that the following be considered in pre-test genetic counselling:
- (a) the nature of the condition to be tested;
  - (b) the potential consequences of not being tested;
  - (c) the alternatives to genetic testing and their pros and cons;
  - (d) the type of sample required, test procedure and possible risks;
  - (e) the consequences foreseeable as a result of testing, including implications for family members, and available support;
  - (f) test reliability and clinical validity, emphasising that not all mutations are detectable, that some mutations are of uncertain significance, and the extent to which results indicate probability, or degree of certainty of developing the disease;
  - (g) the treatment or management options;

- (h) the turn-around time and how the results will be conveyed to the patient; and
  - (i) an assurance to the patient of confidentiality of test results and counselling records, and explanation of circumstances that might require disclosure of the patient's test result (if necessary).
- 4.84 Where appropriate, it may be advisable also to consider the following in pre-test genetic counselling:
- (a) possible third parties' interest in the patient's genetic information, and the likely consequences;
  - (b) further use of genetic information and test samples, and their management; and
  - (c) the possibility of unexpected findings (such as parentage discrepancy even though the test is not a parentage test) and whether the patient will want to know such findings.

***Post-test Follow-up***

- 4.85 We are of the view that follow-up support should be provided to patients in the form of post-test counselling. Patients will often have queries on the result of their genetic tests and the implications. Healthcare professionals should attempt to address these queries in post-test counselling. In particular, we propose that the following concerns be anticipated and addressed:
- (a) the implications of the genetic test result for the patient himself or herself, whether the result is positive, negative or inconclusive;
  - (b) the treatment or management, and/or support options;
  - (c) the possible implications for family members;
  - (d) any psychological, social and ethical issues or concerns;
  - (e) any requirement or obligation to disclose the test result to a third party (if any); and
  - (f) the protection of the patient's privacy and confidentiality of his or her genetic test result.
- 4.86 Genetic test results may reveal cases that require long term follow-up. In such cases, the genetic counsellor is expected to:

- (a) conduct a periodic review of the management plan;
- (b) monitor the patient's adherence to the plan;
- (c) clarify any doubts and answer any questions;
- (d) give psychological support; and
- (e) inform the patient of relevant developments in genetic medicine.

4.87 In certain cases involving children tested positive for a serious genetic condition, it may be prudent to discuss the implications of the test result with the parents in the absence of the child. This is to allow parents to ask questions freely and to minimise any risk of misunderstanding on the part of the child.

**Recommendation 19: Genetic counselling should be offered to all individuals before and after they undergo clinical genetic testing.**

**Recommendation 20: Genetic counselling should generally be conducted in a non-directive manner and should provide sufficient information and appropriate support to the individual and his or her family members.**

#### *Professional Diversification and Development*

4.88 Currently in Singapore, there are no uniform standards or practice applicable to genetic counselling, which is usually carried out by physicians. However, genetic counselling can be a prolonged process and given the rapid development in medical genetics, specialised knowledge will increasingly be required. Individuals involved in genetic counselling must be committed and prepared to invest the time, and should possess and maintain up-to-date knowledge of gene technology. It may be desirable to involve others such as medical geneticists, nurses or healthcare therapists who have the necessary skills in counselling. However, the responsibility for overseeing the case, including counselling, remains with physicians as they carry ultimate clinical responsibility for their patients.

4.89 We propose that the relevant authority provides professional training and accreditation in medical genetics and genetic counselling to healthcare professionals working in this field.

**Recommendation 21: The relevant authority should provide professional training and accreditation in medical genetics and genetic counselling to healthcare professionals.**

## **V. Direct Supply of Genetic Tests to the Public**

- 5.1 In Singapore, as in many other countries, access to clinical genetic tests and services is mainly through healthcare professionals or healthcare institutions. Healthcare professionals are also responsible for interpreting genetic test results, providing pre- and post-test counselling to the patient regarding the value and implications of the test and the significance of the test results, and if need be, treatment and follow-up. However, recent developments in the availability of genetic testing kits and services direct to the public allow increasing access to genetic tests without a medical consultation.
- 5.2 Since the publication of the NMEC Gene Technology Guidelines in 2001, there have been important changes in the biomedical landscape in Singapore and elsewhere, including the development of advanced gene technologies and the provision of genetic services. A conventional demand-supply evaluation is illustrative. On the demand-side, the Singaporean public is gaining sophistication in knowledge of health and health-related matters. One factor that may have contributed to this social phenomenon is the increased availability of medical information from various sources, especially the Internet. When considered in light of hectic lifestyles, “face-saving” or privacy concerns and escalating healthcare costs, the prospect of a “do-it-yourself” approach to certain health-related matters may appear attractive. On the supply-side, advances in gene technology have simplified the usage of many genetic tests and enabled manufacturers to produce them at much lower cost. Considering these developments in the context of low-cost marketplaces such as the Internet, it is foreseeable that some may increasingly choose to bypass medical professionals to obtain direct access to genetic tests and services.
- 5.3 The commercialisation of genetic testing services and the ensuing direct supply of genetic testing kits to the public have become a growing concern in a number of countries. The UK HGC recently carried out an extensive review of this development and published a report, *Genes Direct: Ensuring the effective oversight of genetic tests supplied directly to the public* (2003). It found that commercial genetic testing services are likely to be increasingly marketed in the UK and in some other developed countries. In such direct supply, the public gains access to genetic tests without a conventional face-to-face consultation with a medical professional. It is possible, following a telephone call or an electronic mail, for an individual to post his or her tissue sample to a laboratory where genetic analysis is performed. Alternatively, certain do-it-yourself home test kits may be procured over the counter or through the Internet. In the absence of a medical consultation, the HGC was concerned that the possible harms far outweigh the interest of individuals in obtaining genetic information about themselves. Two possible harms from direct genetic testing were identified:



- (a) Misinformation, leading to false assurance and a delay in seeking proper medical assistance, or causing unnecessary alarm resulting in expensive unnecessary medical investigations or treatment, or a misguided reproductive decision; or
  - (b) inappropriate testing of children or other adults without proper consent.
- 5.4 We share the concerns of the HGC. If direct access to genetic testing is allowed in Singapore, the likelihood of misinformation is high. First, there is a lack of assurance that the genetic tests supplied by manufacturers are of a satisfactory quality and standard. Second, there is a high likelihood that the test result may be misinterpreted by an untrained person, with the probabilistic nature of predictions made from genetic information adding to interpretive difficulties. Third, it is unrealistic to expect suppliers of genetic testing kits to provide long-term counselling and other support services of satisfactory standards, particularly for the diagnosis or prediction of serious conditions.
- 5.5 There is no specific legislation regulating access to, or supply of, genetic testing kits and services in Singapore. The Centre for Medical Device Regulation of the Health Sciences Authority has established a system for the voluntary registration of medical devices and is currently in the process of setting up a framework for the regulation of medical devices.
- 5.6 The NMEC, in its Gene Technology Guidelines, strongly discouraged genetic testing by manufacturers and suppliers of genetic testing kits and the advertising or marketing of predictive genetic tests to the public. We agree that the advertising of predictive genetic tests to the public should be strongly discouraged. However, we are of the view that a more comprehensive system of control over public access to genetic testing should be devised in light of recent developments in gene technology. We propose that the relevant authority develop an oversight framework for the supply, direct to the public, of those genetic tests and services which are likely to cause serious harm if freely accessible. Consumers should on the other hand have easy access to accurate and impartial information to help them decide on the relevance of the tests or services. We reiterate that genetic testing should generally be conducted through the intermediation of a qualified healthcare professional and that tests that provide predictive health information should not be directly offered to the public.

**Recommendation 22: Genetic testing should generally be conducted through a qualified healthcare professional. Tests that provide predictive health information should not be offered directly to the public. The advertising of direct genetic tests to the public should be strongly discouraged. The relevant authority should develop an oversight framework for the supply of direct genetic tests, services and information to the public.**

## **VI. Ethical Considerations in Human Genetic Research**

- 6.1 Human genetic research is the study of genes, their functions, how they are associated with health and disease and how genetic and environmental factors influence health. The study may involve research participants or pre-existing records, or otherwise, genetic information derived from genetic tests, and may entail the use of tissue samples.<sup>36</sup> Tissue samples may be from healthy individuals, from patients or from people who have died.
- 6.2 Significant research is currently taking place throughout the world to examine the genetic basis of common diseases such as cancer, heart disease and diabetes, and important discoveries are emerging. Ultimately, it is hoped that human genetic research will enable or facilitate the development of new or more reliable ways of diagnosing, preventing and treating genetic disorders effectively. The treatments envisaged extend across a broad spectrum from pharmacological, gene or cell-based therapies, to simple changes in a person's environment or lifestyle.
- 6.3 Human genetic research is not conducted with the aim of providing research participants with specific information about their genetic status or health. Generally, genetic information derived from research is of unknown or uncertain predictive value. Therefore, special care must be taken to prevent inadvertent release of immature data.
- 6.4 If there is a likelihood that the research will yield individual data of clinical significance, the research participant should be told of this possibility prior to participation in the research, and whether he or she would be informed accordingly if desired. Where genetic tests of known clinical or predictive significance are used on research participants or on tissue samples that identify an individual, specific consent must be sought and appropriate counselling offered. In either case, if a research participant subsequently requests a test to confirm his or her genetic status, he or she should be advised to consult a physician.
- 6.5 Researchers have an obligation to protect the privacy of research participants and their family members, and to ensure confidentiality of all genetic information derived from the research, including information about the participant's relatives, who may not be part of the research project. Identifiable genetic information derived from the research should not be disclosed to any third party.

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<sup>36</sup> Human tissues refer to "all kinds of human biological materials derived from living or cadaveric donors, including solid body tissues, organs, fetuses, blood and other body fluids and their derivatives, cord blood, embryos, gametes (sperm or eggs) or any part or derivative thereof". BAC, *Human Tissue Research* (November 2002), paragraph 2.1.

- 6.6 The overall ethical framework for human biomedical research has been set out in our previous reports: the Human Stem Cell Report, the Human Tissue Research Report and the IRB Guidelines. We strongly encourage researchers to refer to these reports for further details. In particular, researchers should take note of the following:
- (a) All human genetic research requires the approval of an appropriately constituted research ethics committee or an IRB. In our IRB Guidelines, we emphasised the critical role that researchers, institutions and IRBs play in ensuring the protection of the safety, health, dignity, welfare and privacy of research participants. All the matters reviewed in this Part fall within the purview of IRBs approving human genetic research.
  - (b) As a general principle, where the research involves the use of stored tissue samples or genetic information, consent is required from the person from whom the tissue was derived or to whom the information relates. Such consent would normally have been taken at the time tissue was donated. The IRB should consider if any consent requirement arises where the research involves legacy tissue, stored human tissue or genetic information, that has been anonymised.
  - (c) Tissue donors should be free to choose between making a general gift, which means that the tissue may be used for any type of research, or a restricted gift, which restricts the use of the tissue to types of research specified by the donor.<sup>37</sup> Research participants should be informed that when they donate any tissue for research, including genetic research, they will no longer have any claim to property rights in the tissue.
  - (d) When researchers plan to use tissue samples from abroad, both the researchers and the IRB reviewing the proposal must be satisfied that the tissue samples have been ethically obtained.
  - (e) Participation in genetic research is voluntary. Researchers need to seek the informed consent of prospective research participants, whether or not they are also patients. In particular:
    - (i) where an attending physician is also the researcher, it is necessary for consent to be taken separately through an independent third party to avoid conflicts of interest and to ensure that the patient's participation in the research is genuinely voluntary;
    - (ii) where tissue samples provided for clinical use are also intended for research, informed consent for the research is required in addition to the consent for taking the tissue for clinical use.

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<sup>37</sup> BAC, *Human Tissue Research* (November 2002), Section 13.1.9.

Consent is also required if there is an intention to store the tissue for other future research; and

- (iii) where vulnerable persons are involved, their informed consent or that of their legally authorised guardians must be sought. In such cases, the IRB should be satisfied that there is no appropriate alternative test population and that the research is dependent on their participation.

6.7 When the research involves human embryos for reproductive purposes, written approval from the MOH is required in addition to approval by the IRB. In any case, no research should be performed on any embryo more than 14 days old.<sup>38</sup>

6.8 Researchers conducting human genetic research should provide research participants with sufficient information in an understandable form to enable them to make an informed decision. The participant should be informed of the following prior to the research:

- (a) the experimental nature and purpose of the study;
- (b) the possible benefits to others and to science;
- (c) why he or she is invited to participate, and the voluntary nature of the participation;
- (d) the procedure and the risks (if any);
- (e) whether he or she will be informed (if desired) if clinically relevant information is obtained from the research;
- (f) where relevant, the significance and implications of the genetic information derived from the research for the participant and his or her family, in which case counselling provisions as per Part IV Section D would apply;
- (g) the possibility of being re-contacted in the future;
- (h) the use and storage of the tissue contributed for current and any future IRB approved research;
- (i) the arrangement to ensure the participant's privacy and the confidentiality of records;

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<sup>38</sup> MOH, *Guidelines for Private Healthcare Institutions Providing Assisted Reproduction Services: Regulation 4 of the Private Hospitals and Medical Clinics Regulations (Cap 248, Rg 1)* (2001).

- (j) who to contact for questions about the research or in the event of an adverse occurrence arising from it;
  - (k) the right to withdraw from the research at any time;
  - (l) assurance that refusal to consent without giving any reasons, or withdrawal from the research at any time, will not compromise the quality of any care that may be given to the participant and/or the family;
  - (m) the procedure for the disposal of the participant's information or tissue upon withdrawal or completion of the research, if not stored for future research; and
  - (n) possible commercial uses, if any.
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## GLOSSARY

<b>Assisted reproduction</b>	The use of clinical and laboratory techniques to increase chances of conceiving a baby. An example is <i>in vitro</i> fertilisation, or <b>IVF</b> .
<b>Asymptomatic</b>	Having no signs or symptoms of disease.
<b>Alzheimer's disease</b>	A degenerative brain disease of unknown cause that is the most common form of dementia, that usually starts in late middle age or in old age as a memory loss for recent events spreading to memories for more distant events and progressing over the course of five to ten years to a profound intellectual decline characterized by dementia and personal helplessness, and that is marked histologically by the degeneration of brain neurons especially in the cerebral cortex and by the presence of neurofibrillary tangles and plaques containing beta-amyloid.*
<b>Carrier</b>	Someone who carries only one copy of a <b>mutant gene</b> in question. A carrier usually shows no symptoms or very mild symptoms for the disease gene that he or she carries, as two copies of the disease gene are required for a full-blown manifestation of the disease. A carrier has the risk of transmitting the mutant gene to the next generation.
<b>Chromosome</b>	Structure in a cell that contains DNA and proteins. With the exception of sperm and egg cells and red blood cells, each human cell with a nucleus contains two sets of chromosomes, one inherited from the mother and one from the father. Each set consists of 23 chromosomes, 22 autosomes (non-sex chromosomes) and one sex chromosome, either X or Y. These human cells thus contain 46 chromosomes and are termed diploid. A male diploid cell has an X and a Y chromosome, whereas a female diploid cell contains two X chromosomes. Sperm and egg cells are haploid and contain only 23 chromosomes. Each chromosome contains genes arranged linearly, and is made up of proteins and <b>DNA</b> .
<b>Clinical validity</b>	The accuracy with which a test determines the presence or absence of a clinical condition or which a test predicts a predisposition.
<b>Congenital</b>	Existing at or dating from birth.
<b>Cystic fibrosis</b>	Cystic fibrosis (CF) is an inherited disease characterized by an abnormality in the body's salt, water- and mucus-making cells. It is chronic, progressive, and is usually fatal. In general, children with

CF live into their 30s. Children with CF have an abnormality in the function of a cell protein called the cystic fibrosis transmembrane regulator (CFTR). CFTR controls the flow of water and certain salts in and out of the body's cells. As the movement of salt and water in and out of cells is altered, mucus becomes thickened. The thickened mucus can affect many organs and body systems including:

- respiratory - sinuses and lungs
- digestive - pancreas, liver, gallbladder, intestines
- reproductive - more so in the male, where sperm-carrying ducts become clogged
- sweat glands \*

**Diagnostic chain** The chain of events or procedures that begins from the collection of sample and ends with a diagnosis based on analyses of the sample.

**DNA** DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Each DNA is a linear molecule made up of nucleotides or bases. There are four different types of bases in DNA and the order in which these bases are arranged determines the protein to be formed.

Each individual's body contains an identical set of DNA in nearly all of its cells. A great fraction of cellular DNA is located in the cell nucleus (where it is called nuclear DNA), while the remaining can be found in the mitochondria (where it is called mitochondrial DNA).

**Down's syndrome** A congenital condition characterized by moderate to severe mental retardation, slanting eyes, a broad short skull, broad hands with short fingers, and by trisomy of the human chromosome numbered 21.\*

**Duchenne muscular dystrophy** A severe progressive form of **muscular dystrophy** of males that appears in early childhood, affects the muscles of the legs before those of the arms and the proximal muscles of the limbs before the distal ones, is inherited as an X-linked recessive trait, is characterized by complete absence of the protein dystrophin, and usually has a fatal outcome by age 20.\*

**Early-onset** The early manifestation or occurrence of a disease normally characterised by delayed development. For example, Alzheimer's disease usually occurs in late middle-age years or old age, but early-onset Alzheimer's disease may occur in early middle-age years.

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<b>Familial adenomatous polyposis</b>	A disease of the large intestine that is marked by the formation especially in the colon and rectum of numerous adenomatous polyps which typically become malignant if left untreated, that may be either asymptomatic or accompanied by diarrhoea or bleeding, and that is inherited as an autosomal dominant trait.*
<b>Gene</b>	A gene is the basic physical and functional unit of heredity. It is made up of DNA which carries instructions to make molecules of <b>RNA</b> and proteins. Every person has two copies of each gene, one inherited from each parent. Most genes are commonly found in all people, but about one percent of each person's <b>genome</b> is slightly different from that of another. The slight difference is what makes people physically unique.
<b>Gene therapy</b>	Treatment of a genetic disorder by inserting functional genes in order to replace, supplement, or manipulate the expression of non-functional or abnormal genes. Gene therapy has thus far only advanced into clinical trials and is not yet an established therapy.
<b>Genetic variant</b>	Genetic variance is the differences in <b>phenotypes</b> and <b>genotypes</b> in a population.
<b>Genome</b>	The complete set of genetic instructions for making an organism is called its genome. The genome contains the master blueprint for all cellular structures and activities for the lifetime of the cell or organism. Found in every nucleus of a person's many trillions of cells, the human genome consists of tightly coiled threads of DNA and associated protein molecules, organised into structures called chromosomes.
<b>Genotype</b>	A specific set of alleles (variant forms of a gene) at particular position on the chromosome.
<b>Germ cell (Germline)</b>	The cell (or cell line) from which sperm and egg (gametes) are derived.
<b>Glucose-6-phosphate dehydrogenase deficiency</b>	A hereditary metabolic disorder affecting red blood cells that is controlled by a variable gene on the X chromosome, that is characterized by a deficiency of glucose-6-phosphate dehydrogenase conferring marked susceptibility to haemolytic anaemia which may be chronic, episodic, or induced by certain foods (as broad beans) or drugs (as primaquine), and that occurs especially in individuals of Mediterranean or African descent.*
<b>Haemoglobin</b>	The substance inside red blood cells which binds oxygen molecules and transport them from the lungs to other tissues.



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<b>Haemophilia</b>	A sex-linked hereditary blood defect that occurs almost exclusively in males and is characterized by delayed clotting of the blood and consequent difficulty in controlling haemorrhage even after minor injuries.*
<b>Huntington's disease</b>	A progressive chorea that is inherited as an autosomal dominant trait, that usually begins in middle age, that is characterized by choreiform movements and mental deterioration leading to dementia, and that is accompanied by atrophy of the caudate nucleus and the loss of certain brain cells with a decrease in the level of several neurotransmitters.*
<b>Hypothyroidism</b>	Deficient activity of the thyroid gland; <i>also</i> : a resultant bodily condition characterized by lowered metabolic rate and general loss of vigour.*
<b>Immunogenetic status</b>	The genetic makeup of the immune system of an individual.
<b>Institutional Review Board (IRB)</b>	A committee appointed by an institution to review the ethical standards of biomedical research proposals.
<b><i>In vitro</i> fertilisation (IVF)</b>	A clinical and laboratory procedure whereby the eggs and sperms from a couple are extracted and fertilised outside their bodies. Such a procedure is a kind of assisted reproduction aimed at increasing the chances of a couple conceiving a baby.
<b>Jaundice</b>	A yellowish pigmentation of the skin, tissues, and certain body fluids caused by the deposition of bile pigments that follows interference with normal production and discharge of bile (as in certain liver diseases) or excessive breakdown of red blood cells (as after internal haemorrhage or in various haemolytic states).*
<b>Karyotype</b>	The chromosomes of a cell can be stained by a dye to become observable under the microscope and to display characteristic banding patterns. The analysis of a set of chromosomes arranged in corresponding sizes and banding patterns is called a karyotype.
<b>Late-onset</b>	The development of a hereditary disorder beginning only in late childhood or adulthood.
<b>Metabolite</b>	A product of biochemical processes in a cell or organism.
<b>Muscular dystrophy</b>	Any of a group of hereditary diseases characterized by progressive wasting of muscles.*

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<b>Mutation</b>	<p>A gene mutation is a permanent change in the DNA sequence that makes up a gene. It ranges in size from one DNA base to a large segment of a chromosome.</p> <p>Gene mutations can be inherited from a parent or acquired during a person's lifetime. If a mutation occurs in an egg or sperm cell during a person's life, there is a chance that the person's children will inherit the mutation.</p> <p>Most mutations do not cause genetic disorders. For example, some mutations alter a gene's DNA base sequence but don't change the function of the protein made by the gene.</p>
<b>Neonatal</b>	<p>Of, relating to, or affecting the newborn and especially the human infant during the first month after birth.</p>
<b>Phenotype</b>	<p>The observable characteristics of the expression of a gene.</p>
<b>Preimplantation genetic diagnosis (PGD)</b>	<p>A procedure whereby early embryos created by IVF are evaluated to determine the presence of one or more genetic conditions. It is then followed by the selection and implantation of unaffected embryos into the uterus.</p>
<b>Preimplantation tissue typing</b>	<p>A procedure whereby early embryos created by IVF are tested for tissue compatibility with an existing sibling. This is then followed by the selection and implantation of tissue compatible embryos into the uterus with the aim of bringing about the birth of a child who can provide a matched tissue donation. It can be used as the sole clinical objective or in combination with PGD to avoid a serious genetic condition in the resulting child.</p>
<b>Prenatal genetic diagnosis</b>	<p>Tests performed during pregnancy to determine if a foetus is affected with a particular genetic disorder.</p>
<b>Presymptomatic testing</b>	<p>Testing of an asymptomatic individual to determine if the individual has inherited a defect in a specific gene for a late-onset disease which confers on him or her an almost 100% risk of developing the disease at a later stage in life.</p>
<b>Protein</b>	<p>Large and complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function and regulation of the body's tissues and organs.</p>
<b>RNA</b>	<p>RNA, or ribonucleic acid, is mainly involved in the translation of genetic information coded in DNA to make protein molecules in the cell.</p>

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<b>Scientific validity</b>	The reliability of a test performed in the laboratory. A validated test should consistently detect the presence of its gene substrate and should consistently show negative results in the absence of its gene substrate.
<b>Sex-linked</b>	A disease gene that is situated on either the X or Y chromosome is said to be sex-linked. An X-linked disease, for example, is caused by a genetic defect in the X chromosome.
<b>Sickle-cell anaemia</b>	A chronic anaemia that occurs primarily in individuals of African descent who are homozygous for the gene controlling haemoglobin S and that is characterized by destruction of red blood cells and by episodic blocking of blood vessels by the adherence of sickle cells to the vascular endothelium which causes the serious complications of the disease (as organ failure).*
<b>Somatic cell</b>	All the body cells except the reproductive (germ) cells.
<b>Susceptibility (Predisposition) testing</b>	Testing of an asymptomatic individual to determine if the individual has inherited a genetic variant or variants, which may increase his or her risk of developing a multi-factorial disease such as Alzheimer's disease, diabetes and certain cancers, some time in the future.
<b>Thalassaemia</b>	Any of a group of inherited hypochromic anaemias and especially Cooley's anaemia controlled by a series of allelic genes that cause reduction in or failure of synthesis of one of the globin chains making up haemoglobin and that tend to occur especially in individuals of Mediterranean, African, or southeastern Asian ancestry – sometimes used with a prefix (as alpha-, beta-, or delta-) to indicate the haemoglobin chain affected; called also <i>Mediterranean anaemia</i> .*
<b>X-linked</b>	See <i>sex-linked</i> .

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\* From Merriam-Webster Medical Dictionary

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## **MEDICAL, ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETIC SCREENING PROGRAMMES**

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### **Genetic Testing**

#### ***Introduction***

Over the last decade, there has been tremendous, almost exponential, growth in the knowledge we have about the roles genes play in causing disease. It is estimated that the genetic bases of more than 1600 diseases have been identified while even more are being investigated. As a consequence, genetic testing has moved from the realm of the imagination into the world of reality. Twenty years ago, only a handful of genetic tests existed. Today, there are more than 700 different genetic tests available.

#### ***Definition of Genetic Tests***

There is no universally accepted definition of what constitutes a genetic test.<sup>1</sup> A genetic test can be defined by its objective. Namely, it is any test or procedure performed to identify individuals with or at risk of developing a genetic disorder. This broad definition incorporates history taking, physical examinations, and laboratory tests as examples. If a genetic test is restricted to laboratory techniques that are used to achieve the above aim, then a genetic test is a laboratory test that can be based on protein, RNA, DNA or chromosome analysis. This definition can be further narrowed to tests that only directly analyse DNA, RNA or chromosomes.

There are several main reasons why different definitions of genetic tests exist. First, the impact genetic testing has made in medical practice is not yet comprehensive. Hence, clinical diagnostic criteria are still the main means of diagnosing many genetic conditions (e.g. Neurofibromatosis Type 1, Marfan Syndrome).<sup>2, 3</sup> Second, a genetic condition can be diagnosed through different types of laboratory tests. For example, Tay Sach's Disease can be diagnosed based on protein or DNA analysis.<sup>4</sup> Cost and clinical indications drive the choice to use a particular test. Third, with a global push towards regulation of genetic testing, there are concerns that the broader definitions would impinge upon the use of many common laboratory tests. Tests that are not primarily used to detect genetic diseases but can indirectly reveal a genetic disorder particularly represent this threat (e.g. full blood count, blood lipid profile). Given these reasons, there is a trend towards using the narrowest definition when defining a genetic test.



### ***What Are the Reasons for Doing Genetic Testing?***

Genetic testing is usually done for the following purposes:

1. to confirm a specific diagnosis in a symptomatic individual (diagnostic testing);
2. to ascertain the risk of having a particular condition in an asymptomatic individual (predictive/susceptibility testing);
3. to ascertain the risk of transmitting a condition (carrier testing);
4. to ascertain if a foetus has a clinically significant genetic disorder (prenatal diagnosis);
5. for identity or forensic testing;
6. for paternity or relationship testing; and
7. for research.

The first four objectives can be grouped under the heading “clinical genetic testing”. Most clinical genetic testing is physician initiated. Doctors tend to offer genetic testing when there is suspicion that a gene contributes to the pathogenesis of the disease, and when such testing is available. The knowledge of the genetic basis of a disease and availability of genetic tests is highly dependent on the type of genetic disorder involved. The current situation is biased towards single gene disorders as these have been the simplest for researchers to decipher. Single gene disorders are one of the three main groups of genetic disorders. The other two are chromosomal and multi-factorial disorders.

#### *1. Single Gene Disorders*

A single gene disorder is caused by a change in a single gene. There are many different types of single gene disorders. Individually, they are usually rare but, overall they affect ~2% of the population over a lifetime. If the gene for the disease has been identified, it is likely that genetic testing is available or will be available soon for clinical use.

#### *2. Chromosomal Disorders*

Individuals with chromosomal disorders have either a deficiency or excess of a chromosome or of part of one. Problems are caused by such deficiencies or excesses. Down’s syndrome is an example of this disorder type. Chromosomal disorders are relatively common. About 15% of pregnancies end in first trimester miscarriages, half of which are due to chromosomal defects. In addition, ~0.7% of babies born have chromosomal defects. Karyotype and fluorescent *in situ* hybridisation (FISH) are common tests used to identify chromosome defects.

#### *3. Multi-factorial Disorders*

This group of diseases arises due to the interplay of multiple factors that can include both genetic and environmental factors. Multi-factorial disorders encompass many diseases ranging from birth defects in babies to common disorders in adults (e.g. heart disease, diabetes mellitus). It is estimated that this group of disorders affects

more than 60% of the population. Genetic testing is currently not available for most of these diseases because the contribution of genetic variation to the disease process is not yet fully understood.

### ***Who Has Access to Genetic Testing?***

Access to clinical genetic testing is mainly through physicians. This is reinforced by the fact that most laboratories require a physician to countersign the order forms as well as provide documentation that informed consent was obtained. Identity or forensic testing is used mainly by law enforcement and legal services. Paternity or relationship testing is the one form of genetic testing that the public can freely access.

Access to research genetic testing is a more complex matter. It is largely determined by whether an individual meets a researcher's requirements and whether the individual gives informed consent. The individual must be willing to undergo tests to advance scientific and medical knowledge. There is usually no direct benefit to the individual participating in the research study. Oversight of ethical concerns in research is administered by Institutional Review Boards (IRBs).

### ***What is the Process of Clinical Genetic Testing Like?***

If a doctor determines that it is appropriate to offer a patient genetic testing for clinical purposes, he must obtain informed consent prior to testing. Informed consent is the process by which a person is made fully aware of his options and participates in his choices about health care. In genetic testing, this process is also called genetic counselling. Issues that should be discussed include the following:

1. Genetic testing is voluntary and consent is required to proceed;
2. Time should be taken to ask all questions needed to make an independent personal decision. After consent is given, withdrawal of consent can be done at any time or the disclosure of the results postponed;
3. The major medical facts of the disorder (diagnosis, prognosis, treatments available, inheritance pattern, and risks of recurrence in the family);
4. The implications of genetic testing (implications to other family members, detection of non-paternity, and possibility of psychological stress);
5. Sample required and possible side effects of the sample taking procedure;
6. Test procedure and expected turnaround time;
7. Accuracy of test results;
8. Confidentiality of results; and
9. Alternatives to gene testing.

The result of genetic testing is almost never released directly by the laboratory to the patient. As the interpretation of test results are complex, a follow-up visit is usually arranged so that a qualified person can explain the results and implications to the individual in simple layman language. The individual's reaction, expectations and questions will have to be addressed and follow up treatment instituted if indicated.

### ***What is the Current Situation in Singapore?***

In Singapore, there are many clinical genetic tests locally available. For tests that are only available abroad, it is usually quite simple for the physician to send a sample there for testing. Clinical genetic testing is mainly physician initiated. Patients initiate a small proportion of genetic testing, and usually request carrier, prenatal or presymptomatic diagnoses. Direct test requisition by the public is very limited as most genetic testing centres require the intermediation of a qualified healthcare professional (e.g. signature of a referral physician stating that the appropriate matters were explained and counselled). The exception is paternity and relatedness testing, where direct access by the customer is possible.

### **Genetic Counselling**

Genetic counselling refers to the process of helping individuals understand their risks of having a genetic disorder, the risks of passing on a genetic disorder to the next generation and/or choices available to them. It enables a person to make an informed decision about the options available to them.

There are two main groups of individuals who benefit from genetic counselling: (1) individuals at risk for passing on a genetic disorder; and (2) individuals participating in a screening programme.

Individuals at risk of passing on a genetic disorder are usually identified because there is:

1. a previous affected child or family history of birth defects such as cleft lip/palate, neural tube defects, club foot and congenital heart disease;
2. a previous affected child or family history of mental retardation or developmental delays;
3. a previous affected child or family history of a known or suspected genetic disorder;
4. a known chromosomal abnormality in the family;
5. a history of multiple miscarriages or still births; or
6. the individual is a female above the age of 35.

### ***Special Considerations in Genetic Counselling***

Except for cases with children, the process of genetic counselling is quite standard. In children's cases where the prognosis or implications are grave, it is sometimes prudent not to have the child present. This will enable full disclosure to the parents and for the parents to ask questions freely without inhibition. In addition, it will reduce the risks of the child misunderstanding the complicated and complex matters that are likely to be raised and discussed.

Personnel who are familiar with the conditions, testing and interpretation of the results should carry out genetic counselling. This includes individuals such as physicians,

geneticists, genetic counsellors and nurse clinicians. Average doctors and nurses with no experience or training in genetic conditions are likely unable to provide adequate counsel.

The need for genetic counselling, especially in population based screening programs, will create manpower problems in light of the large numbers involved. For common screening tests where the indications, procedures and outcomes are relatively standard, this can be overcome (1) by having non-medical practitioners such as genetic counsellors and nurse clinicians to take the lead and front line, and (2) by disseminating information through written material. There should still be a physician/geneticist involved in the event of an unusual circumstance or result. For less common conditions, the physician/geneticist should be the primary person involved.

In several foreign countries, a genetic counsellor has a master's degree in genetic counselling and has passed a certification examination. In addition, many belong to professional organisations that recommend professional standards for genetic counsellors. These organisations include:

1. The American Board of Genetic Counselling
2. The National Society of Genetic Counsellors
3. The American Board of Medical Genetics
4. The American College of Medical Genetics
5. Australian Society of Genetic Counsellors
6. Canadian Association of Genetic Counsellors
7. European Society of Human Genetics

Genetic counselling will probably reduce ethical, legal or social concerns arising from genetic screening or testing. Hence, it is important to ensure that it occurs and is of an acceptable standard.

### **Medical Issues in Clinical Genetic Testing**

One of the biggest medical challenges in clinical genetic testing is accurate interpretation of test results. This requires expert knowledge about the patient, disease and accuracy of the tests. Accuracy of the test is dependent on two main factors: 1) integrity of the diagnostic chain (i.e. ensuring no sample switch, contamination etc.) and 2) advantages and limitations of each particular test. The two examples below illustrate the complexity involved in clinical genetic testing.

*Example 1: Genetic testing for diagnostic purposes.* A positive test result is relatively straightforward and interpretation is uncomplicated. A positive test confirms the clinical diagnosis, may give a prediction of the course of illness, can lead to a better choice in treatment and can be used to identify at-risk family members. The interpretation of a negative test result is less intuitive. If an affected person tests negative, the clinical diagnosis is not necessarily wrong. This negative test result may have arisen because (1) a mutation is present but the test could not find it or (2) another gene is causing the disease. What it does mean is that the individual's outlook and

treatment is not tailored, and at-risk family members are not likely to benefit from predictive testing.

*Example 2: Genetic testing for predictive purposes* (i.e. a test used to determine if an asymptomatic person is at risk of developing a genetic disorder). The utility of predictive testing hinges on (1) whether we know the mutation in the family and (2) the extent of the gene's contribution to the disease process.

- (1) Assuming we have identified the mutation in the family, the genetic tests serve to answer the question "Does this individual have the family's mutation?" If this person tests negative, then he/she is unlikely to develop that disease. If this person tests positive, then he/she has a risk of developing that disease. However, this risk may be complicated to quantify because (1) the certainty of having disease may not be 100% (non-penetrance), (2) lack of genotype-phenotype correlation.
- (2) If we don't know the mutation in the family, the genetic tests serve to answer the question "Is there a significant mutation present in this gene?" If this person tests positive, then he/she has a risk of developing that disease. Similar to the above situation, this risk may be difficult to quantify because (1) the certainty of having disease may not be 100% (non-penetrance) or (2) a lack of genotype-phenotype correlation exists. If the person tests negative, this does not exclude the possibility of still being at risk because (1) a mutation may be present but a test could not find it, or (2) another gene is causing the disease.

### **Legal, Social and Ethical Issues in Clinical Genetic Testing**

Clinical genetic testing and population genetic screening programs are already a part of medical practice, and it is likely that more tests and programs will be established as the knowledge of the roles genes play in the disease process grows. Apart from medical implications, there are also many legal, ethical and social implications. Examples include access to genetic tests, the use of genetic tests in subgroups that are potentially vulnerable to being abused, risks for psychological stress and risks for discrimination.

#### ***Access to Genetic Tests***

Currently, access to direct testing by the public is very limited as most genetic testing laboratories require the mediation of a qualified healthcare professional (e.g. signature of a referral physician stating that the appropriate matters were explained and counselled). If genetic testing is directly available to the public, the potential consequences may include:

1. more privacy and confidentiality if anonymous testing is allowed;
2. greater ease in using genetic tests;
3. unethical use of genetic tests (e.g. vulnerable individuals may be tested for the benefits of others) or unethical motivations (e.g. eugenics); and

4. the tested individual may not be fully aware of the implications of testing and suffers untoward consequences (e.g. misinterpretation of results leading to unnecessary medical/social interventions).

To minimise the potential harm to the individual being tested, it is probably prudent to continue to limit direct access to genetic testing. In reality, however, this may be difficult to achieve as genetic tests are likely to be available in other countries. If the local authorities limit local direct access, the motivated individual may still be able to have access to direct testing by travelling to another country, for example, or by requesting testing via the internet. One can only hope that genetic testing laboratories will shoulder the onus of maintaining good standards of practice. Even then, one wonders if the public would be able to discern and understand the significance of such measures.

### ***Genetic Tests and Vulnerable Groups***

There are certain subgroups of the population that may be more likely to be harmed by genetic testing. These individuals are usually considered to be vulnerable either because (1) the person being tested is unable or incapable for providing consent (e.g. minors or mentally incompetent individuals); or (2) there are concerns about the validity of the consent (e.g. less educated persons, language issues, prisoners or students).

Minors with genetic diseases tend to fall into one of these groups:

1. Symptomatic at diagnosis;
2. Asymptomatic at evaluation, at risk of developing disease childhood/adulthood, availability of intervention or treatment during childhood;
3. Asymptomatic at evaluation, at risk of developing disease adulthood, availability of intervention or treatment only during adulthood; and
4. Asymptomatic at evaluation, at risk of developing disease, no intervention or treatment available.

The issue of testing minors in groups (1) and (2) is quite clear; it is generally accepted that these individuals can be tested because test results are likely to directly benefit them. The issue of genetic testing in minors in groups (3) and (4) is more controversial. The concern is that the person giving consent may have a vested interest in the outcome of the genetic tests, and this interest may not be in the best interest of the child. Moreover, one should also consider protecting the child's right to make his/her own decision when he/she is an adult. The counter argument is that science is rapidly advancing and intervention or treatment in childhood may become available, and to maximally benefit from such advancement, a person must know whether he has the disease. This issue has been widely debated and it is generally felt that genetic testing should not be performed in minors in groups (3) and (4). Every effort must be made to protect the privacy of the child and his right "not to know" his genetic risk.<sup>5,6</sup>

There are also other vulnerable groups that pose challenges to the medical community. Mentally incompetent individuals are one such group. The physician needs to determine that the legal guardian providing consent does not benefit more from the

results than the affected individual. Non-educated persons and individuals with language issues are another vulnerable group as they may not be able to comprehend and give truly informed consent. These situations involve less educated persons and individuals with language issues. Prisoners and students are also vulnerable as they may feel coerced into giving consent to participate in genetic tests. In such cases, precautions should be taken to ensure that free and informed consent is possible (e.g. having an independent review committee). As mentally incompetent persons are unable to provide informed consent for genetic testing, genetic testing may only be allowed if there are direct benefits for the mentally incompetent individual.

### ***Risks for Psychological Stress***

The process of genetic testing may put an individual under a lot of psychological stress (e.g. guilt, anxiety, self-doubt, fear and despair) because no treatment is available. To reduce the amount of stress, doctors should ensure patients that there is an acceptable turnaround time for genetic tests and that counselling can be provided to help them cope.

### ***Risks for Discrimination***

There are concerns that genetic testing results may lead to discrimination due to misinterpretation of test result implications. In particular, there is great concern that there will be discrimination by employers, insurance providers and society. Will insurance company understand and correctly comprehend such complex results? Will they take the conservative view and err on the side of caution and discriminate against such at risk individuals? Will employers do likewise? Will these individuals be socially stigmatised? Some of these scenarios have yet to be played out in reality, while others have occurred (e.g. job discrimination in sickle cell trait carriers as a consequence of poor public understanding of the condition).<sup>7</sup>

To maximise the health benefits of genetic testing, it is important to address these concerns. One means of safeguarding against discrimination is to address the confidentiality of genetic testing. Under current practices, genetic results along with other non-genetic results are released whenever a standard medical report is requested. We should continue to allow medical personnel easy access to such results, as access will enhance management of the patient. We may want to consider restricting access by non-medical persons (e.g. insurers and employers) as they may not be able to understand or correctly comprehend such complex results.

Another means is to ensure that genetic tests are conducted with accuracy and offer a comprehensible interpretation of results. Ensuring accuracy of the test itself is fairly easy as there are acceptable laboratory standards available. Ensuring accurate interpretation by other health professionals and clear communication of that piece of information to the patient is much more difficult. We may need to restrict the interpretation of such results to appropriately qualified persons and may need to standardise certain aspects of test result reporting. However, if we choose to regulate

genetic testing services, we must ensure that our regulations keep up to date with the rapidly changing technology. If not, we will do more harm by hindering medical care.

## **Population Genetic Screening Programmes**

### ***Definition and Aim of a Population Genetic Screening Programme***

Most genetic tests are performed on individuals for reasons that are particular to that patient's condition. When a test is used to test large numbers of persons to determine their status with regards to a genetic condition, this test usually becomes part of a population genetic screening programme whose aim is to reduce the morbidity and mortality in the general population. While many of the issues previously raised do apply, there are additional special considerations to bear in mind.

In a population genetic screening programme, history taking, physical examination and/or tests are used to presumptively identify persons who may have a genetic disease, who may be at risk of developing a genetic disease or who are predisposed to having children with a genetic disease. The persons identified by such means are then referred for diagnostic/ confirmatory tests. This approach is usually chosen when the diagnostic/confirmatory test is not the ideal tool for use on the general population (e.g. it is riskier, more expensive, more time consuming etc.).

### ***How Do We Decide If a Genetic Screening Programme is Worthwhile?***

As a population genetic screening programme may touch the lives of many persons, it is important that its benefits must outweigh its costs or disadvantages. This is usually ascertained by determining if a screening programme

- Targets a suitable disease;
- Uses a suitable screening test;
- Uses a suitable diagnostic test; and
- Administers a suitable screening process.

A suitable disease is one that has significant morbidity and mortality, occurs at significant frequency in the population, has a period where one can intervene, and where intervention has been shown to be effective. A suitable screening test is one that has a high test accuracy and reliability and is relatively cheap, free from risk and acceptable to the population. A suitable diagnostic test is one that can accurately identify people with the disease or at risk for it. A suitable screening process is one that has a reasonable turnaround time, is capable of recalling persons and is carried out in a socially and ethically accepted manner.

### ***What is the Process of Genetic Screening Like?***

If a person fulfils the criteria for having a screening test, the individual will be counselled on relevant issues that are similar to those discussed in clinical genetic testing (see above). The one exception is the implication of test results. Individuals who



test positive on a screening test are only at risk of having the disease and may not necessarily have the disease. These individuals are then referred for further diagnostic testing to ascertain if they truly have the condition.

An analogy of this process can be found in the airport. A gun on an airplane is a condition that can potentially lead to increased morbidity and mortality. If one is able to detect it prior to it being on the airplane, one can reduce morbidity and mortality. A gate-type metal detector is a suitable screening test. It is relatively cheap, does not harm the passengers, can be done efficiently and has an acceptable rate of accuracy and reliability. Hence, it is acceptable to most passengers. If a passenger “tests positive” on the screening, this does not necessarily mean that the passenger has a gun. The passenger is then referred to a diagnostic test (e.g. a hand wand metal detector or a check by a law enforcer) to determine if the passenger truly has a gun. To be effective, these elements must be part of a reliable screening process. In other words, the system must be used to screen all passengers and administered in a reasonable time frame so as to avoid delaying air travel etc.

### ***Are Population Genetic Screening Programmes Subject to Medical Research?***

The primary aim of a genetic screening programme remains the safeguard or promotion of immediate well being of the screened subject. At certain points, the performance of the screening program will be and should be audited. Indices such as sensitivity, specificity and cost effectiveness may be derived with the intention of assessing the utility and safety of the program. One of the consequences of this primary aim may be the publication of the assessment in a research journal.

Research as a primary objective is usually confined to the development phase of a genetic screening test or program. The aims of such research are usually (1) to develop a test that will discern between asymptomatic people at an increased risk and asymptomatic people at no increased risk, and (2) to assess the effectiveness and feasibility of the test at a population level. When research is the primary aim, consent and ethical approval are required.

### ***What are the Population Genetic Screening Programmes Available in Singapore?***

There are several population genetic screening programmes currently available in Singapore. Their aims remain true to the general philosophy (i.e. testing large numbers of persons in order to determine their status with regards to a genetic condition so as to reduce the morbidity and mortality in the general population). The genetic conditions tested include chromosomal disorders, risk for blood group incompatibility, thalassaemia, foetal abnormalities and certain metabolic disorders.<sup>8</sup> These are conducted during several key times in a person’s life.

1. Pre-pregnancy:
  - a. Screening for a history of infertility, miscarriages, or abnormal children
  - b. Full blood count (Haemoglobin, mean corpuscular volume)
  - c. ABO/Rh blood grouping

2. Pregnancy
  - a. Maternal: Triple maternal serum screen
  - b. Foetal
    - i. Ultrasound scan for structural abnormalities
    - ii. Amniotic fluid for alpha-foeto-protein
3. Postnatal
  - a. Physical exam at birth
  - b. Congenital hypothyroidism
  - c. Glucose-6-Phosphate Deficiency
  - d. Screening for hearing loss
  - e. Screening for metabolic diseases in certain sub-populations

Most of these screening programmes are carried out after obtaining verbal consent. For mostly historical reasons, written informed consent is not widely used; these programs were established in previous decades when written consent was not practiced. While these programmes have become socially acceptable and even expected, the rapid expansion of genetic knowledge means that more genetic screening programmes are likely to come into existence. Thus, the issue of consent will need to be examined. Should written consent be required for future genetic screening programmes? Should it be an active process i.e. informed consent (opting in) or a passive process i.e. informed dissent (opting out)?

*Case illustration: screening programme for Down syndrome*

Down syndrome is a genetic disorder of significant occurrence. A significant proportion of the population finds it acceptable to screen for Down syndrome in the antenatal period so as to have the choice to intervene. Ideally, the test used should be highly accurate and reliable. However, tests with such desired accuracy and reliability require obtaining a sample from the foetus. Such a procedure has an estimated 0.5% risk of causing harm to the mother and the foetus. For women 35 years and above, the risk of having a child with Down syndrome is ~0.5%, hence it is ethical to offer these invasive tests as both a screening and diagnostic test since the risk of harm is equal to the risk of having a child with the disorder.

However, for women below 35 years old, it is not ethical to use this as a screening test because their risk of having a child with Down syndrome is much less than the risk of harm from the procedure. Needing a different approach, non-invasive screening tests were developed. These tests involve a combination of blood tests and ultrasound scans of the foetus. Using certain cut-off values, the screening process will pick up about 90% of pregnancies with Down syndrome; however, 5% of normal pregnancies are also flagged (false positive). In order to sort this out, these individuals are then offered the invasive diagnostic test.

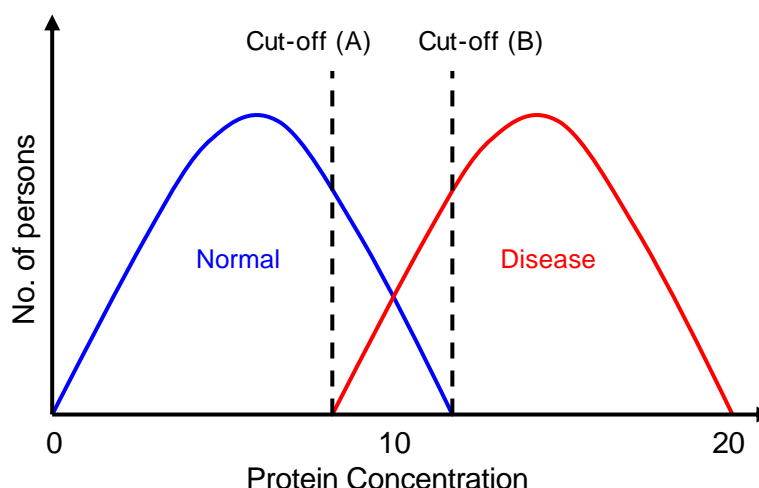
If a couple is not keen to undergo such testing (e.g. it poses a risk to the baby, or they have no intention to terminate the pregnancy) then they should think twice about having such screening tests. As such issues are difficult to anticipate and appreciate

prior to testing, it is essential that genetic counselling be given and consent taken prior to undergoing the screening tests.

### ***What are the Medical Implications of a Genetic Screening Programme?***

One major implication of the demands placed on a justifiable screening programme is its effect on the type of disease the programme can screen. These criteria favour conditions that have significant morbidity and mortality, occur at significant frequency in the population and have a period during which intervention has been shown to reduce morbidity and mortality. Diseases that are rare, not treatable or do not improve with treatment are unlikely to be selected for a population screening programme. Exceptions do occur, but usually involve conditions that are associated with specific sub-populations (e.g. Ashkenazi Jews and Tay Sachs's Disease, Caucasians and Cystic Fibrosis<sup>7,9,10</sup>).

Another implication is the possibility that a screening programme may miss affected persons and/or falsely alarm unaffected persons. Ideally, the screening test should have high accuracy and reliability, and be capable of completely distinguishing the affected from the unaffected. In reality, however, this may be difficult because the test values in affected and unaffected individuals may overlap (see figure). In such instances, a cut-off value must be chosen for use in differentiating between a "normal" and an "abnormal" test result. If the cut-off point is placed high (B), the test will be very specific and will pick up only those who are truly affected. However, it will miss some of the affected and give these individuals a false sense of security (a false negative result). If the cut-off point is chosen low (A), then the test will be very sensitive and will pick up all who are truly affected, but will also label many normal individuals as "abnormal" (a false positive result). In this scenario, a more definitive diagnostic/confirmatory test is then needed to differentiate between true positives and false positives. If a person tests "abnormal" on the diagnostic test, then they have or are at risk of the disease. If they test "normal", then they are unlikely to have the disease. Thus, the decision as to which cut-off value to use must take into consideration the disease involved, the cost effectiveness, the consequences of missing those with the disease and the amount of anxiety afflicted on those labelled falsely as affected.



The dissemination of accurate and comprehensible information is an important criterion for an effective screening program. However, the objectives, screening process and potential need for further testing are difficult issues for both the public and medical community to anticipate and appreciate. In addition, the interpretation of a screening test result requires a physician who understands the accuracy, reliability and cut-off values of the test as well as the disease involved. Two major challenges therefore arise: (1) how to ensure that the individual is aware of the consequences of their choice to participate; and (2) how to ensure that physicians have the correct knowledge to interpret the tests results.

The first challenge involves the issue of informed consent. How do screening programs ensure that their participants have given informed consent? This is achieved through the process of genetic counselling where a trained professional explains such matters to the individual. Educational pamphlets can also be used to further ensure that an individual is fully informed. The issues that need to be discussed generally include the following:

1. the nature of the condition being screened including diagnosis, prognosis, treatments available, inheritance pattern, risks of recurrence in the family;
2. that participation is voluntary;
3. the sample required and possible side effects of the sample collecting procedure;
4. the screening process;
5. the implications of a positive or negative test, and potential need for further diagnostic testing;
6. the potential to uncover undisclosed non-paternity, if applicable to the test; and
7. the confidentiality of results. Genetic screening results are accorded the same level of confidentiality as regular medical records.

The second challenge concerns the education of medical and paramedical staff. This can be facilitated by using continuing medical education programs that are already in existence in many countries, including Singapore. In addition, educational websites can be set up to provide information for both the public and professional community. Printed educational material can also be distributed through the registry of medical professionals. Finally, the results of screening tests can be issued with the correct test

interpretation to reduce the burden on the individual physician to interpret the test findings.

### **Conclusion**

The influence of genetics in medicine is growing and will continue to grow. While it carries with it much promise for improving the prevention and treatment of diseases, there are potential obstacles and repercussions that may hamper this vision. Some of these issues have been highlighted in this paper. We have a unique opportunity to recommend ways of safeguarding ourselves before a negative incident happens, and we should seize this chance. After all, prevention is the best cure.

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# **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.

*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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## GENETIC TESTING IN ONCOLOGY

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### Introduction

Cancer in Singapore accounted for 28.0% of deaths in 2002, making it the most important cause of mortality.<sup>1</sup> This continues the trend of increasing cancer incidence and deaths over the last decade.<sup>2</sup>

The path to understanding the genetic basis of cancer has led us to study the human genome in detail. The use of such genetic information in the clinics for adult-onset disorders like cancer has the potential to transform oncology practice.

As we seek knowledge, we should not deny patients and their families some of the benefits genetic testing might bring. In some families, early detection or preventive surgery has transformed the outcome for mutation carriers. In other instances, a person who does not carry the mutation that runs in the family has avoided uncomfortable and sometimes costly screening tests.

Although most of the familial cancers and the use of genetic testing has been in “rare” cancer families, this has changed with the discovery of susceptibility genes for the commoner cancers such as breast<sup>3</sup> and colorectal cancers.<sup>4, 5</sup>

However, we have been better at discovering new genes, which is not matched by our understanding of how these genes cause diseases. Given these limitations, we should recognise that inappropriate testing can sometimes cause harm.

### *What is Genetic Information?*

Information about a person’s genetic makeup may be obtained in several ways:

1. by taking a family history of a genetic disease;
2. by observing external characteristics; and
3. by analysing blood or bodily tissue containing DNA, associated proteins or other biochemicals.

In almost all cases, genes are not the sole determinants of disease. There is environmental interaction including diet, smoking and other local factors. In addition, because the full pathway of genes causing disease is sometimes not fully elucidated, downstream influences from other genes may additionally modify the outcome of a particular gene effect.

We know that disease-causing mutations may be in single genes or may involve the interaction of several genes (polygenic diseases). Sequence variants, or **polymorphisms**, which refers to DNA sequence changes that have no effect or a minor effect on protein function and production, may sometimes confound our understanding of the genes and disease association. Current use of clinical genetic testing in oncology tracks mostly single genes as the cause of cancer, although more work now involves polymorphisms and the interaction of multiple genes.

In this paper, genetic information refers primarily to that obtained through analysis of blood or bodily tissues.

### ***Genetic Information and Oncology***

Work involving cancer genes has been especially rapid because cancer is a global disease. Studying these genes has improved our awareness of biochemical and signalling pathways and their role in carcinogenesis.

Treating cancer can be costly. Prevention can create enormous public health and economic impact. People who are highly likely to develop cancer can be identified for targeted prevention efforts. Genetic information can identify individuals at higher risk for certain cancers.

### ***Definitions***

A genetic test analyses the status of a particular gene and includes the analysis of human DNA, RNA, chromosomes, proteins and certain metabolites to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes.

Broadly, adult genetic testing can be divided into:

- (a) *Diagnostic Genetic Testing* – to aid the diagnosis, treatment and management of symptomatic individuals.
- (b) *Carrier Testing* – to detect individuals who possess a single copy of a gene which follows an autosomal recessive pattern of inheritance. Such an individual will not normally develop any disease or disorder but may pass on the gene to his or her offspring.
- (c) *Presymptomatic Genetic Testing* – to determine whether individuals who have a family history of a disease, but no current symptoms, have the gene mutation.
- (d) *Predictive Testing* – to determine the probability that a healthy individual with or without a family history of a certain disease might develop that disease.<sup>6</sup>

Most of the issues surrounding genetic testing are not related to diagnostic genetic testing in a cancer-affected individual, but instead involve genetic testing when no

cancer has yet been detected. There is also a distinction from detection of changes in cancer cells (somatic mutation) that may guide cancer therapy but are not heritable.

There are limitations to the ability of genetic tests to predict diseases. Besides the quality of the test itself (even for single genes), variable penetrance, expressivity and genetic heterogeneity can compound our interpretation of such tests.<sup>7</sup>

### **Issues of Concern in Genetic Testing**

Genetic information can be obtained from a very small amount of material (the DNA in a single cell). It is convenient, and does not require lengthy follow up or history taking.<sup>8</sup> Genetic information, however, may also be obtained without the knowledge or consent of the person from a sample obtained in the past for another purpose or from cells shed unknowingly. There is concern that third parties such as employers and insurance companies may be interested in the information from genetic testing.

#### ***Predictive Genetic Testing is Different from Conventional Medical Testing***

A conventional medical test provides information about a patient's current status, which may have implications for the patient's current care. In contrast, a predictive genetic test informs of a future possibility of disease.<sup>9</sup>

Such results bring an element of uncertainty about not only the timing of illness, should it appear, but also about the severity of the illness and whether present intervention can be effective.

Information pertaining to predictive genetic testing also has implications for other related family members. To some extent, genetic information informs the risk of an unaffected parent, sibling or child when a family member is found to carry a deleterious mutation. On the other hand, when a person has cancer, his immediate relatives are at risk not only because of shared genes but also because of shared environmental influences.

### **Clinical Aspects of Cancer Genetic Testing**

#### ***Indications for Genetic Testing for Cancer Susceptibility***

Cancer is not inherited, but the susceptibility to cancer is inherited. In familial cancer syndromes, inherited **germline mutations** are replicated in all cells of an individual. Predictive genetic testing hopes to identify cancer-susceptible individuals early enough to implement cancer screening, surveillance and prevention.

As a general principle, cancer genetic testing<sup>10</sup> should be offered only when:

1. the individual has personal or family history features suggestive of a genetic cancer susceptibility condition;
2. the test can be adequately interpreted; and
3. the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

Hereditary cancer syndromes can be well defined and test results can influence subsequent medical care. In some instances, genetic testing has become part of the standard management of these families. (Examples are familial adenomatous polyposis, medullary thyroid cancer)

However, this is not true of all cancer syndromes. New genes are discovered and new tests developed daily. As predisposition testing is an evolving science, a continual assessment of the use of these new tests in clinical practice is needed.

There are many cancer susceptibility genes and syndromes,<sup>11</sup> a possible list of cancer predisposition syndromes where testing could be considered are found at the American Society of Clinical Oncology (ASCO) website ([www.asco.org](http://www.asco.org)).

It is known that subjects undergoing genetic testing may have a wide range of emotional response from panic to relief.<sup>12</sup> Personal interpretation of results and risks figures can also be coloured by an individual's experiences of cancer within the family and circle of friends. Knowing results can create chain effects and actions for individuals and their families. Uncertain results can create frustrations and a false sense of security. Certain interventions in response to genetic test results have unknown efficacy.

Since not all tests are useful and may cause harm in some situations, the process of cancer genetic testing should only be performed with pre and post-test counselling. There should be a familial risk assessment to identify suitable at-risk individuals, as none of the tests have been recommended as screening tests. Pre- and post-test counselling should be part of the process of genetic testing.

### ***The Role of Familial Risk Assessment***

Familial risk assessment is practised by centres offering genetic testing and counselling. It involves gathering a detailed family history. The purpose is to compile detailed cancer and non-cancer diagnoses about the family and exposure to carcinogens, and includes up to three generations in the pedigree.

The pedigree has to be interpreted with the understanding that reduced gene penetrance and variable phenotype expressivity can occur. A genetic counsellor, physician or nurse counsellor usually does the risk assessment.



In pedigrees where a clear Mendelian pattern of cancer susceptibility is inherited, cancers may exist in every generation of the pedigree. In a cancer predisposition syndrome, multiple cancers can occur in a family.

However, clustering of cancers does not always indicate transmission of a susceptibility gene. Cancers in a family can also arise from shared lifestyle, diet or environmental carcinogens. Examples include tobacco exposure resulting in lung cancers, and hepatitis B carriers with hepatomas.

**Sporadic** cancers (arising in the absence of heritable susceptibility mutations) common in the population arise from complex interactions between multiple genes and the environment. Sporadic cancers may appear in large families — particularly if they occur at a later age. Risk assessment should provide some guidelines to the subject for individual health decision making.

Several professional societies have recognised the need to improve care in this area. The ASCO has, for example, issued policy and guidelines to cancer specialists in this area<sup>10,13</sup> and plan training programs.<sup>14</sup>

### ***Pre-Test and Post-Test Counselling***

**Pre-test counselling** is a process of communication and is part of the informed consent process for genetic testing. Elements of informed consent<sup>10</sup> for cancer genetic testing should cover the topics in Table 1.

***Table 1. Basic elements of informed consent for germline DNA testing***

- |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"> <li>1. Information on the specific test being performed</li> <li>2. Implications of a positive and negative result</li> <li>3. Possibility that the test will not be informative</li> <li>4. Options for risk estimation without genetic testing</li> <li>5. Risk of passing a mutation to children</li> <li>6. Technical accuracy of the test</li> <li>7. Fees involved in testing and counselling</li> <li>8. Risks of psychological distress</li> <li>9. Risks of insurance or employer discrimination</li> <li>10. Confidentiality issues</li> <li>11. Options and limitations of medical surveillance and screening following testing</li> </ol> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Part of the session should be devoted to providing information for individuals who seek genetic counselling. Understanding technical language, the probabilistic nature of risks and cancer information can be difficult even when language is not a barrier.<sup>15</sup> In multicultural Singapore, communication of such information can be even more difficult.

Pre-test counselling is best performed by a trained professional who has knowledge of cancer syndrome genetics and is familiar with the proposed test. In Singapore, trained professionals include genetic counsellors, nurse counsellors and doctors.

**Post-test counselling** helps to place results in perspective for the individual. Results from genetic tests can cause relief or distress in individuals.

Mutation carriers can feel relief at clearing uncertainties<sup>16</sup> and begin a discussion of prevention measures. Conversely, non-carriers can experience "survivor guilt" when they realise that they do not share the same risks as affected relatives.<sup>17</sup>

Genetic test results can be reported as negative, positive or inconclusive for a suspected mutation. In a report by Giardiello in 1997, almost one third of physicians misinterpreted the results of commercial APC gene testing in familial adenomatous polyposis.<sup>18</sup> Given the large number of genes unknown today, a negative result could mean that an inappropriate gene was tested. A true negative result is informative only when the mutation that occurs in affected members of a family is known.

It is clear that genetic tests do not detect all the mutations in affected cases. In addition, some cancer syndromes may have genetic tests available, but the impact on medical management may be uncertain (e.g. TP53).<sup>19</sup> Furthermore, inconclusive test results can lead to stress.

Careful handling and counselling after testing is important. There should be a discussion about the possible risks and benefits of early-detection and prevention modalities with a trained professional. Many of these decisions are very personal and may involve handling information for at-risk siblings or even parents.

### **Maintenance of Genetic Test Information**

There is public concern that insurance companies may discriminate against individuals perceived to have an elevated risk of cancer from their genetic test results.

In a paper by Matloff, genetic specialists were posed a hypothetical situation where they had a 50% chance of carrying a mutation for a hereditary cancer.<sup>20</sup> Eighty-five percent of respondents said they would undergo genetic testing. However, the majority would not bill their insurance company or would use an alias for fear of discrimination.

In countries such as the United States where health insurance is common and needed to obtain a reasonable level of health care, this issue is especially important. Although Singapore's health care structure is different, implications for life insurance applications remain.

Historically, family histories of cancers have long been used clinically for assessing a person's risk. Insurance premiums are increased for those at risk of inherited diseases. In some situations, it may also be possible for a genetic test to inform that a person who

has a family history of cancer actually does not carry the susceptibility gene. Genetic tests are heterogeneous and the accuracy, reliability and predictive value for risk need to be evaluated for their use.

The indiscriminate use of genetic tests is of concern. The United Kingdom Human Genetics Commission publication discusses some of the issues related to insurance and employer use of personal information.<sup>8</sup>

Genetic information is privileged, confidential, medical information. There are standard safeguards in hospitals regarding access to and use of medical information that includes computerised medical records. No information should be released without the patients' consent.

Although discrimination based on genetic information has not been reported in Singapore, fear of discrimination may prevent people who might benefit from genetic testing from doing so.<sup>21</sup>

While the UK Human Genetics Commission ([http://www.hgc.gov.uk/business\\_publications.htm](http://www.hgc.gov.uk/business_publications.htm)) and the American Society of Clinical Oncology have recognised that this is an area of concern, different countries approach the subject differently.<sup>10</sup> In the UK, a Genetics and Insurance Committee<sup>8</sup> has been set up to oversee and discuss the issues with the industry and independent experts.

### **Research Genetic Testing**

While researchers are interested in the academic aspects of cancer causation and in discovering which genes are important in making some individuals susceptible, subjects may not directly benefit from knowing these findings.

Much of what we have learnt about cancer genetics is from high-risk individuals and families who have selflessly provided information and samples for research. There should be scrupulous ethical and legal safeguards for research participants. On the other hand, these safeguards should not stifle research efforts.

Improving technologies and powerful biotechnological tools creates enormous potential to form large databases of genetic information. Even with minuscule samples, a den of information can be mined and stored. The information can also be mined from archival samples.

The Bioethics Advisory Committee has set guidelines in the Human Tissue Research Report on 12 November 2002 (<http://www.bioethics-singapore.org/resources/reports.html>).

Use of information from subjects tested on research protocols should be based on institutional guidelines with ethics committee oversight and approval.

Consent for genetic testing research should require careful explanation of the nature of the study supplemented with written information.

The difference between clinical and research testing should be made clear to participants. For example, clinical genetic testing in the United States means that the laboratory has to follow certain (Clinical Laboratory Improvement Amendments, CLIA) guidelines (<http://www.cms.hhs.gov/clia/>). Guidelines ensure quality assurance and quality control methods in molecular diagnostics. Research laboratories may not follow stringent guidelines for collecting, transport and storage of biological materials.

In clinical testing, an individual chooses to undergo genetic testing wishing to know the outcome. In research testing, the individual may choose not to find out anything about his/her genetic status. The handling of research testing results should be made known to the subject before participation in the protocol.

For protocols in which the subjects find out their cancer predisposition status, pre- and post-test genetic counselling should be provided to help them understand the implications of the results.

Guidelines are available for research involving genetic testing (UK Advisory Committee on Genetic Testing October 1998).<sup>22</sup>

### **Testing Children for Cancer Susceptibility**

In general, genetic testing for adult onset disorders is not undertaken if the child is healthy and the test result has no direct medical application. Children may have difficulty understanding the information on genetic testing, although this may vary depending on maturity and age. Children may also have a different view of testing from their parents or surrogate decision-maker. Genetic testing in children is a complex subject and several societies have addressed it.<sup>10, 23-26</sup>

When the genetic test may detect conditions for which treatment or preventive measures are available (e.g. FAP), testing of minors should proceed according to established consent guidelines for other necessary medical treatments in children.

### **Economics of Genetic Testing**

Newer and novel oncology drugs for the treatment of advanced cancer are expensive. This contrasts the cost of gene identification and prevention of common cancers. True negatives identified on genetic testing may also avoid costs of unnecessarily early screening. In our current healthcare system, genetic testing is not recognised as reimbursable by Medisave.

However, there should be an ongoing review as new studies showing cost effectiveness<sup>27</sup> and efficacy<sup>28-31</sup> in cancer prevention have emerged.

The whole framework of regulation should encompass judicious testing of high-risk individuals in a system of risk assessment. Audits and studies of these efforts should be undertaken. Given that cancer risk and attitudes towards prevention can be different for our population in Singapore, we also need to address these with further research to integrate genetic testing into cancer prevention services.<sup>32</sup>

## Conclusions

Genetic testing in oncology practice is a tool that needs to be wielded with care. Providing information in the form of genetic counselling has become a standard of care for individuals undergoing genetic testing for cancer predisposition.

A framework to develop and deliver these services would allay public anxiety over abuse of genetic information and discrimination by employers and insurers. Proper implementation could lead to better prevention for cancer.

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## GENETIC COUNSELLING AND GENETIC TESTING: HEREDITARY CANCER SYNDROMES

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In this paper, issues that are related to genetic counselling and genetic testing of hereditary cancer syndromes are discussed. These are largely adult-onset syndromes, and many of the issues will be related to the individual and the family in the adult context. Specific issues such as testing in minors and reproductive issues will be discussed only briefly, predominantly in the context of familial adenomatous polyposis.

### Introduction

A number of distinct hereditary cancer syndromes have been described in the last decade, including familial adenomatous polyposis,<sup>1, 2</sup> hereditary breast and ovarian cancer syndrome due to *BRCA1/2* mutations,<sup>3, 4</sup> hereditary non-polyposis colorectal cancer,<sup>5</sup> and Li Fraumeni syndrome.<sup>6</sup> The causative genes have been elucidated for some of these syndromes,<sup>1, 3, 4, 7-11</sup> and genetic testing to identify mutation carriers of certain distinct hereditary cancer syndromes is now clinically available.<sup>12-16</sup> As genetic testing is a complex issue that may have medical, psychological, ethical, social, and legal implications on the individual and the family, pre- and post-test genetic counselling is an integral part of the testing process.<sup>17</sup> Many reputable laboratories offering cancer genetic testing require pre-test counselling before processing the sample.

Specialised clinics providing cancer risk assessment and genetic counselling have been established in the two major cancer centres in Singapore, National University Hospital and the National Cancer Centre, for about four years. The common hereditary cancer syndromes for which genetic testing is currently available to local patients include the following:

1. *BRCA1/2* sequencing for hereditary breast and ovarian cancer syndrome.
2. *hMLH1/hMSH2* sequencing for hereditary non-polyposis colorectal cancer.
3. Protein truncation test for the *APC* gene for familial adenomatous polyposis.
4. Microsatellite instability testing for hereditary non-polyposis colorectal cancer.<sup>18</sup>
5. Testing for common mutations in the *RET*-proto-oncogene for patients suspected to have multiple endocrine neoplasia type II.<sup>19, 20</sup>



## Who Should Receive Genetic Counselling?

Only individuals or families suspected clinically to have hereditary cancer syndrome (strong familial cancer clustering or young onset cancer) will benefit from genetic counselling and genetic testing.<sup>17</sup> Genetic counselling and genetic testing for hereditary cancer syndromes will not benefit the general risk patient and should not be offered routinely.

As a general rule, genetic counselling and the option of genetic testing in the context of hereditary cancer syndromes should only be offered to adults above the age of 18 who are able to make an autonomous and informed decision regarding genetic testing (*see testing of minors for exceptions*).

## Who Should Conduct Genetic Counselling?

Pre- and post-test genetic counselling is an integral part of genetic testing. A person who understands the medical, psychological, social, ethical, and legal implications of genetic testing should conduct the counselling. The counsellor should be able to evaluate hereditary cancer syndromes, be familiar with indications for genetic testing, be able to interpret test results, and be familiar with potential psychological, ethical, social, and legal issues that may arise. Inadequate pre-test counselling may result in ethical, social, and legal implications that were not anticipated by the patient. In the United States, a physician, nurse educator, or genetic counsellor with appropriate training typically carries out cancer genetic counselling. The American Society of Clinical Oncology periodically holds workshops to update management issues in cancer genetics for providers, and has developed continuing medical education materials.<sup>21, 22</sup> Providers may also be credentialed in Familial Cancer Risk Assessment and Management through the Institute of Clinical Evaluation, USA. Two medical oncologists in Singapore have been credentialed in this way.

## Guidelines for Cancer Predisposition Testing

In 1996, the American Society of Clinical Oncology recommends that practicing physicians recognise three categories of indications for genetic testing of hereditary cancer syndromes:<sup>17</sup>

### *Category I*

Category I includes families with well-defined hereditary cancer syndromes, for which genetic test results will change medical care. Category I is considered standard management. For example, genetic testing for familial adenomatous polyposis is considered standard as effective surveillance and preventive options exists for mutation carriers.<sup>12, 23, 24</sup> Other conditions that are included in Category I include multiple endocrine neoplasia type II<sup>19, 20, 25</sup> and retinoblastoma.<sup>26, 27</sup>

### *Category II*

Category II includes hereditary syndromes in which the medical benefit of identifying a mutation carrier is presumed but not established. Genetic testing of these conditions may provide some medical benefit, but the risks and limitations must be extensively discussed with the patient. In this category, a positive test result may lead to earlier surveillance or consideration of preventive options, although these risk management options have not been proven to reduce morbidity and mortality. A negative test result may be of value if it occurs in the context of a known mutation in the family. Examples include *BRCA1/2* in hereditary breast and ovarian cancer syndrome and *hMLH1/hMSH2* in hereditary non-polyposis colorectal cancer.<sup>28,29</sup>

### *Category III*

Category III includes hereditary syndromes for which genetic testing is unlikely to change clinical management. This category includes syndromes in which germline mutations have been identified only in a small number of families, such that genetic testing is of low yield and likely to be uninformative. It also includes syndromes for which the medical benefits of identifying mutation carriers are not apparent. Examples of syndromes included in Category III include *CDKN2A* for melanoma families<sup>30, 31</sup> and *STK11* for Peutz-Jeghers syndrome.<sup>32, 33</sup>

The American Society of Clinical Oncology recommends offering clinical genetic testing only for syndromes in Category I and Category II. Genetic testing for Category III is considered research with unknown clinical implications and should not be offered in the clinical setting.<sup>17</sup>

## **Pre-Test Counselling**

This is a process in which the patient and/or the family is given information on the nature of the hereditary cancer syndrome that is being suspected, the tests available to make a diagnosis, and the screening and preventive recommendations. This is a non-directive and interactive process, and the patient is given information on potential benefits and risks of testing to facilitate an informed decision.<sup>34-36</sup>

### *Components of pre-test counselling*<sup>21</sup>

#### Assess

- Personal and family medical history
- Risk perception and motivation for testing

#### Educate

- Basic genetics and inheritance
- Cancer genetics and risk

#### Discuss

- Potential benefits, risks, and limitations of genetic testing
- Test procedure

- Management options (surveillance and preventive measures)
- Anticipatory guidance
- Psychological issues

These issues are discussed carefully and extensively to allow the patient to make an informed decision regarding genetic testing. Counselling should be conducted in a language the patient understands and in a manner appropriate for the patient's intellect and level of medical knowledge. Printed materials summarising key issues that have been discussed can facilitate the retention of information. For example, patient education pamphlets on hereditary breast and colorectal cancer syndromes are available to patients counselled at the Clinical Cancer Genetics Service in the National University Hospital. More than one session may be required to discuss all issues and to allow the patient to assimilate the information. Adequate time should be given to patients to make a decision regarding genetic testing.

### ***Assessment of Risk***

The patient's personal and family cancer history is reviewed to determine the likelihood that the patient has a hereditary cancer syndrome.<sup>37-40</sup> In general, genetic testing is only recommended if the predicted risk of finding a mutation is at least 10%.

### ***Exploration on Risk Perception and Motivations for Genetic Testing***

The patient's perception of cancer risk and risk of having a hereditary cancer syndrome is assessed. The motivations for seeking genetic counselling / genetic testing are explored.<sup>41-45</sup> These may include using genetic information to make medical decisions (e.g. screening, preventive strategies), to help family members such as children and siblings, to make reproductive decisions or other major life decisions, or for empowerment, etc. By understanding the motivations for seeking genetic testing, the counsellor may assess whether the patient's expectations may be met through genetic testing. For example, a high-risk breast cancer patient who hopes to seek reassurance that she does not have a hereditary condition, through genetic testing as an index patient, is unlikely to have her expectation met, as a negative test result in such a situation is uninformative. On the other hand, it would be reasonable for a patient to undergo *BRCA1/2* genetic testing with a view to proceed with prophylactic bilateral mastectomy if tested positive.

### ***Education on Basic Genetics and Inheritance***

The patient and the family is educated on basic genetics, including the likelihood that the patient may have the syndrome, the mode of inheritance of the hereditary cancer syndrome in question, the cancer risks if one is found to have the syndrome,<sup>46-49</sup> and the medical implications on the individual and his family. Testing strategies to confirm the

diagnosis are discussed, including the interpretation of test results and the limitations of testing.

### ***Process of Informed Consent***

To facilitate informed consent, the potential benefits, risks and limitations of genetic testing are discussed.<sup>17, 34, 50, 51</sup>

#### *Potential benefits of genetic testing*

The potential benefits of genetic testing include identifying the cause of young cancers or clustering of cancers in the family, accurate cancer risk assessment for the individual and the family, the use of the risk assessment information to plan screening<sup>52-55</sup> and preventive measures,<sup>20, 56-61</sup> and the use of the information to proceed with predictive gene testing of cancer-free family members. The information may empower the individual and increase compliance to screening and preventive measures.<sup>62-64</sup>

#### *Potential risks of genetic testing*

The process of genetic counselling or genetic testing may cause psychological distress<sup>65-68</sup> as the individual faces the prospect of possibly having a hereditary condition and the difficult decision of whether to undergo genetic testing to confirm the diagnosis. As genetic testing may affect other family members, a decision for or against testing can cause changes in family dynamics, particularly when different family members have different motivations or share different views on testing. A positive gene test result may also cause potential genetic discrimination by employers and insurers.<sup>69-71</sup> An indeterminate result or a negative result in an index patient is uninformative but may cause confusion or a false sense of security in the patient, thus reducing compliance to screening.

#### *Limitations of genetic testing*

One of the major limitations of genetic testing is the fact that a negative test result in an index patient does not exclude the possibility of a hereditary condition. This is because several genes may be implicated in a particular hereditary syndrome, and only a few of the most important may be tested clinically. Furthermore, due to technical limitations, not all mutations in the gene of interest are detectable. In addition, mutations of uncertain significance may be identified.<sup>72</sup> These are missense mutations that are neither clearly benign polymorphisms nor deleterious. Mutations of uncertain significance and a negative gene test result in an index patient are uninformative, and will not help the patient. Even if an individual tests positive for a deleterious mutation, it is still only probable and not certain that cancer will develop. Similarly, an individual who tested negative for a mutation that existed in his family is simply not at risk for hereditary cancer, but may still develop sporadic cancer. Finally, as many hereditary cancer syndromes have only been characterised for a relatively short period of time,

many interventions that are currently recommended clinically have unproven efficacy due to the lack of long-term data.<sup>54, 55, 59, 60</sup>

### ***Management Options***

Management options available to the patients are discussed. For proven mutation carriers, this may include early surveillance programs, and preventive measures such as preventive medications or preventive surgery. For example, celecoxib reduces the number of adenomatous polyps in familial adenomatous polyposis,<sup>73</sup> preventive total colectomy reduces colorectal cancer risk in familial adenomatous polyposis,<sup>74, 75</sup> and preventive mastectomy and oophorectomy reduces breast cancer risk in *BRCA1/2* mutation carriers.<sup>59, 60</sup> Patients are also given management options based on risk estimates from personal and medical history if they choose not to be tested or if test results are uninformative. The individual may then compare the two sets of management options and make an individual decision regarding the potential impact of genetic testing on management options.

### ***Anticipatory Guidance***

The technique of anticipatory guidance may be used to facilitate decision-making during the genetic counselling process.<sup>21</sup> The patient is given a hypothetical situation and encouraged to discuss how he or she might feel or do in that situation. For example, the patient may be asked ‘How would you feel if you tested positive for a gene mutation?’ or ‘How do you think genetic testing may help you or your family?’ The same technique may be used to help patients consider how their family may respond to genetic testing, or their possible reactions to the patient being a mutation carrier. This can help patients consider how, when, and which family members they wish to share information with.<sup>76</sup> This technique allows the patient to anticipate the potential impact of genetic testing on themselves and their family.

### ***Addressing Potential Psychological Issues Related to Genetic Testing***

A number of psychological issues may arise as a result of genetic counselling or genetic testing.<sup>65-68, 77, 78</sup> Patients may experience anxiety or fear with the prospect of being labelled as someone with a ‘bad gene’. Individuals may feel guilty that they have a ‘bad gene’ that they could potentially pass to their children. A positive gene test result may lead to loss of self-esteem or depression. Mutation carriers may also face stigmatisation by family members, friends, the workplace, or society. Identifying a gene mutation in the family could impact family dynamics, dividing the family into two distinct groups: a high-risk group with a ‘bad gene’ and a low-risk group with the ‘good gene’. Mutation carriers or close family members of mutation carriers may experience grief or depression because of anticipatory loss.

Physicians/genetic counsellors should be cognizant of these potential psychological issues while counselling patients. During the process, the patient's experience with cancer, perceptions of cancer, its prognosis, and its treatment options are explored to anticipate reactions to test results. Patients' perceptions on prophylactic measures such as surgery to reduce cancer risk should also be explored. The involvement of a psychiatrist early in the process could be important in patients at high-risk for psychological events. In many established centres in the west, the cancer genetics team often comprises of a psychiatrist to manage such issues.

### **Genetic Testing Procedure**

This generally involves a blood test. Genetic testing performed for clinical use should be carried out in a certified laboratory.

### ***Testing of Index Patients***

The initial testing of a cancer-affected individual for a hereditary cancer syndrome is termed testing the index patient. Testing the index patient is laborious and expensive, as the entire gene of suspicion has to be scanned to identify a mutation. The major limitation is that the inability to identify a mutation does not exclude a hereditary condition. A cancer-free subject cannot be tested unless a cancer-affected index patient has been tested in the family and a mutation identified. Possible outcomes of testing index patients include finding a mutation (positive result, informative), finding no mutation (negative result, uninformative), or finding a mutation of uncertain significance (uninformative).

### ***Predictive Testing***

Once a mutation is identified in an index patient, the subsequent testing of cancer-free family members to determine if they carry the same mutation is termed predictive testing. This is highly specific, testing only for the presence or absence of the particular mutation that has been identified in the index patient. Test results are either positive or negative for a mutation, both of which are informative results.

### **Post-Test Counselling**

Issues that will be discussed during this session include:

- i. Test disclosure.
- ii. Test interpretation (meaning of a positive, negative and indeterminate test result).<sup>13, 72</sup>
- iii. Screening recommendations based on genetic test result.
- iv. Preventive recommendations based on genetic test result.
- v. Predictive testing of other family members if a mutation is identified.

- vi. Addressing psychological issues in response to genetic test result.
- vii. Addressing ethical and social concerns in relation to genetic test result.

### ***Procedure of test disclosure***

During this session, genetic test results are conveyed to the patient. Test disclosure via telephone or mail is strongly discouraged, and is best conducted face-to-face. This allows the counsellor to assess the patient's response to the test results, and to provide clarification and emotional support.<sup>21</sup> Results are generally given on a one-to-one basis, even if multiple family members were tested at the same sitting. This allows each individual to have privacy while receiving the test results and expressing reactions, without having to consider the family's reactions. After disclosing individual results and obtaining consent to share test results, the family can be counselled as a group to address further issues, particularly those that may affect family dynamics.<sup>79</sup>

During the post-test counselling session, apart from discussing the medical implications of the genetic test result, a good part of the session may be spent on evaluating potential psychological and social impact on the individual and the family.

### ***Addressing Psychological Issues***

#### ***Possible responses to a positive result***

Patients may become depressed when they learn that they carry a mutation in a cancer-susceptibility gene.<sup>80</sup> This is because an otherwise healthy individual is now predicted to have a high risk of cancer and there is no medical intervention to correct the defective genes. Patients may feel guilty<sup>44</sup> that they have had children and could have passed the mutation to them. On the other hand, many patients who have borne the burden of having a strong family history of cancer for years may actually experience feelings of relief and a sense of closure when they receive a positive test result. Some may feel that uncertainty has been removed, and they are now able to 'move on' and focus on surveillance and preventive measures. Identifying the causative gene mutation that accounted for the patient's cancer or his/her family's cancers can give a sense of empowerment, as the patient may now feel 'in control'.

#### ***Possible responses to a negative result***

In the setting of an identified mutation in the family, a negative test result constitutes a true negative. This result means that the individual is at normal risk for cancer despite the strong family history, and does not require early surveillance that his mutation-carrying family members may require. Relief is a common reaction.<sup>41</sup> Paradoxically, some individuals may experience survivor guilt on learning that they have 'escaped' and not inherited the 'bad gene'.<sup>81</sup> Some may still feel anxiety despite reassurance that they are at normal risk of cancer, and may be reluctant to reduce surveillance.<sup>64</sup>

### *Possible responses to an uninformative result*

Failure to identify a mutation in an index patient and identification of a mutation of uncertain significance are two limitations of genetic testing. Both results are uninformative. This may cause frustration or disappointment, as the test result cannot help the patient. Such a result may cause confusion in the patient, or even worse, a false sense of reassurance. It is thus very important to stress to the patient that this is an uninformative result, and not a true negative result. An indeterminate result may also lead to increased anxiety about cancer risk and management.

### *Addressing Ethical, Legal and Social Issues*

#### *Ethical, legal, or social concerns in relation to genetic counselling or genetic testing*

A number of ethical, legal or social issues may arise in relation to genetic counselling or genetic testing. Genetic counselling for hereditary cancer syndromes should therefore be restricted to trained medical practitioners (physicians or genetic counsellors) who are able to explain these issues during the pre-test counselling process so that the patient may make an informed decision regarding genetic testing. It is important to emphasise to the patient that genetic testing is more complex than most other medical tests (e.g. cholesterol testing, liver function testing). This is because while most other medical tests affect only the individual, genetic testing could have implications on other members. Genetic test results may also have social and ethical implications. Inadequate pre-test counselling may result in ethical, social, and legal implications that were not anticipated by the patient.

#### *Ethical issues in relation to genetic testing*<sup>17, 21, 82</sup>

##### Autonomy versus Beneficence

This is a situation whereby there is conflict between respecting patient autonomy and beneficence to the patient. For example, patient A tests positive for a mutation in a cancer-susceptibility gene but decides against receiving her test results. The physician knows that patient A is at very high risk of developing cancer. The physician now faces the dilemma of promoting patient beneficence or challenging patient autonomy by disclosing test results. The physician may have to counsel patient A again to explain the implications of the result. If patient A insists on not knowing the results, the physician would generally recommend appropriate screening and preventive options without revealing test results.

##### Autonomy versus Beneficence to others

As an example, patient A learns that she carries a mutation in a cancer-susceptibility gene, but refuses to share the results with her family, including her sisters, her husband, and her children. The physician now faces the dilemma between respecting the patient's autonomy and beneficence to the patient's family



members. The physician may have to counsel patient A to explain the implications of her result on her family. If patient A insists on not sharing her test result, immediate family members may be recommended to undergo frequent screening as would be done for high-risk individuals, without revealing test results (*See '7.3.2. Duty to warn family members'*).

### Unwanted disclosure

This may occur in a situation when a key person in the family refuses testing. For example, patient A's maternal aunt tested positive for a mutation in a cancer-susceptibility gene. Patient A wants to know if she carries the same mutation. Under optimal circumstances, patient A's mother would be tested first. Patient A would only be tested if her mother carried a mutation. However, patient A's mother refuses testing as she is afraid to learn that she may be a gene carrier. Given this situation, patient A, who is keen to know her mutation status, proceeds with testing, and finds that she carries the same mutation as her maternal aunt. This means that her mother must also carry the same mutation (obligate carrier). If patient A undertakes certain preventive measures (e.g. undergo bilateral preventive mastectomy), her mother may indirectly learn of her own genetic status.

### Coercion

In the arena of genetic testing, in order for a cancer-free individual to undergo predictive testing, a high-risk cancer-affected family member (index patient) has to be tested first. A situation may be encountered in which cancer-free family members are keen to have genetic testing, while the cancer-affected family member is not. The former may then coerce the latter to undergo testing.

### Reproductive decisions

Individuals who have yet to complete their families may be concerned to know how genetic testing may impact reproductive decisions. Some individuals want to know about prenatal diagnosis.<sup>83</sup> As hereditary cancer syndromes are not uniformly lethal, and the manifestation is in adulthood, prenatal diagnosis with a view to terminate pregnancy is not generally recommended. Patients should be counselled that there is a 50% chance that the foetus is normal, inheriting the defective gene does not mean that cancer will definitely develop, and that future medical advances, including gene therapy, improved cancer screening, diagnosis, treatment and prevention, may become available to the next generation, and may significantly reduce cancer risk or improve cancer cure rates.

### Testing of minors<sup>84, 85</sup>

Genetic testing should only be considered for children if the test is for a childhood-onset disease for which there are known effective interventions, and if the test can be adequately interpreted. Generally, genetic testing should be performed just before the age at which screening for the disease would be appropriate. Examples

of hereditary cancer syndromes for which minors may be tested include familial adenomatous polyposis, multiple endocrine neoplasia type IIA and IIB, and retinoblastoma.

If the medical benefits from a genetic test will not be realised in childhood, genetic testing should be postponed until the child reaches adulthood and able to make an autonomous and informed decision.<sup>84</sup>

#### Genetic testing for minors for familial adenomatous polyposis

This is a condition due to germline mutations in the adenomatous polyposis coli (*APC*) gene, resulting in a propensity to form hundreds to thousands of adenomatous polyps in the colon, and a virtually 100% chance of developing colorectal cancer. Polyps typically form in the teens, and cancer development may occur as early as late teens to early twenties. Mutation carriers are recommended to start screening flexible sigmoidoscopy at age 12-13, and would benefit from prophylactic total colectomy to reduce the risk of cancer. Therefore, the children of a known mutation carrier may undergo genetic counselling with a view to predictive genetic testing as early as age 10-12, to determine if they are mutation carriers.<sup>12, 21, 23, 24</sup> Such counselling is best carried out by physicians or counsellors trained in counselling children. Counselling is typically carried out in the presence of the parents, and assent from the child should be obtained before testing may proceed.

#### Special issues in testing minors<sup>84, 85</sup>

If a minor is to be counselled about genetic testing, the child's autonomy should be respected. While it is recognised that the child may not be able to provide consent, assent from the child is required. Counselling should be conducted in a manner that is appropriate for the child's intellectual capacity and developmental stage. It is also important to understand the family dynamics, keeping in mind the possibility of fragile child syndrome if the child's test is positive, potential impact on parent-child bonding, and potential impact on the other siblings. Furthermore, when a young child undergoes testing, providers and parents should plan to share the results (whether positive or negative) with the child when he or she has sufficient cognitive and emotional maturity to understand them. The provider should convey this expectation to the parents during pre-test counselling. Another ethical dilemma in testing minors is the deprivation of the child of the choice whether to undertake genetic testing as an adult.

### *Legal implications of genetic testing*

#### Duty to warn family members

There have been cases in the United States where legal action was taken against clinicians for failure to warn family members of their risk when a patient is diagnosed with hereditary cancer.<sup>86-88</sup> The American Society of Clinical Oncology

has recently updated its policy statement on genetic testing, and reiterated its stand on protecting patient confidentiality and fulfilling obligations to at-risk relatives through communication of familial risk to the person undergoing testing.<sup>82</sup> The American Society of Human Genetics concurs with the view, but states that the principle of confidentiality is not absolute, and that disclosure may be permitted if all the following conditions are met: (a) attempts to encourage disclosure on the part of the patient have failed; (b) the harm is highly likely to occur and is serious and foreseeable; (c) the at-risk relative is identifiable; and (d) the disease is preventable, treatable, or medically accepted standards indicate that early monitoring will reduce the genetic risk. The society suggests an approach of warning the patient during pre-test counselling of the circumstances that would result in disclosure of genetic information to other family members, regardless of the patient's intentions to disclose.<sup>89</sup>

### *Social implications of genetic testing*

#### Genetic discrimination

##### *Health and life insurance*<sup>69, 71, 90</sup>

A cancer-free individual who tests positive for a genetic mutation that predicts high cancer risk may face discrimination when applying for health and life insurance. Such an individual may have difficulty obtaining insurance coverage for cancer. More insurance companies, especially in the West, are beginning to specifically include statements on genetic testing in the insurance application forms. There are now laws in the United States that protect individuals with a hereditary cancer syndrome from being discriminated against by insurance companies.<sup>91</sup>

##### *Employment*<sup>70</sup>

Similarly, a cancer-free individual who carries a mutation in a cancer susceptibility gene may face discrimination at the workplace. In some states in America, laws have been passed to prohibit or restrict the use of genetic tests as a condition of employment. However, these laws vary from state to state. Currently there are no federal prohibitions against this practice.

### **Longitudinal Follow-Up**

Longitudinal follow-up for a family that has received genetic counselling and/or undergone genetic testing is important to allow periodic review of management plan, and the assessment and promotion of adherence to surveillance measures. In addition, such follow-up allows clarification of issues that the patient or family may have over time, and to provide psychological support. As family history is dynamic, periodic updates of family history may identify new cancers in the family that could change the familial risk assessment. In addition, as cancer genetics is a rapidly evolving field,

maintaining follow-up also allows the family to keep in touch and receive new information, technology or tests that may become relevant to their condition.

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## **MOLECULAR DIAGNOSIS OF ADULT NEURODEGENERATIVE DISEASES AND MOVEMENT DISORDERS**

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### **Introduction**

Molecular genetics provide a powerful tool in the diagnosis of many neurological diseases. Genetic testing of mutations in disease causing genes has allowed us to define and classify many of the heterogeneous inherited neurodegenerative syndromes.<sup>1-5</sup> Confirmation of diagnosis allows early institution of genetic counselling, enables genotype-phenotype correlation, helps select specific patients for clinical drug trials, and ultimately provides a better understanding of pathogenesis and long-term clinical outcome of the disease. As molecular testing may have serious implications for a patient and his family, it should be performed only after careful consideration and a genetic counselling process involving doctors, professional counsellors, and the affected patient and his family.<sup>6</sup>

A number of genetic tests for adult neurodegenerative diseases have been introduced in recent years. Some are solely for research purpose, while others are used routinely in clinical practice. In this paper, we highlight our local experience in the scientific, ethical, social and legal issues of molecular testing of certain diseases such as Huntington's disease, and the autosomal dominant and autosomal recessive cerebellar ataxias. Genetic tests for these diseases are carried out as part of routine clinical care of patients in Singapore.<sup>7-11</sup> In addition, we draw attention to other neurodegenerative and movement disorders for which genetic screening or testing is available locally. Our experience gained from such testings could be applied to a wider spectrum of neurodegenerative diseases when more routine tests are developed. The listing of the diseases below is based on the capability and experience of some of our major institutions and not meant to be exhaustive unless a national survey of such genetic testing capability is carried out.

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## Huntington's Disease and Inherited Ataxias

### *Huntington's Disease*

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder associated with basal ganglia and cerebral cortex atrophy. HD is characterised by involuntary choreiform movements, cognitive impairment, and behavioural abnormalities. It is caused by an unstable expanded CAG repeat within the coding region of the HD gene. Variability in age at onset, tendency of paternal transmission, and sporadic new mutations are some of HD's recognised clinical features.<sup>12</sup>

#### Purpose of test

A genetic test can confirm the diagnosis with abnormal CAG repeats of 40 to over 100 CAG units. Normal chromosomes have 6 to 26 CAG repeats that are inherited in a Mendelian fashion. Sometimes alleles with 36 to 39 repeats are present in unaffected elderly relatives of sporadic *de novo* cases.

#### Selection criteria

Genetic testing is recommended for patients with dementia, involuntary movements, and neuro-behavioural disorders, and/or a positive family history of HD. It should also be considered for patients without family history but with clinical features of HD, particularly when there is a history of ancestors' early death, non-paternity, or adoption.

#### Confirmation of diagnosis

Involves a clinical diagnosis of HD and no genetic test previously for the patient or family member.

#### Presymptomatic testing

Performed for individuals at risk for HD who request this test for purposes like marriage or childbearing.

#### Prenatal testing

Can be considered when one parent is known to carry the HD gene and the couple wants to determine the carrier status of the foetus.

#### Procedure of test

Patients suspected of having HD are usually assessed by a neurologist who has an interest and is familiar with the nature of the test. Genetic counselling by a neurologist regarding the nature and implications of the test is carried out. Patients are usually informed of the test results at their subsequent follow-up between 1 to 3 months.

### Information used for research

Diagnosed HD patients will be approached separately regarding participation in a research project if such research is available. Sometimes collective information regarding the prevalence of the disease and the genetic findings are presented in scientific meetings or for planning educational or healthcare programmes. Strict confidentiality is maintained to ensure that no patient can be identified.

### Accuracy of results

The test is usually repeated twice in the laboratory to ensure accuracy, and is compared with negative controls.

### Some characteristic features

*Repeat Sizes Up to 26 Units* – Normal.

*Repeats of 27 to 35 Units* – There have been no confirmed reports of persons with repeats in this range expressing HD. However, descendants of fathers with repeats in this range can inherit an expanded allele in the clinical range.

*Repeats of 36 to 39 Units* – Some persons may develop HD and others may live into old age without clinical evidence of the disease.

*Repeats of 40 Units or Larger* – All patients with the range of 40 or more will eventually develop HD. However, some individuals with repeats at the low end of this range are reported to exhibit initial symptoms at ages older than common life expectancy.

There is a strong correlation between the length of the expanded CAG repeat with age at onset of the disease. In asymptomatic persons, however, the repeat size cannot reliably predict age of onset. In a study of 63 HD patients and family members in Singapore, the range of CAG repeats in our population's normal and HD alleles is similar to those reported elsewhere.<sup>9</sup>

### ***Autosomal Dominant Cerebellar Ataxias***

Autosomal dominant cerebellar ataxias (ADCAs), frequently referred to as SCAs, are a group of neurodegenerative diseases characterised by cerebellar dysfunction either alone or in combination with other neurological abnormalities. The estimated prevalence of ADCA in Singaporean families is at least 1 : 27,000.<sup>8</sup>

Their clinical classifications (ADCA I: cerebellar syndrome with other neurologic involvement such as pyramidal, extrapyramidal, ophthalmoplegia, dementia; ADCA II: cerebellar syndrome with pigmentary maculopathy; ADCA III: relatively pure cerebellar syndrome) have largely been replaced by a genetic classification since

expansions of coded CAG trinucleotide repeats were demonstrated to cause several dominantly inherited SCAs. At least ten genes have been identified for SCAs 1, 2, 3, 6, 7, 8, 10, 12 and 17, dentatorubral-pallidoluysian atrophy (DRPLA), and ten loci responsible for SCAs 4, 5, 11, 13, 14, 16, 18, 19, 21 and 22 have been mapped. These loci have been numbered based on their order of classification. However, a locus for SCA 9 has yet to be assigned.

In SCAs 1, 2, 3, 6 and 7, the mutation is due to CAG repeat expansions within the coding regions of the gene. SCA 8 is associated with an expansion of a CTG repeat in the 3' untranslated region (UTR) of the *SCA 8* gene that produces antisense mRNA to the *KLHL1* gene on the complementary strand. In SCA 10, the disease-causing expansion occurs in the ATTCT pentanucleotide repeat of intron 9 of *SCA10*, a gene of unknown function widely expressed in the brain. In SCA 12 there is an expanded CAG repeat in the 5' untranslated region (UTR) of *PPP2R2B*, a gene coding for a brain-specific regulatory subunit of the protein phosphatase PP2A. SCA 17 is due to an expanded CAG repeat in TATA box binding protein (*TBP*) gene, which gives rise to an elongated polyglutamine tract in the respective proteins.<sup>13</sup>

#### Purpose of test

A genetic test can confirm the diagnosis when abnormal trinucleotide or pentanucleotide repeats are above the range of normal chromosomes. The genes are inherited in a Mendelian fashion.

#### Selection criteria

Selection criteria include: patients with clinical features of SCA such as cerebellar ataxia, pyramidal and extrapyramidal signs and with a family history of ataxia; or a history of ancestors' early death, non-paternity, or adoption in the presence of suspected clinical features described above.

It has to be emphasised that a wide phenotypic overlap amongst the SCAs and inter-familial and intra-familial phenotypic variability exists even for each SCA subtype. Based on the history and ancestry of Singaporeans, we previously demonstrated a founder effect for specific SCA subtypes and the association of ethnicity-specific SCA subtypes. SCA 2 is relatively common amongst the Malay race. Priority testing for SCA 3 and SCA 2 for ethnic Chinese, and SCA 2 in ethnic Malays may be cost effective and relevant locally.<sup>8</sup> Clinical features that were highly predictive of a positive DNA SCA test in our population included presence of a positive family history, chorea and dystonia, muscle and tongue fasciculations, gaze-evoked nystagmus, and hypertonia.<sup>7</sup>

#### Some characteristic features

*SCA 1* – Hypermetric saccades and hyperreflexia.

*SCA 2* – Markedly reduced velocity of saccadic eye movements, areflexia and changes similar to those seen in olivopontocerebellar atrophy on brain imaging. May show pure parkinsonian phenotype.

*SCA 3* – Combinations of protruded eyes, muscle fasciculations, spasticity, chorea, gaze-evoked nystagmus, parkinsonism and peripheral neuropathy. May show pure parkinsonian phenotype.

*SCA 7* – Macular degeneration.

*SCAs 5, 6, 10 and 11* – Relatively pure cerebellar signs.

*SCA 8* – Mild sensory neuropathy with frequent late-onset spasticity.

*SCA 12* – Head and hand tremors.

*SCA 17* – Intellectual deterioration and dysphagia.

*DRPLA and SCA 10* – A history of seizures with ataxia.

#### Confirmation of diagnosis

A clinical diagnosis of SCA, and no genetic test done previously for the patient or family member.

#### Presymptomatic testing

Performed for those at risk of developing SCA, who request this test be performed for purposes like marriage or childbearing.

#### Prenatal testing

Can be considered when one parent is known to carry the SCA gene and the couple wants to determine the carrier status of the foetus.

#### Procedure of test

Patients suspected of having SCA are usually assessed by a neurologist who has an interest and is familiar with the nature of the test. Genetic counselling regarding the nature and implications of the test is carried out by a neurologist. Patients are usually informed of the test results at their subsequent follow-up between 1 to 3 months.

#### Information used for research

Diagnosed SCA patients will be approached separately regarding participation in a research project if such research is available. Sometimes collective information regarding the prevalence of the disease and the genetic findings are presented in

scientific meetings or for planning educational or healthcare programmes. Strict confidentiality is maintained to ensure that no patient can be identified.

#### Accuracy of results

The test is usually validated and repeated twice in the laboratory to ensure accuracy, and is compared with negative controls.

#### General features shared by most SCAs

1. Anticipation, where there is progressive increase of expanded CAG repeats in successive generations. Those with larger CAG repeats display earlier ages of onset with greater disease severity than those with relatively smaller repeats.
2. Appearance of a critical size of repeat for most of the SCAs, above which the disease would manifest.
3. Influences of parental origin on repeat size instability. Paternal transmission of many SCAs (such as SCAs 1, 2, and 3) may result in a severe, rapidly progressive phenotype at a young age.

#### Exceptions

1. In some SCAs, the disease and normal allele sizes overlap in an intermediate range. Alleles in the intermediate range show reduced penetrance in SCA 2. In SCA 7, the intermediate alleles do not cause disease but can give rise to *de novo* expansion to disease causing size in subsequent generations.
2. Some SCAs (such as SCAs 1 and 2) have non-CAG repeat (CAA, CAT) interruptions. The CAT interruptions introduce histidines into the polyglutamine tract in the protein product, ataxin 1, which may prevent pathogenicity of expanded polyglutamines in SCA 1. The presence of the CAT interruptions on normal alleles is useful for distinguishing normal from diseased alleles for allele sizes of 36 to 44.
3. SCA 8 exhibits instability of repeat with a bias towards expansion in maternal transmission and frequent contraction in paternal transmission. SCAs 1, 2, 3, and 7 may show length changes during intergenerational transmission with a predisposition to expansion in subsequent generations.
4. In SCA 6, the CAG repeat size shows no size instability in parent-to-child transmission, even though anticipation has been reported. SCAs 1, 2, 3, 5, 10 and 14 also show anticipation, whereas SCAs 8, 12 and 13 do not.

#### ***Autosomal Recessive Cerebellar Ataxias***

This is a heterogeneous group of autosomal recessively inherited disorders that are characterised by progressive ataxia, and whose disease onset frequently occurs at a young age. However, milder variants with later disease onset have been described. The term early-onset cerebellar ataxia is ascribed to those recessive ataxias in which neither gene mutations nor chromosomal loci are known.

The affected gene and causative mutations have been described for Friedreich's ataxia, ataxia telangiectasia, autosomal recessive ataxia with oculomotor apraxia, autosomal recessive spastic ataxia of Charlevoix-Saguenay, abetalipoproteinemia, ataxia with isolated vitamin E deficiency, Refsum's disease, and cerebrotendinous xanthomatosis. However, routine genetic testing is available for Friedreich's ataxia (FRDA). Biochemical tests are available for some of the recessive ataxias.

### *Friedreich's Ataxia*

FRDA, the most frequent recessive ataxia is characterised by onset in adolescence, progressive gait and limb ataxia, dysarthria, lower limb areflexia, loss of proprioception, and cardiomyopathy. Ninety-six percent of FRDA patients are homozygous for a GAA repeat expansion in the first intron of the X25/frataxin gene.<sup>13</sup>

#### Purpose of test

A genetic test can confirm the diagnosis when abnormal trinucleotide repeats are above the range of normal chromosomes. The genes are inherited in a Mendelian fashion.

#### Selection criteria

The test is used to confirm diagnosis in patients with the typical phenotype of FRDA. The test is used as a diagnostic screen in patients whose family history is compatible with autosomal recessive inheritance and whose progressive ataxia is otherwise unexplained. Other selection criteria include a history of ancestors' early death, non-paternity, or adoption in the presence of suspected clinical features described above.

#### Confirmation of diagnosis

A clinical diagnosis of FDRA and no genetic test done previously for the patient or family member.

#### Presymptomatic testing

Performed for those at risk of developing FDRA and who request this test be performed for purposes like marriage or childbearing.

#### Prenatal testing

Can be considered when one parent is known to carry the FDRA gene and the couple wants to determine the carrier status of the foetus.

#### Procedure of test

Patients suspected of having FDRA are usually assessed by a neurologist who has an interest and is familiar with the nature of the test. Genetic counselling by a neurologist



regarding the nature and implications of the test is carried out. Patients are usually informed of the test results at their subsequent follow-up between 1 to 3 months.

#### Information used for research

Diagnosed FDRA patients will be approached separately regarding participation in a research project if such research is available. Sometimes collective information regarding the prevalence of the disease and the genetic findings are presented in scientific meetings or for planning educational or healthcare programmes. Strict confidentiality is maintained to ensure that no patient can be identified.

The normal repeat length range is from 6 to 36 units, whereas expanded alleles have 90 to 1,300 repeats. Age of onset is inversely correlated with the size of the shorter allele. Heterozygous mutations (GAA expansion) and point mutations in the frataxin gene are less common. Atypical clinical features (e.g. disease onset in adulthood or preservation of muscle reflexes) have been described in those with homozygous mutations (GAA expansions). Finding of a heterozygous GAA expansion in a symptomatic individual suggests the presence of a point mutation on the second allele.

### **Routine Biochemical Screening of Recessive Ataxias**

#### ***Ataxia Telangiectasia (AT)***

AT is an autosomal recessive disorder characterised by cerebellar ataxia with onset in early childhood, oculocutaneous teleangiectasias, a high incidence of neoplasia, radiosensitivity, and recurrent infections. More than 200 mutations exist in ATM, the gene involved in AT, which encodes a member of the phosphoinositide-3 kinase family involved in cell cycle checkpoint control and DNA repair. The most useful test is determination of serum-foetoprotein, which is elevated in 90% of AT patients.

#### ***Abetalipoproteinemia***

Abetalipoproteinemia is an autosomal recessive disorder characterised by a gradual onset of ataxia, limb weakness, disturbed sensation, retinal degeneration, and diarrhoea. It is caused by mutations of the gene encoding a subunit of a microsomal triglyceride transfer protein. The diagnosis can be made by lipid electrophoresis showing low serum cholesterol (<70 mg/dl) and nearly absent, very low-density lipoproteins, acanthocytosis in blood smears, and reduced serum vitamin E levels.

#### ***Wilson disease***

Wilson disease is caused by mutations in the gene for a copper-transporting p-type ATPase called ATP7B, located on chromosome 13q14-q21. The disease is characterised by a combination of neurological (e.g. parkinsonism, chore, dystonia etc), hepatic (cirrhosis, liver failure), or psychiatric dysfunctions (depression, personality changes). More than 170 mutations have been described so far, most being point mutations or

small deletions. Mutational analysis is difficult because of the large size of the gene and the various mutations. A diagnosis in a symptomatic individual can be made based on low serum ceruloplasmin, high urinary copper and/or increased hepatic copper content, Kayser-Fleischer ring, and copper deposits on imaging.

## **Parkinson's Disease, Dystonia and Alzheimer's Disease**

### ***Parkinson's disease***

Parkinson's disease (PD) is a progressive neurodegenerative disease characterised by loss of dopaminergic cells in the substantia nigra pars compacta and by the presence of Lewy bodies. The cardinal clinical symptoms and signs of PD are bradykinesia, rigidity, tremor, postural instability and freezing attacks.<sup>14, 15</sup> Ten gene loci have been identified by linkage analysis on human chromosome 4q21-23 (PARK 1), 6q25-27 (PARK 2), 2p13 (PARK 3), 4p15 (PARK 4), 4p13 (PARK 5), 1p35-p36 (PARK 6), 1p36 (PARK7), 12p11.2-q13.1 (PARK 8), 1p36 (PARK 9), and 1p32 (PARK 10).<sup>15</sup> Genetic susceptibility and gene-environmental interaction in Singaporean PD population and those reported in the literature have not been conclusive.<sup>16-22</sup>

Mutations in the alpha-synuclein (PARK 1), Parkin (PARK 2), ubiquitin carboxy-terminal hydrolase (PARK 5), PINK1 (PTEN-induced kinase 1) (PARK 6), DJ1 (PARK 7) and LRRK 2 (leucine-rich repeat kinase 2) (PARK 8) genes have been described.<sup>15</sup> In particular, mutations in the Parkin gene on chromosome 6, first reported in Japanese patients with an autosomal-recessive syndrome of juvenile parkinsonism, is of great significance as mutations in Parkin are much more common than mutations in other genes.<sup>23-25</sup> Many different mutations of Parkin have been identified, including exon deletions or duplications, and point mutations.<sup>24, 25</sup>

Epidemiologic data of Parkin gene mutations in the Singaporean PD population is currently being determined. The Parkin gene is large and more than 100 different types of mutations have been described. It is difficult to distinguish the phenotype between those with and without Parkin mutations. However, genetic testing can be considered in young-onset cases involving levodopa-responsive parkinsonism, particularly in patients less than 20 to 30 years of age and with a family history suggesting a possible recessive inheritance. In Caucasian populations, mutations can be detected in 50% of families with autosomal recessive parkinsonism, and 70% in those with age of onset less than 20 years old. However, we do not recommend genetic testing in the general PD population because the chance of detecting Parkin mutations is low. Furthermore, heterozygous Parkin mutations have been described in healthy controls and exonic Parkin rearrangements (not uncommon) are difficult to detect unless quantitative gene dosage studies are carried out. Due to technical complexity and the lack of clarity regarding the pathogenicity of some Parkin mutations/variants, genetic testing for Parkin mutations should thus preferably be considered in a research setting.

More recently, PINK 1 mutations have been found in young onset and recessive forms of PD. In addition, a common LRRK 2 mutation in exon 41 has been found in a number

of White PD patients with or without family history. More information and research are still needed at this time before we consider genetic testing for these genes in our local clinical setting.

### ***Dystonia***

Dystonia is characterised by excessive spasms of both agonist and antagonist muscles resulting in abnormal posturing. Primary dystonia is of idiopathic origin, but a number of disease causing genes or genetic loci have been discovered for a number of dystonia syndromes. The most extensively studied is DYT 1 (Dystonia Musculorum Deformans), which exhibits an autosomal dominant inheritance with reduced (30 to 40%) penetrance. DYT 1 is caused by an underlying GAG in a Torsin A gene on chromosome 9q34. This mutation is present in a number of families of diverse ethnic background.

Most patients develop dystonia before the age of 26 years. One or more limbs are almost always affected and over 95% have an affected arm. The DYT 1 GAG-deletion accounts for 90% of early-onset limb dystonia in the Ashkenazi population, compared to about 50% in the non-Jewish population.

Genetic testing is recommended for patients with early-onset limb dystonia before the age 26 years, and for patients with late-onset dystonia who have a family history of early dystonia onset (<26 years).

### ***Alzheimer's disease***

Alzheimer's disease (AD) is the most common neurodegenerative disease in most countries. Disease causing mutations are rare in AD and other inherited dementias, and hence routine genetic testing is not carried out locally. While apolipoprotein E4 allele is an established risk factor for AD, it is not useful for diagnosis or presymptomatic assessment.

## **General Considerations of Genetic Testing in Adult Neurodegenerative Diseases**

There are presently no universally accepted guidelines for genetic testing of adult neurodegenerative diseases, though some guidelines designed to help clinical neurologists have been proposed by a Movement Disorder Society task force<sup>1</sup> and also by a European consortium.<sup>2, 3</sup> Like other genetic diseases without a definitive cure, there are a number of ethical, social, legal, and psychological issues to consider for such genetic testing. These include informed consent, confirmatory testing, prenatal diagnosis, predictive testing and asymptomatic testing for children, confidentiality, insurability, finances, employment, disability, and marriage. Genetic counselling forms the cornerstone of any genetic testing programme.<sup>1-3, 6, 13</sup>

Patients should be provided with information regarding the clinical features and course of their disease, the mode of inheritance and penetrance. They should be counselled on

the testing's potential implications for them and their families. Genetic counselling for all asymptomatic family members is equally important. In predictive testing, psychological counselling by trained persons is essential.

The neurologist should ensure that the patient or legal guardian is capable of understanding the process and of making informed choices. Without the written consent of the patient, such tests should not be performed at the request of members of the patients' families or other third parties. Test results should never be disclosed to a third party without written consent from the patient.

### **Specific Considerations**

There is general consensus that testing in at-risk asymptomatic children is not encouraged, particularly when no effective treatment is available.

If the attending neurologist does not have thorough experience with inherited disorders, referral to a colleague with experience in these disorders is suggested.

Unlike some inherited disorders that present at birth or in childhood and greatly decrease lifespan, patients who carry the disease-causing gene in some of the adult neurodegenerative diseases may not develop any symptoms till middle age (such as HD) or even till old age (such as SCA 6). Furthermore, one cannot predict with any certainty when an asymptomatic individual will develop symptoms in an event of abnormal genetic findings. These considerations will pose potential ethical dilemmas for the physician when issues such as termination of a pregnancy need to be discussed. The implications of asymptomatic testing on the employment, insurance, and general life planning on the person tested are grave and needs to be thoroughly examined. Guidelines for presymptomatic diagnosis issued by the International Huntington's Disease Society and the World Federation of Neurology research group for Huntington's disease are useful references.<sup>12</sup> In general, discussion of such issues during the genetic counselling process must be dealt with carefully on an individual basis. There must also be adequate follow-up care for psychological problems. This will require careful management by a combined team of experts including the neurologist, genetic counsellors, psychologists, and social workers. The neurologist who has been taking care of the patient or a neurologist with experience in dealing with the disease should preferably lead the team and determine the individual needs of the patient.

Due to certain cultural beliefs and practices amongst our various ethnic groups, sensitivity and skill is needed to manage patients and their relatives when genetic testing is discussed.<sup>4, 5</sup> For instance, we have encountered difficulties in getting some at-risk relatives and family members of SCA patients to come forward for an examination. In some instances, patients have falsely given a negative family history. The disease is perceived as a curse to the family due to ancestral misdoings. They would generally try to avoid the truth through denial, or hide their condition from friends and relatives.

## Conclusion

The armamentarium of genetic testing and screening of adult neurodegenerative diseases in Singapore will continue to expand. A molecular diagnosis programme should ideally be managed by a team of neurologists, psychologists, and other trained personnel with the necessary experience in managing the diseases. These persons should be committed to providing such services and should have a good knowledge of the ethical, psychological, cultural, and legal issues in our population.

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## **PRENATAL GENETIC SCREENING AND TESTING**

April 2005

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### **Preamble**

Genetic Screening is a highly contentious subject as it evokes different emotions and sensitivities. This broad arena includes Prenatal Screening and Testing for which there is currently no uniform approach in Singapore. This paper will attempt to objectively discuss the merits of establishing a standard protocol, bearing in mind the concerns of conscientious objectors and different interest groups even within the medical profession. It will be limited to the field of Prenatal Screening and Testing, as I cannot profess to be an expert in other areas.

### ***Rationale for Genetic Screening***

Genetic disorders like Haemophilia and Huntington's disease exist in every population. In our population the prevalence of Thalassaemia remains an issue. But over the past decade, an additional problem has arisen. The increasing maternal age of conception has led to an increased risk of having chromosomally abnormal conceptions, commonly Down syndrome. As such, universal screening should be practiced. Identified "at-risk" individuals can then be counselled and offered Prenatal Testing to determine if their progeny is affected. The prevalence of genetic disorders within the population can serve as a guide to decide what types of screening should be made available to the people.

### ***Goal of Pregnancy Screening***

In the case of Pregnancy Screening for Birth Defects, the goal is to ensure that parents are able to determine if they will have a normal, healthy baby. If test results indicate defects, such information early in the pregnancy allows parents the time to receive adequate counselling regarding the expected prognosis of the conditions. This will then facilitate the making of informed and deliberate choices, rather than hasty and emotive decisions. For the vast majority of women, however, screening will produce negative results. Negative results achieve the other objective, which is to give parents reassurance and peace of mind for the rest of the pregnancy.

### ***Rationale for Prenatal Testing and Diagnosis***

After undergoing universal screening and prenatal testing, at-risk individuals should be offered adequate counselling. For more specific problems (e.g. Haemophilia A or B), prenatal testing should be available to determine if the progeny is affected.

Prenatal diagnosis should be performed to give parents and physicians information about the health of the foetus. Use of prenatal diagnosis is not readily acceptable for paternity testing, except in cases of rape or incest, or for gender selection, apart from sex-linked disorders. The woman should be an important decision maker in all matters related to reproduction. There needs to be a clear understanding that testing is purely voluntary and there should be no coercion.

### **Pregnancy Screening**

Universal screening should be made available to all patients. All patients should be given adequate information to choose for themselves whether or not they want to receive screening during pregnancy. Screening should strictly occur on a voluntary basis.

### ***Pre-requisites***

**Public education** and **pre-test counselling** should be required before a screening test is offered. Every test should be offered in a manner in which individuals and families can freely refuse or accept according to their wishes and moral beliefs. Religious leaders and community leaders should be given regular updates on the most current pregnancy screening tests so that they can advise their wards about the acceptable mores. **Pre-test counselling** makes **post-test counselling** for patients with positive screen results (and eventually an affected foetus) much less difficult because prospective parents are better prepared. Pre-test counselling should include the general characteristics of the major disorders that the test may identify. The characteristics of the disorder(s) should also be described in terms of effects on the future child, on the parents and on family life.

Pre-test counselling should emphasise that most conditions diagnosed in the foetus cannot be treated before birth and that knowing about the condition may not help the foetus. The information also does not guarantee a healthy baby, as there are other conditions that may not be identified before birth.

### ***Synopsis of Available Methods***

Different modes of screening exist and may include history taking, using maternal age at delivery or maternal serum biochemistry with or without the use of ultrasound. With the advent of new diagnostic technologies, it becomes possible to look at screening service delivery in a different way, which may result in reduced family anxiety, more informed choice and a more efficient use of the healthcare professionals' time.



## Thalassaemia Screening

### *Understanding Thalassaemia*

There are two forms of Thalassaemia commonly found within our local population:  $\alpha$  and  $\beta$  Thalassaemia.

a **Thalassaemia** is mainly a gene deletion problem. The deletion of four alleles by the combination of two *cis* carriers would lead to a severely affected and lethal state of Bart's Hydrops. This condition also increases the risk of hypertensive disorder in the mother during pregnancy, putting her life in jeopardy. Hence prenatal diagnosis potentially prevents increased morbidity and possibility of mortality not only for the foetus but also for the mother.

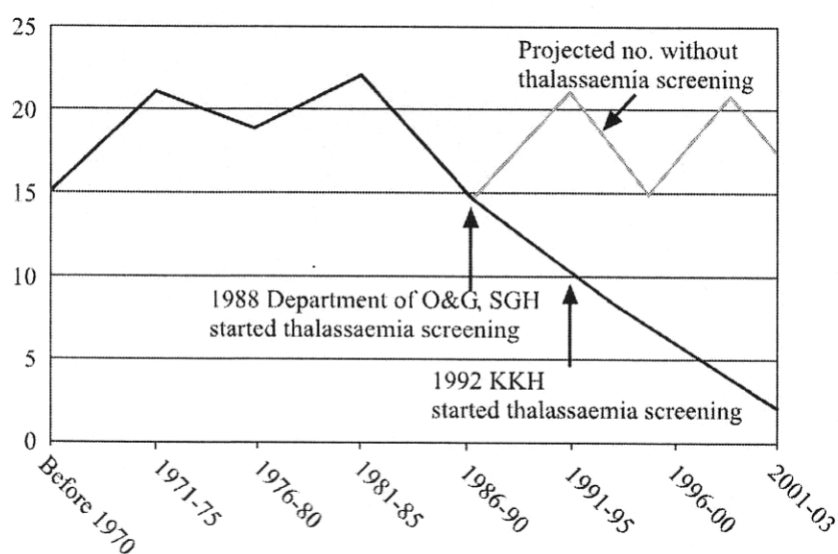
b **Thalassaemia** is a multifactorial problem and involves many different genetic permutations. Prenatal diagnosis is thus more difficult and should be performed when one can identify the specific marker for that couple. A  $\beta$  Thalassaemia major is a severely handicapped person requiring regular blood transfusions and the continuous use of iron chelating agents to maintain some semblance of a decent quality of life.

### *Testing for Thalassaemia*

The gene prevalence of Thalassaemia in our local population is approximately 3%. The carrier state is compatible with good quality life. It is impossible to distinguish a carrier from a normal person without performing targeted blood tests. A simple blood test should be performed on both the male and female partner. In the screening phase, testing involves only a Full Blood Count or more specifically, the Hb level and the MCV of the red corpuscle. Should the Hb be below 10g/dl and the MCV be below 80 fl, a Hb Electrophoresis should be sent and genetic testing can then be performed if needed. [GSH Yeo, KH Tan, TC Liu. The Role of Discriminant Functions in Screening for Beta-Thalassaemia Traits During Pregnancy. Singapore Med. J. 1995 Dec; 36(6):615-8.]

Since the initiation of routine Thalassaemia screening, the number of  $\beta$  Thalassaemia major births in Singapore has fallen dramatically from an average of 15 to 20 cases a year to that of one case per year. See graph of Number of Beta-Thalassaemia Major Births in Singapore 1997–2003.

### Number of $\beta$ Thalassaemia major births in Singapore, 1997-2003<sup>1</sup>



The **Thalassaemia Registry** is a rich resource of data because many family trees have been mapped and their specific genetic defects/deletion identified. Those with affected relatives can easily avail themselves of the resources available when the need arises.

## Down Screening

### *Understanding Down Syndrome*

Down syndrome is the most common chromosomal abnormality syndrome in humans. Humans were built with two sex chromosomes and two copies of each of the other 22 chromosomes. Trisomies occur when there are three copies of a chromosome. These children usually have decreased intelligence, but increased unselfconsciousness, openness and affection. Children with Down syndrome face many medical and development problems. Early intervention programmes can be very helpful in helping children with Down syndrome to develop to their full potential and thus be less of a social burden to their immediate families and society.

The extra chromosome may be derived from either the mother or father. Non disjunction is found in 95% of Down syndrome, the other 5% are caused by Translocation, Mosaicism or partial trisomy. The risk for many chromosomal defects increases with maternal age. Additionally, because foetuses with chromosomal defects are more likely to die in *utero* than normal foetuses, the risk decreases with gestation.

<sup>1</sup> Recent Developments in Obstetric Care and Maternal Foetal Medicine in Singapore, Annals Academy of Medicine, November 2004, Vol.33 No.6

### *Testing for Down Syndrome*

Screening tests are used to look for potentially at risk pregnancies with the aim of performing a diagnostic test to confirm if the pregnancy is really affected. There are many modes of screening as the following table shows:

Screening Test	DR (%)	FPR (%)
MA	30 (or 50)	5 (or 15)
MA + foetal NT at 11-14 weeks	75 (or 70)	5 (or 2)
MA + foetal NT and serum $\beta$ -hCG and PAPP-A at 11 – 14 weeks	90 (or 80)	5 (or 2)
MA + foetal NT and NB and serum $\beta$ -hCG and PAPP-A at 11 – 14 weeks	97 (or 90%)	5 (or 2)
MA + serum biochemistry at 15-18 weeks	60-70	5
Ultrasound for markers at 16 – 23 weeks	75	10 – 15

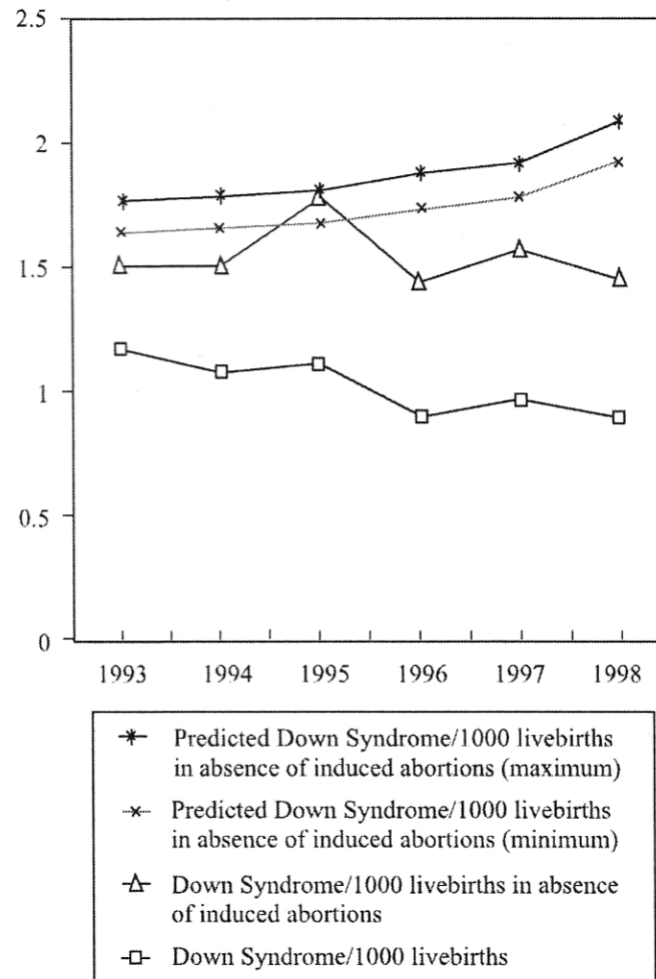
$\beta$ -hCG, beta human chorionic gonadotrophin; DR, detection rate; FPR, false positive rate; MA, maternal age, NB, nasal bone; NT, nuchal translucency; PAPP-A, pregnancy associated plasma protein A. (Ultrasound Obstet Gynecol 2003; 21:313-321)

In Singapore, First Trimester Screening using the MA, foetal NT and serum  $\beta$ -hCG and PAPP-A at 11 to 14 weeks was started in August 2003. Until Dec 31 2004, 1859 women had been screened and total of four anomalies had been detected, two cases of Trisomy 21, one of Trisomy 13 and one of Trisomy 18. Two of these cases were to mothers aged 28 and 29, respectively, who would have not been offered testing based on maternal age.

The test quickly gained recognition in the second half of 2004 when KK Women's and Children's Hospital and other centres started offering it to its patient population. With this test in place, the trend of increased public awareness of pregnancy screening and its benefits is set to improve.

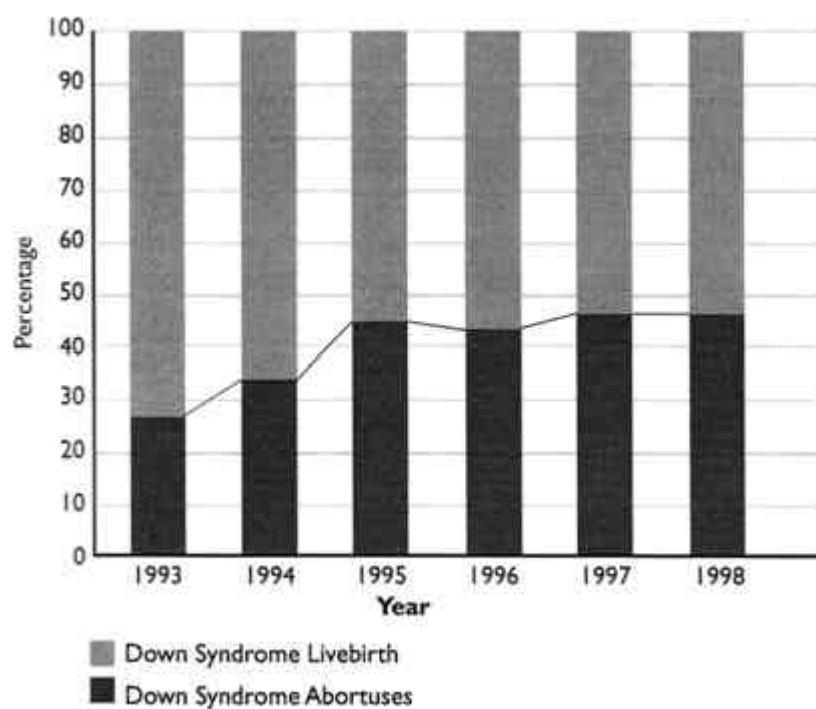
**Down screening has contributed definitively to the reduction of Down syndrome live births over the years**

**Down syndrome per 1000 livebirths in Singapore from 1993 to 1998<sup>2</sup>**



<sup>2</sup> Recent Developments in Obstetric Care and Maternal Foetal Medicine in Singapore, Annals Academy of Medicine, November 2004, Vol.33 No.6

### Trend of Down Syndrome Livebirths vs Abortions 1993-1998<sup>3</sup>



### Down syndrome livebirths, stillbirths and abortions, and actual and expected Down syndrome livebirth rates, Singapore 1993 to 1998<sup>4</sup>

	1993	1994	1995	Year 1996	1997	1998	Total (93-98)
Down Syndrome Livebirth	59	53	54	44	46	39	295
Down Syndrome Stillbirth	2	1	0	0	0	1	4
Down Syndrome Abortuses	22	28	43	34	38	32	197
Total	83	82	97	78	84	72	496
Total Livebirths I	50225	49554	48635	48577	47333	43664	287988
Down Syndrome rate /1000 livebirths	1.17	1.07	1.11	0.91	0.97	0.89	1.02
Down Syndrome to livebirths ratio	1:851	1:935	1:901	1:1104	1:1029	1:1120	1:976
Expected Down Syndrome Livebirths in the absence of induced abortions	76	75	87	70	75	64	447
Expected Down Syndrome rate/1000 livebirths in absence of induced abortions	1.51	1.50	1.79	1.44	1.59	1.46	1.55
Expected Down Syndrome to livebirths ratio in absence of induced abortions	1:661	1:665	1:558	1:692	1:629	1:686	1:645

I Report on Registration of Births and Deaths 1998, Singapore Immigration and Registration

<sup>3</sup> Birth Prevalence of Down Syndrome in Singapore from 1993 to 1998, Singapore Med J, 2002 Vol 43(2): 070-076

<sup>4</sup> *Ibid.*

## Screening for Other Chromosomal Disorders

Lethal chromosomal abnormalities (e.g. Trisomy 13, Trisomy 18 and Triploidy) can be detected through screening methods similar to those of Down syndrome. Less lethal forms of XO, XXY, XXX, XYY etc can only be predetermined through karyotype as these do not present any physical abnormalities in general. The significance of detecting these prior to birth are again for the parents to be fully counselled as to the long term prognosis of their children, as early intervention in childhood may be required for some anomalies and lethal anomalies should not pose a threat of operative deliveries to the mother.

## Screening for Structural Birth Defects

Structural defects are more likely to be associated with genetic disorders (e.g. 50% of Down syndrome affected foetuses have a cardiac anomaly). In the National Birth Defect Registry, structural anomalies account for a large proportion of the registered anomalies. Cardiac anomalies are the most common at 7 to 8 per 1000 live births, whilst chromosomal abnormalities including Down syndrome account for only 3 per 1000 live births.

Structural anomalies usually necessitate early neonatal and paediatric surgical care to correct or decrease harm to the baby's development. Prenatal diagnosis helps give prospective parents the opportunity to prepare for their child's special needs and to cope with the "well-wishers" around them.

The use of ultrasound equipment provides a clear view of the state of the developing foetus. Anomalies can be detected as early as the 11th week of pregnancy. Certain structural defects are incompatible with life (e.g. anencephaly, Barts' hydrops and hypoplastic left heart syndrome). Early detection again allows the relevant paediatric surgeons to pre-empt the birth and decide on the mode of operations that may be required. Conjoined twins can be detected from the first trimester by the presence of a single yolk sac with two foetal poles.

Ultrasound for genetic markers can be performed as part of a genetic sonogram. The chance of a chromosomally affected child is detected on the presence or absence of these markers. Likelihood ratios have been derived for the presence of many different individual markers. However, these are rarely used in the practice by regular obstetricians. A reduction of the age related risk of Down syndrome is reduced by 50% should the genetic sonogram prove negative for any marker.

Ultrasound screening for foetal anomalies is currently performed by varying practitioners (e.g. sonographers, general practitioners and the majority of obstetricians and gynaecologists). A genetic sonogram is only as good as the person who performs the scan and the equipments used.

## Screening for Genetic Disorders

If there is a known family history of a genetic disorder (e.g. Huntington's disease, Haemophilia) then screening the mother for the risk of having an affected progeny should be discussed with her and the partner. In certain types of diseases in which there is no treatment (e.g. Huntington's disease), some people have questioned the need to screen for it. Sex-linked diseases (e.g. Haemophilia, Red/Green colour blindness) are potentially preventable if the mother refuses to pass these onto her children. If the mother is determined to be a carrier, prenatal diagnosis for each pregnancy should be offered to her or the possibility of pre-implantation genetic screening can be discussed.

## Genetic Testing

### *What is Genetic Testing?*

**Genetic Test** (as defined by the National Institutes of Health, Department of Energy Working Group on Ethical, Legal and Social Implications of Human Genome Research) is the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease related genotypes, mutations, phenotypes or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers and establishing prenatal and clinical diagnosis. Prenatal, newborn and carrier screening, as well as testing high-risk probability thau and excess or deficiency of the metabolite indicates the presence of heritable mutations in single genes.

It must be emphasised that little can be done to change a pre-existing genetic defect or even to improve the resulting situation. Negative test results may not rule out future occurrence of disease whilst positive tests do not mean that the disease will inevitably develop.

In the realm of prenatal diagnosis, a genetic test involves the harvesting of foetal tissue either through an **amniocentesis, chorionic villous sampling or cord blood sampling** for a full karyotype. Each of these procedures carries a risk of pregnancy loss. As such, one should not assume that all persons of high-risk status or those with positive screen results will immediately undergo such an invasive diagnostic test.

## Diagnostic Procedures

### *Amniocentesis*

**Amniocentesis** is currently the most frequently performed diagnostic procedure in Singapore, as it follows the most common prenatal screening test – the second trimester serum screening test. The second trimester screen is performed at 15 to 20 weeks and gives a 5% positive screen rate to determine 65% of Down syndrome. By the time a

diagnostic test is performed and a full karyotype is obtained, the pregnancy is therefore usually far advanced at 20 weeks gestation. This inevitably leads to great psychological and physical distress, as a decision not to continue with the pregnancy is not only ethically and emotionally difficult but also physically stressful and not without morbidity.

The use of **FISH** (Fluorescent In Situ Hybridisation) or **PCR** (Polymerase Chain Reaction) has led to improvements in this area, as it can determine the presence or absence of a Trisomy within 24 to 48 hours. It gives information only about the chromosome tested. Other karyotypic anomalies cannot be identified without the full karyotype. Thus, these procedures remain as a rapid first step to reduce anxiety prior to receiving full information.

### ***Chorionic Villous Sampling***

**Chorionic villous sampling** is performed at 11 to 14 weeks and readily obtains a large amount of foetal DNA. This procedure is favoured for genetic testing of Thalassaemia and Haemophilia. Technically, it is a more demanding test for the clinician. This test can be offered immediately following a positive screen from the First Trimester serum screen and Nuchal Scan.

As these procedures are invasive and pose a risk of miscarriage, informed consent is imperative. Currently, these procedures can be performed not only for those with a positive screen but can also be performed as an initial investigation. Rigorous training programmes are set out to ensure there are fairly uniform levels of expertise available amongst the practitioners.

### ***Role of Laboratories in Genetic Testing***

Not only are the persons performing these tests should be accredited, the **laboratories** responsible for chromosome culture should also be of the highest quality. Genetic testing should be governed by guidelines and standards set for the laboratories by the Ministry of Health and other international accreditation bodies.

### **Information Available with regards to Prenatal Screening / Testing**

Prenatal Screening is acceptable to the general public as evidenced by its use of currently available methods (e.g. ultrasound and second trimester screening for Down syndrome). Obstetricians, clinics and some family physicians offer prenatal screening.

There are no predetermined schedules for offering these screening tests and they are offered at the discretion of the doctor concerned. The quality of the available pre-test and post-test counselling has been improving by continuing medical education of medical staff in general.



Foetal Maternal Medicine specialists in Singapore have been the driving force in improving public knowledge with regards to prenatal screening and diagnosis.

In Singapore, a **National Birth Defect Registry** was set up for the purpose of maintaining a registry of all the various birth defects so that epidemiological data can be easily obtained and studies can be performed to determine local patterns to facilitate prenatal screening. The data is collated from abortions performed for abnormalities, from miscarriages/stillbirths registry and from perinatal units.

### **Accuracy of Screening Tests**

The traditional method of prenatally screening based on maternal age at delivery yields the lowest detection rate of approximately 30%. The current widely available method of second trimester serum testing allows 65% of Down syndrome for a 5% screen positive rate. These are either based on double or triple analyte testing involving serum beta HCG, alpha foetoprotein with or without unconjugated estriols. The ultrasound examination of the nuchal translucency alone detects 75% of Down syndrome cases.

Presently, the most promising method combines maternal age, nuchal translucency and first trimester serum testing to yield a detection rate of 89% for Down screening and 90% of other chromosomal anomalies using alternative algorithms. The analytes include serum free  $\beta$ -hCG and PAPP-A. The addition of the nasal bone imaging has improved the accuracy further with a reduction in false positives.

Screening tests using cervical swabs or foetal blood to isolate foetal cells are still not optimised. One is unable to determine a full karyotype from the few isolated cells. These tests could prove, however, to be THE way to screen each pregnancy because they are non-invasive to the foetus.

### **Medical and Legal Considerations**

Again, a screening test merely identifies a woman at an increased risk for an anomaly, but does not permit a diagnosis. This has to be emphasised to her and her partner, if required, and consent must be taken prior to the test.

No screening test is compulsory and all benefits and potential problems arising after screening should be discussed prior to signing the consent form. Options following a screen test positive must be advised.

### **Ethical Considerations**

More importantly, ethical tenets should be followed in all things pertaining to this realm. These include:

1. Respect for autonomy of choice: respecting the self-determination of individuals and protecting those with diminished autonomy.
2. Beneficence: giving the highest priority to the welfare of persons and maximising their health.
3. Non maleficence: avoiding and preventing harm to persons or, at least, minimising harm.
4. Justice: treating persons with fairness and equity, and distributing the benefits and burdens of health care as fairly as possible in society.

## **Conclusion**

Prenatal screening should be offered universally to all women who desire to know the health status of the child they bear. All women must thus be aware of the available screening tests and the purpose of each test. There must also be clear understanding of the difference between a screening test and a diagnostic test.

Education about genetics for the public and health care professionals is now of paramount importance because genetics is playing an increasing role in medical practice and many people are concerned about the possible abuse of this new knowledge. Geneticists and health care professionals must also learn from the support and advocacy groups representing those with genetic disorders.

Accreditation and self-evaluation should also be performed for those who wish to provide prenatal screening services.

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## PREIMPLANTATION GENETIC DIAGNOSIS

July 2003

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### Introduction

Inherited genetic diseases have been a problem for some families attempting to conceive a child. If affected parents or carriers of genetic disorders wished to avoid transmitting a condition to their child, they can choose to have prenatal diagnosis of their foetus. Amniocentesis or chorionic villus sampling enables cells from the foetus to be collected and sent for genetic analysis. They could then choose to terminate the pregnancy if the foetus is affected.

Preimplantation genetic diagnosis (PGD) is the prevention of the birth of affected children in couples at genetic risk by sampling and genetic testing of nuclear material obtained from blastomeres or polar body biopsy of the embryo thus enabling selection and transfer of only normal embryos to achieve a normal pregnancy and birth of a healthy baby. In this way, couples do not have to experience the agony of aborting affected foetuses.

### Background

The first clinical PGD was reported by Handyside and co-workers<sup>1</sup> who described the sexing of preimplantation embryos at risk for sex-linked disease by performing embryo biopsy at the cleavage stage and sexing with Y-specific DNA amplification. A few years later, the introduction of fluorescent in situ hybridisation (FISH), a method in which fluorescent labelled, chromosome-specific probes are hybridised to metaphase or interphase chromosomes were reported, allowing sexing of embryos as well as aneuploidy screening.<sup>2</sup> Single gene disorders have been diagnosed with the polymerase chain reaction (PCR). DNA analysis is performed either on biopsied blastomeres or on sampled first and second polar bodies.

### Biopsy Methods

#### *Polar Body Biopsy*

The first and second polar bodies contain the complementary genotype to the oocyte. To remove the polar bodies, the oocyte is held with a holding pipette with the polar body at the 12 o'clock position. Using a sharp needle, a slit is made in the zona

pellucida tangentially to the polar bodies. With a thin pipette, the polar bodies are removed from under the zona and transferred to a PCR tube or glass slide for analysis.

### ***Cleavage Stage Biopsy***

This is the most widely used technique. The advantage of cleavage stage biopsy is that the genetic constitution of the embryo is completely formed and thus comparable to genetic material obtained at prenatal diagnosis. Embryos are usually obtained after intracytoplasmic sperm injection (ICSI). This avoids contamination with sperm, which is important when PCR is used and reduces the possibility of failure of fertilisation with insemination. A hole is made in the zona pellucida of the embryo by applying Acid Tyrode's solution or using a laser. A pipette is inserted through the hole and one blastomere is aspirated and removed from the embryo for analysis. Diagnosing one or two cells isolated from 8-16 cell embryos may occasionally fail to detect mosaicism.

## **Methods of DNA Analysis**

### ***In Situ Hybridisation***

In situ hybridisation permits the analysis of genetic material of a single nucleus in metaphase or interphase, by incubating a fixed dried cell with a specific probe, which binds to the gene of interest. The gene probe is labelled with fluorescent markers (FISH) and allows numerical chromosome analysis.

The advantage of FISH is that, since the cells do not have to be in metaphase, interphase nuclei and even arrested cells can also be analysed. The choice of appropriate probes allows the exact identification of the chromosomes. Unfortunately, only limited numbers of chromosomes can be analysed at one time. However, new developments in the near future, e.g. comparative genomic hybridisation (CGH), spectral karyotyping (SKY) and DNA chips will allow analysis of all chromosomes.

### ***Polymerase Chain Reaction***

PCR allows amplification of well-defined DNA sequences enzymatically in an exponential way. The boundaries of the amplified fragment are determined by a couple of primers which anneal to the denatured template DNA and which then form the starting point of a DNA polymerase to synthesize the complementary strand. The gene of interest is thus amplified for identification.

Contamination is an important problem in single-cell PCR: when the sample contains only two copies of the DNA under investigation, one copy of extraneous DNA can lead to misdiagnosis. Two sources of contamination can be distinguished. The first, from cellular sources, contains whole genomic DNA, while the second is carry-over contamination from products of former PCR reactions.

Another problem encountered with PCR is allele drop-out (ADO) where an affected allele may fail to amplify during PCR. ADO would create a particular problem for the correct diagnosis of autosomal dominant diseases if the affected allele would fail to amplify and in compound heterozygotes when autosomal recessive diseases were concerned.<sup>3</sup>

### **Indications**

Although PGD is an early form of prenatal diagnosis, it will not be an alternative for chorionic villus sampling or amniocentesis in all cases. There are several situations in which PGD would be beneficial:

- (i) In parents who have a genetic diseases or are carriers and have concurrent fertility problems necessitating treatment with IVF.
- (ii) Some parents have personal histories of prenatal diagnosis followed by termination of pregnancy for affected foetuses. Some may feel they cannot cope with another failure and would prefer IVF and PGD.
- (iii) Another group of patients have moral, emotional or religious objections to termination of pregnancy and see PGD as the only way to have unaffected children.

### **Current State of the Technique**

Since the first report of clinically applied preimplantation genetic diagnosis<sup>1</sup>, the numbers of fertility centres performing PGD and the numbers of PGD treatments have risen steadily.

The European Society of Human Reproduction and Embryology (ESHRE) formed a PGD Consortium in 1997 to study the long-term efficacy and clinical outcome of PGD. Their latest published report includes data from 1318 PGD cycles and 215 babies.<sup>4</sup> The data was collected from 25 IVF centers who are actively practicing PGD (Table 1). Apart from these centres involved in the Consortium, other centres in the USA, Russia, Belarus, Colombia, Cyprus, Finland, Jordan and Turkey are performing PGD.

Apart from aneuploidy diagnosis, several genetic diseases have been tested for. These include autosomal dominant, autosomal recessive and sex-linked disorders (Table II).

The data for PGD for the years 1999-2001 showed that a total of 5985 oocytes were retrieved, a fertilisation rate of 62% was achieved, 48% were suitable for biopsy, biopsy was successful in 99% of cases and 85% of embryos had a diagnosis. Pregnancy rate was 19% per oocyte recovery and 23% per embryo transfer.

## **Problems Encountered with PGD**

Couples wishing to avail themselves to PGD will have to undergo IVF. This involves time, expenses and at the end of a cycle, the uncertainties of success at a pregnancy. It is a process of decreasing numbers as the embryos diagnosed as suitable for transfer will be few.

The possibility of a misdiagnosis will be dependent on the experience, care and technical expertise of analysis. Sources of error include mosaicism, contamination of DNA material for PCR and allele drop-out. Hence, most centres still recommend that couples having PGD undergo a confirmation test with prenatal diagnosis.

Single cell genetic analysis of cleavage stage embryos is susceptible to extrinsic technical errors as well as intrinsic errors related to nuclear and chromosomal abnormalities (Table III). Several misdiagnoses have been reported in the literature. As errors can arise from diverse causes, it is clinically important to develop a model so that patients can be accurately counselled about the risks of misdiagnosis. This model should include source of variation from the cell chromosomes, recombination, contamination and amplification. Data on the frequency of haploid, diploid or more complex mosaic cells can be obtained through FISH studies. About 90% of cells have both parental chromosomes (diploid and tetraploid cells) and 10% of cells lack at least one parental chromosome.

## **Future Applications of PGD**

In future, improved genetic and DNA analysis techniques will improve the accuracy of diagnosis of the preimplantation embryo. There will also be more genes that can be identified and some other applications would include diagnosis of Mendelian disorders using linked polymorphic markers and structural chromosomal abnormalities using centromeric and telomeric probes.

As deranged chromosome complements have been identified in first trimester pregnancy failures, aneuploidy screening and transfer of euploid embryos may in future be used to improve assisted reproductive technology success rates, especially in older patients with repeated IVF failures and recurrent abortions.

It is possible that with improved genetic diagnosis, other less fatal or debilitating genetic disorders may be presented as choices for PGD, e.g. HLA screening and BRCA gene testing for cancer predisposition.

## **Guidelines and Licensing**

Legitimate concerns about potential misuse of embryo screening and selection make it essential that a sustained public debate about these issues occurs as technical progress

continues. Some of the discomfort that surrounds new uses of PGD stems from a sense in many countries that there is no effective oversight of its development and use.

In the UK, the Human Fertilisation and Embryology Authority (HFEA) has legal authority over which clinics are licensed to do PGD and for what indication. Additional uses of PGD may occur only if the HFEA is satisfied that the uses are within statutory guidelines and the clinic program is qualified to undertake the work. In addition, the HFEA uses a public consultation process to assess public attitudes and draw up guideline for new uses. The HFEA has provided a regulatory model that other countries could emulate.

In the US, no agency exists at the state or federal level that plays a role comparable to the HFEA. How PGD is used and for what indications is thus left largely to the discretion of providers offering those services and the patients who seek it.<sup>6</sup>

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**Table I. Centres Involved in ESHRE PGD Consortium**

1	Sydney IVF
2	University of Adelaide
3	Melbourne IVF
4	Centre for Medical Genetics, VUB, Brussels
5	ULB Erasme, Brussels
6	Centre for Preimplantation Genetic Diagnosis, Aarhus University Hospital, Aarhus
7	Hopitaux Beclere et Necker, Paris
8	Institut de Genetique et de Biologie Moleculaire et Cellulaire, Strasbourg
9	St Sophia's Childrens Hospital, University of Athens
10	IVF and Genetics, Athens
11	SISMER, Bologna
12	PGD Working Group, Maastricht
13	Stichting Klinische Genetica Zuid-Oost Nederland, Maastricht
14	Department of O&G, Samsung Cheil Hospital, Sungkyankwan University, Seoul
15	Instituto Dexeus, Barcelona
16	Unitat de Biologia Cellular, Univ. Autonoma, Barcelona
17	Department of Clinical Genetics, Karolinska Hospital, Stockholm
18	Sahlgrenska University Hospital, Goteborg
19	Assisted Conception Unit, St. Thomas' Hospital, London
20	Department of O&G, University College, London
21	Institute of O&G, RPMS, Hammersmith Hospital, London
22	Department of O&G, Baylor College of Medicine, Houston, Texas
23	Jones Institute for Reproductive Medicine, Norfolk, Virginia
24	New York University Medical Center, New York
25	Institute of Reproductive Medicine and Science, St Barnabas Medical Center, New Jersey



**Table II. Genetic diseases that have been tested with PGD**

Autosomal recessive	<ul style="list-style-type: none"> <li>• Cystic fibrosis</li> <li>• Beta-thalassaemia</li> <li>• Spinal muscular atrophy</li> <li>• Tay-Sachs disease</li> <li>• Rh Isoimmunisation</li> <li>• Gaucher disease</li> <li>• Sickle cell anaemia</li> </ul>
Autosomal dominant	<ul style="list-style-type: none"> <li>• Myotonic dystrophy</li> <li>• Huntington's disease</li> <li>• Charcot-Marie-Tooth disease</li> <li>• Neurofibromatosis type I</li> <li>• Marfan syndrome</li> <li>• Osteogenesis imperfecta</li> </ul>
Sex-linked	<ul style="list-style-type: none"> <li>• Duchenne and Becker's muscular dystrophy</li> <li>• Haemophilia</li> <li>• Fragile-X syndrome</li> <li>• Mental retardation</li> <li>• Wiskott-Aldrich syndrome</li> <li>• Charcot-Marie-Tooth</li> <li>• Retinitis pigmentosa</li> </ul>

Table III. Summary of Potential Diagnostic Errors with PGD using PCR

Source of Diagnostic Error	Possible Cause
<b>Extrinsic errors: alleles</b>	
Amplification failure	PCR failure
Allele drop-out	Degradation of target DNA
<b>Extrinsic errors: contamination</b>	
Related DNA	Maternal cumulus cells or paternal sperm DNA
Unrelated DNA	DNA in reagents or operator DNA
Carry-over DNA product	Amplified products
<b>Intrinsic errors : nuclear abnormalities</b>	
Binucleate	Failure of cytokineses or abnormal karyokinesis
Multinucleate	Abnormal karyokinesis
Anucleate	Cytoplasmic fragmentation
<b>Intrinsic errors : chromosomal abnormalities</b>	
Haploid	2 <sup>nd</sup> polar body
Tetraploid	Failure of karyokinesis or derivation from binucleate cells
Higher order polyploidy	Endoreduplication/endomitosis
Aneuploidy	Non-disjunction, chaotic chromosomal segregation or chromosome loss

## LEGAL AND ETHICAL ISSUES PERTAINING TO PREIMPLANTATION GENETIC DIAGNOSIS

July 2003

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### **Introduction**

Preimplantation Genetic Diagnosis (PGD) is a procedure that aims to weed out genetically defective embryos before they have a chance to develop. It is a procedure that is done in conjunction with *in vitro* fertilisation (IVF). Hence it is necessary to outline the legal and ethical implications of IVF as they are relevant to the discussion of the issues related to PGD.

### **Relevant Legal Issues**

#### ***Eligibility/Access to Treatment***

Currently, there is no specific legislation relating to the entitlement of a person to gain access to treatment services. In the Singapore context, due to the social and economic mores of our society, this treatment (if approved) will be restricted to only married heterosexual couples who may or may not be fertile.

However in the absence of any legislation or case law supporting this situation, potential problems may arise in the event a determined couple who does not fit into this category wants to have this procedure performed. There is nothing to stop them from trying to enforce their desire in court.

But given the prevailing situation in Singapore which is generally a non-litigious society and where such unconventionality is frowned upon, it is an unlikely scenario. However in order to avoid this problem, it is necessary to list down clearly the prerequisites that must be fulfilled in order to be eligible and have access to treatment and draw up a list of guidelines to make sure they are strictly enforced to avoid any ambiguity.

### ***Conscientious Objection***

The right to ‘conscientious objection’ is contained in section 6 of the Termination of Pregnancy Act (Cap 324). Section 6 provides as follows:

6. —(1) Subject to subsection (3), no person shall be under any duty whether by contract or by any statutory or legal requirement to participate in any treatment to terminate pregnancy authorised by this Act to which he has a conscientious objection.

(2) In any legal proceedings the burden of proof of conscientious objection referred to in subsection (1) shall rest on the person claiming to rely on it and that burden may be discharged by such person testifying on oath or affirmation that he has a conscientious objection to participating in any treatment to terminate pregnancy.

Although it is a provision that relates to the termination of pregnancy, it may be invoked in an analogous situation such as the performing of a PGD or IVF procedure. Essentially, the right to conscientious objection allows a doctor, nurse or other individual to refuse to ‘participate’ in a licensed activity to which they have such a conscientious objection. Such a matter of conscience is widely understood to cover religious, moral or other principled beliefs that lead the individual to conclude that the activity is wrong.<sup>1</sup>

In trying to establish when such a right may be used, difficulties may arise. It is not clear whether the individual must object to participating in a whole class of activity or whether he may also object to participating only in particular situations or parts of a licensed activity.

An example cited by Ian Kennedy and Andrew Grubb of how such a right may be exercised is as follows. Would an individual’s objection to being involved in embryo biopsy fall within such a right even if he has no objection to IVF in principle? There is no clear answer though they are of the view that it may be argued that this right only permits an individual to have a conscientious objection to a class of activity but does not allow an individual to pick and choose which parts of the licensed activities he is prepared to be involved in.<sup>2</sup>

### ***Consent to Use and Control of Genetic Material***

Consent is relevant in two distinct ways. First, there is a need for those who are donating genetic material and those being treated for infertility to consent to the medical procedure. Secondly, the issue of consent arises with regard to the future use or storage of an individual’s genetic material.

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<sup>1</sup> Ian Kennedy, Andrew Grubb, *Medical Law: Text with Materials*, 2<sup>nd</sup> ed Butterworths, London (1994)

<sup>2</sup> *Ibid*

*Consent to the procedure*

A donor of genetic material or a patient undergoing infertility treatment must consent to the medical interventions involved. This is to avoid any later difficulties that may arise in trying to establish the legitimacy of the child born after treatment.

In Singapore, the Law Reform Committee of the Singapore Academy of Law produced a report on the status of children born through artificial conception in 1995. A bill entitled the Status of Children Act has been proposed so as to clear up the issue of the legitimacy of a child conceived in such a manner. Though not yet enacted into law, it would be useful to refer to it. The URL is as follows:

[http://lwb.lawnet.com.sg/legal/lgl/html/freeaccess/lrcr/artificial\\_conception.pdf](http://lwb.lawnet.com.sg/legal/lgl/html/freeaccess/lrcr/artificial_conception.pdf)

*Control of gametes and embryos*

The issue at hand here concerns the extent to which the providers of gametes and embryos may exercise legal control over their genetic material. Currently there is no legislation or Singapore cases which addresses the issue in question. What may be helpful here is the position in England under the Human Fertilisation and Embryology Act 1990 (Cap. 37 of 1990) (“the HFEA”). There is an elaborate scheme of consents that vests control of gametes and embryos in the providers of the genetic material. Schedule 3 to the Act requires that a gamete provider must, at the time that the gametes are procured, indicate in a written consent what use(s) those gametes may be put to. The gametes (or any resulting embryos) may only be used in accordance with those consents.

It is recommended that a regime that will specifically address this issue as to who has control over such genetic material be established. It will be prudent to state clearly who possesses such control and how excess genetic material will be treated (destroyed, used for further research, etc). It is emphasized that this issue of consent with respect to control is a very important issue that needs to be clarified before anything medical procedure begins.

The current state of the law is not clear. However there is a great potential that a Pandora’s box may be opened if such a regime is not properly established before treatment begins. Issues such as whether these embryos are to be considered as human or not and who has the right to decide the fate of the genetic material are examples of the thorny issues that may arise if this issue is not properly addressed prior to the beginning of treatment.

It will be useful to see how the US attempts to address this issue. The American Bar association has come up with a discussion draft entitled ‘Model Assisted Reproductive Technologies Act’ which may be view online at [http://www.abanet.org/ftp/pub/family/art\\_monograph.doc](http://www.abanet.org/ftp/pub/family/art_monograph.doc).

### *Medical Confidentiality*

Every doctor has a duty of confidentiality to his patients, a duty founded in the medical codes of ethics and the law. The basis of the common law duty of confidence is for the benefit and protection of the patient. Hence it is not absolute and may be waived or released by the patient.

In the context of PGD, it follows therefore that a doctor is not to disclose to the parties involved each of the other's medical information in the absence of the parties' consent. A breach of patient confidentiality renders a doctor liable to disciplinary action by the profession as well as legal liability with respect to the patient. A patient may file a negligence suit in the event any unauthorised disclosure of confidential information causes him damage.<sup>3</sup>

In order to avoid legal liability, a doctor must obtain a patient's consent to communicate information about his medical condition. Such consent may be obtained expressly or impliedly. Disclosure should only be done in appropriate circumstances and patients should be told when such information is to be disseminated.

### *Negligence*

As a tort, negligence consists of a legal duty to take care and breach of that duty by the defendant causing damage to the plaintiff.<sup>4</sup> With respect to medical law, there are two aspects of medical negligence that are of relevance here namely negligent counselling and negligent diagnosis.

#### *Counselling and negligence*

One of the most significant issues in recent years is the amount of information which a patient ought to be given if a doctor is acting with due professional skill and care. If the doctor fails to give the patient the amount of information which ought to be given, it is now generally held to amount to negligence in law.<sup>5</sup>

If a genetic counsellor or doctor fails to advise prospective parents of the risk (however small) of genetic illness in the foetus, the parents of an afflicted child may choose to raise an action against him in respect of his negligence. In the United Kingdom, there is no doubt that damages will be awarded in respect of negligent counselling.<sup>6</sup>

The concept of informed consent whereby a doctor is under a fiduciary duty to ensure that a patient understands what the risks are involved in undergoing or foregoing certain treatment forms part of the law in the US and Canada. Singapore however does not ascribe to that practice as we follow the English position which provides that so

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<sup>3</sup> Catherine Tay, *Medical Confidentiality: Ethical & Legal Issues*

<sup>4</sup> Michael A. Jones, *Textbook on Torts*, 5<sup>th</sup> ed Blackstone Press Ltd, London (1997)

<sup>5</sup> Douglas Cusine, *Legal issues in human reproduction*, Dartmouth Publishing Co Ltd, England (1989)

<sup>6</sup> Mason & McCall Smith, *Law and Medical Ethics*, 4<sup>th</sup> ed Butterworths, London (1994)

long as the doctor follows the practice adopted by a responsible body of doctors in relation of what or what not to tell, he or she will not be negligent.

### *Diagnosis and negligence*

The *Bolam* test is the controlling test in Singapore with respect to medical negligence. It is stated as follows:

“The test is the standard of the ordinary skilled man exercising and professing to have that special skill. A man need not possess the highest expert skill at the risk of being found negligent ... it is sufficient if he exercises the ordinary skill of an ordinary competent man exercising that particular art.”

In essence, a doctor will not be found negligent if he exercises reasonable care and skill. Even if there is a body of opinion that takes a contrary view, a doctor is not negligent if he is acting in accordance with such a practice. Thus liability only arises if a doctor fails to match that standard of care in carrying out his duty as a professional.

### **Relevant Ethical Issues**

Artificial reproductive techniques raise difficult ethical issues. Objections to such procedures include the argument that they should not be acceptable because they are ‘unnatural’. Such techniques are deemed ‘unnatural’ in the sense that the ‘sacred process’ of life is the prerogative of God and should not be interfered with.<sup>7</sup> This argument promotes the view that procreation should only be done in the way God intended which is through sexual intercourse. However as argued by Athena Liu, this line of argument is vague and is clearly not a belief rigidly adhered to by those who are prepared to use artificial techniques to procreate and thus should not seriously suggest that these people’s view should be converted.

A second interpretation of the ‘unnatural’ argument is based on the belief that these techniques contravene the ‘natural law’. The objection here is that such reproductive techniques sever the link between the natural and legitimate end of sex and are thus contrary to natural law. This view however fails to establish what useful purpose it seeks to uphold and should not pose a serious threat to such artificial reproductive techniques.

Yet another objection to such procedures is the fear of potential abuse that will lead to the development of a eugenics programme. Using PGD to avoid transmitting a genetic predisposition or a characteristic trait that is deemed undesirable or to choose the sex to select the desired qualities of the unborn child is unacceptable.<sup>8</sup> Hence it is recommended that PGD be strictly used only in situations where the goal is to prevent

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<sup>7</sup> Athena Liu, *Artificial Reproduction and Reproductive Rights*, Dartmouth Publishing Co Ltd, England (1991)

<sup>8</sup> *Supra* n. 1

the transmission of a serious genetic disease. Guidelines should be drawn up and strictly adhered to so as to quell such fears that eugenics practices may emerge.

Another significant ethical issue is with respect to embryos that are not implanted. There are religious and ethical objections to such embryos being used for research and experiment purposes. These views are founded on the basis that such practices are tantamount to meddling with the sanctity of life. However, proponents of experimentation argue that embryonic research is necessary for human welfare for the development and refinement of present procedures as well as to lead to a greater understanding of early embryonic development, survival and implantation and its subsequent evolution.<sup>9</sup>

### **Conclusion**

As outlined above, the legal issues pertaining to PGD should be viewed in conjunction with those of IVF as they are inextricably linked. It would be wise if a doctor is cognisant of all the possible pitfalls and take all the necessary precautions to avoid them.

As for the ethical issues, there will always be fears and objections against procedures of this nature. Sometimes the opposition may be vociferous in their objection. However, so long as there are strict guidelines in place to ensure that doctors do not attempt to 'play God' and that the sanctity of life is given its due respect, such procedures should be given the go ahead for the betterment of Mankind.

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<sup>9</sup> Supra n. 7



# ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETICS RESEARCH

A CONSULTATION PAPER

THE BIOETHICS ADVISORY COMMITTEE

SINGAPORE

5 April 2005

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## ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETICS RESEARCH

### I. Introduction

- 1.1 The Bioethics Advisory Committee (BAC) was established by the Cabinet in December 2000 to examine the potential ethical, legal and social issues arising from research in the biomedical sciences in Singapore, and to recommend policies to the Life Sciences Ministerial Committee.
- 1.2 Three sets of recommendations have since been published and accepted by the government:
- (a) on human cloning and human stem cell research - *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*, June 2002 (Human Stem Cell Report);
  - (b) on human tissue banking and human tissue research - *Human Tissue Research*, November 2002; and
  - (c) on the ethics governance of human biomedical research - *Research Involving Human Subjects: Guidelines for IRBs*, November 2004 (IRB Guidelines Report).
- 1.3 We believe that human welfare can be elevated through the responsible development and application of biomedical science. The mapping of the human genome has contributed to a better understanding of the role of genetics in many common diseases such as cancer, heart diseases and diabetes. This has in turn fuelled the hope that new and more effective means of diagnosis and treatment of diseases may be developed through the increasing application of gene technology in medicine.
- 1.4 Genetic tests can help in the diagnosis, prevention and treatment of serious genetic disorders but they also present ethical, legal and social concerns to both individuals and society. These issues are varied and complex, with long-term ramifications. Many countries and international organisations are beginning to attend to these issues, some of which may have imminent ethical, legal or social impact.
- 1.5 Genetic information derived from genetic testing may disclose far greater details about an individual's health than medical information derived from a doctor's medical examination and interview. It provides information that has broader implications extending to family members<sup>1</sup> and future generations. Occasionally, unexpected information, for instance, information about parentage or information on the likelihood that an apparently healthy individual may develop a serious genetic condition later in life, may be revealed. The result of a genetic test, especially one that is positive for a serious genetic disorder for which there is no treatment, may have

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<sup>1</sup> For the purposes of this Consultation Paper, the terms "family" or "family members" refer not only to persons who are biologically or genetically related to the individual concerned but also to those whom the individual regards as family members in the broader sense of the family as a social unit.

significant psychological impact on an individual and possibly on his or her family. Due to the shared and predictive nature of genetic information, family members and third parties such as insurers and employers, may have an interest in a person's genetic information, and there is a need to ensure that genetic testing is conducted with due consideration and protection of the individual's interests and rights.

- 1.6 In light of the broad scope of genetic testing, we focus on two main aspects in this Consultation Paper:
- (a) genetic testing for certain specified purposes; and
  - (b) the genetic information thereby derived.
- 1.7 The use of genetic testing and genetic information for non-medical purposes can give rise to social and economic implications. As genetic information may be misinterpreted or misused, it carries the potential of causing harm if suitable measures of information control are lacking. However, we do not consider it appropriate to address these issues in this Consultation Paper but will continue to closely monitor them. Another aspect of genetic testing that is not considered in this Paper is the use of genetic information from linked medical registries and genetic databases for research. The ethical, legal and social issues that may arise are manifold and likely to have long-term implications for all levels of society. We intend to address these issues separately.
- 1.8 While some view genetic information as distinct from other medical information, our preference is for it to be treated as similar to medical information. We believe that the conduct of genetic testing should be limited to medical or related purposes. Healthcare professionals and biomedical researchers must ensure the safety, health, dignity and welfare of their patients or human subjects.
- 1.9 Ethical issues arising from genetic testing in Singapore has been considered by the National Medical Ethics Committee (NMEC)<sup>2</sup> in its *Ethical Guidelines for Gene Technology* (NMEC Gene Technology Guidelines) published in February 2001. In this Paper, we build on some of NMEC's Guidelines and provide specific recommendations relating to the ethical conduct of genetic testing in a clinical setting, the direct supply of genetic tests to the public and the proper derivation and interpretation of genetic information. We have placed particular emphasis on the importance of sound and effective counselling, which we regard as indispensable to the ethical conduct of genetic testing.
- 1.10 This Consultation Paper is prepared by the Human Genetics Subcommittee (HGS)<sup>3</sup> with the following objectives:

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<sup>2</sup> The NMEC was established in January 1994 to assist the Ministry of Health in addressing ethical issues in medical practice and to ensure a high standard of ethical practice in Singapore.

<sup>3</sup> The HGS was constituted by the BAC in March 2001 to specifically address the ethical, legal and social issues relating to research and development in human genetics and gene technology. Members of the HGS are listed in Annex A.

- (a) to consider the ethical, legal and social issues arising from the conduct of genetic testing in Singapore; and
- (b) to seek public feedback on the proposed recommendations.

1.11 After thorough consideration of all the views and comments received, we will present our final recommendations to the Life Sciences Ministerial Committee.

## II. Genetic Testing and Genetic Information

- 2.1 The demand for genetic testing in the healthcare and health-related sectors of many scientifically advanced countries has been rising steadily and has in turn fuelled the application of genetic testing for a diverse range of diseases. Consequently, more than 1,000 different genetic tests may now be conducted by clinical and research laboratories.
- 2.2 In recognition of the growing importance of genetic testing in the healthcare sector, the NMEC Gene Technology Guidelines were issued to assist physicians in managing this development. The Guidelines defined “gene technology” as “the use of techniques for the analysis and/or manipulation of DNA (deoxyribonucleic acid), RNA (ribonucleic acid) and/or chromosomes”<sup>4</sup> and focused on gene technology in the context of medical practice and doctor-patient relationship.

### Defining Genetic Testing

- 2.3 In this Consultation Paper, we seek to address some of the more pertinent ethical, legal and social issues in the conduct of genetic testing for clinical and research purposes. **Genetic Testing** is the use of tests which are designed specifically to detect genetic differences, for purposes that include, but are not limited to the following:
- (a) *Confirmatory Diagnosis* performed to confirm the diagnosis of a specific genetic disorder in an individual who already has signs or symptoms of that disorder. A positive test result identifies the definitive genetic cause of the disorder;
  - (b) *Carrier Testing* conducted to identify individuals with a genetic or chromosomal abnormality that generally does not affect the person’s health but puts him or her at higher risk of having a child with a specific genetic disorder;
  - (c) *Prenatal Genetic Diagnosis (PND)* conducted on a foetus or a pregnant woman so as to identify a specific genetic disorder;
  - (d) *Preimplantation Genetic Diagnosis (PGD)* conducted on an early embryo so as to identify a specific genetic disorder prior to the transfer of the embryo to the womb;
  - (e) *Predictive Testing* conducted on asymptomatic individuals to determine if they are at risk of developing a genetic disorder in the future;
  - (f) *Genetic Screening* conducted on healthy individuals to determine their status with regards to a specific genetic disorder; and
  - (g) *Genetic Testing* for research.

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<sup>4</sup> NMEC Gene Technology Guidelines, Section 1.1

Accordingly, **Clinical Genetic Testing** is genetic testing conducted for the diagnosis, prevention or treatment of a genetic disorder in a patient for purposes (a) to (f) of the above paragraph.

2.4 Genetic tests are commonly accomplished by the following methods:

- (a) direct testing, where tests are performed on the DNA or RNA specific for a gene;
- (b) cytogenetic testing, where the chromosomes are examined; and
- (c) linkage testing, where markers co-inherited with a disease-causing gene are examined.

Biochemical, functional, or immunological methods have also been used in Genetic Testing. However, for the purposes of this paper, Genetic Testing does not include these methods when they are not primarily designed to detect specific genetic defects but are instead used to screen for overall biochemical, physiological, or anatomical abnormalities.

### Defining Genetic Information

2.5 The practice of Genetic Testing in Singapore has largely been directed at addressing medical concerns. Hence, Genetic Testing is generally conducted through a physician and in the context of a physician-patient relationship. Genetic test results, or the **Genetic Information** that is derived from Genetic Testing, are filed together with other medical records of the patient. Generally, the law requires that medical records be treated as strictly confidential. Information provided or derived during the course of patient management should only be used for the treatment of the patient concerned unless important public interest (such as an immediate or imminent danger to the life of a third party) requires its disclosure regardless of the consent of the patient. As such, Genetic Information is not treated any differently from regular medical records.

2.6 The ethical, legal and social status of Genetic Information relative to other medical information is perceived differently by various authorities and ethics bodies. On the one hand, the US Task Force on Genetic Testing<sup>5</sup> and the European Commission's Expert Group on the ethical, legal and social implications of genetic testing have argued that both Genetic Information and other medical information should be accorded the highest level of ethical and legal safeguards.<sup>6</sup> On the other hand, certain characteristics of Genetic Information require that it be set apart from medical information in some circumstances. Some of these distinctive features have been articulated by the UK Human Genetics Commission (HGC) and the joint proposal of the Australian Law Reform Commission (ALRC) and the Australian Health Ethics Committee (AHEC) of the Australian National Health and Medical Research Council (NHMRC).

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<sup>5</sup> US Task Force on Genetic Testing, *Promoting Safe and Effective Genetic Testing in the United States* (1997). The Task Force is established by the National Institutes of Health-Department of Energy Joint Working Group on the Ethical, Legal and Social Implications of Human Genome Research.

<sup>6</sup> European Commission Expert Group, *25 Recommendations on the Ethical, Legal and Social Implications of Genetic Testing* (2004).



2.7 In its report *Inside Information: Balancing Interests in the Use of Personal Genetic Data* (2002), the HGC identifies four overlapping categories of personal genetic information. These are observable genetic information (such as eye colour), private (or non-observable) genetic information (such as carrier status for a genetic condition, for example thalassaemia), sensitive genetic information and non-sensitive genetic information. The HGC observed that it is the predictive feature and significance for individuals and their family members, future reproductive choices and subsequent generations that render Genetic Information sensitive in a healthcare context. It further sets out the following features of personal genetic information that distinguish it from other forms of information:

- (a) It is almost uniquely identifying, and so it is capable of confirming, denying or revealing family relationships;
- (b) It may be obtained from a very small amount of material, possibly without consent of the person;
- (c) It has predictive power, which may be given exaggerated symbolic significance;
- (d) It may be used for purposes other than those for which it was originally collected;
- (e) It may be of interest to others, including relatives who may be affected, insurers and employers;
- (f) It may be important for establishing both susceptibility to rare inherited disease and the likely effectiveness of some treatments; and
- (g) It can be derived from stable DNA recovered from stored specimens or even archaeological material after many years.

2.8 The ALRC and the AHEC adopted a similar analysis and crystallised these features into essentially three unique characteristics in their report *Essentially Yours: The Protection of Human Genetic Information in Australia* (2003):

- (a) It is ubiquitous in its ready availability in various forms (such as hair or fingernail) for genetic test to be conducted by various parties;
- (b) It has a familial dimension so that it is important not only to the individual but also to that individual's family due to the possible hereditary impact; and
- (c) It is predictive in its informational impact on the individual's future health.

While the ALRC and the AHEC stop short of categorising Genetic Information as distinct from medical information, they did propose that a commensurate level of legal protection may be required where there is a likelihood of special threat to privacy or discrimination. On this subject, both the Council of Europe and the

Bioethics Committee of Japan's Council for Science and Technology have stated similar positions.

- 2.9 The most distinctive feature of Genetic Information is perhaps its predictive value. However, we note that other information such as a smoking habit, which is related to the cancer-causing effect of tobacco, and exposure to certain toxic substances are also predictive health information. Nevertheless, we recognise that a potential misuse of Genetic Information may be attributed to the failure to properly comprehend its predictive nature. For instance, mutations in some disease genes (such as in Huntington's disease) are definite in giving expression to "disease" conditions or symptoms within the normal average lifetime of carriers. But for many other disease genes, mutations only confer a percentage chance of developing a particular genetic disease. Even if it is known that this genetic disease will occur within the lifetime of the carrier, it is uncertain when this will occur, or how severe it will be, since scientists do not yet know what conditions influence disease onset and severity. Where the prediction based on Genetic Information is uncertain, an unnecessary psychological burden (and possibly economic and social burdens as well) may be imposed on the carrier and his or her family.
- 2.10 The current practice of Clinical Genetic Testing in Singapore is through physicians registered under the Medical Registration Act. Such a "physician-based" system is also found in many leading scientific jurisdictions. Consequently, it is incumbent on physicians and other healthcare professionals working with or under the supervision of physicians to ensure that the conduct of genetic testing is in line with a system of ethical procedures. In most cases, physicians are the main points of contact with patients and accordingly bear ultimate responsibility towards them.
- 2.11 In light of the current practice of Genetic Testing in Singapore, as well as the current use of Genetic Information thereby derived, we are of the view that Genetic Information should not be treated differently from medical information. By this, we refer to Genetic Information as accessed and managed through the intermediation or under the supervision of a physician for a healthcare or health-related purpose. We do, however, recognise that there are occasions when Genetic Information – especially sensitive and non-observable Genetic Information – should be accorded greater ethical and legal safeguards when it is accessed and used by third parties for non-medical purposes. Indeed, history informs us that misuse of Genetic Testing and Genetic Information can lead to grave injustice and immense hardship not only for those immediately affected, but for their family members as well. For these reasons, many jurisdictions have introduced, or are considering, regulatory measures for governing access to, and the use of, Genetic Testing and Genetic Information outside of the healthcare context. Accordingly, we focus on the ethical conduct of Genetic Testing that provides non-observable and sensitive Genetic Information.

**Recommendation 1: Genetic Information derived from Clinical Genetic Testing should be confined to a healthcare context, owing to its complex nature and the need for professional input. Accordingly, it should be regarded as medical information and the highest ethical standard should be applied in its derivation, management and use.**

### III. General Ethical Considerations

- 3.1 As with many other types of technologies, Genetic Testing not only presents healthcare benefits, but also possible harms if misused. In this Part, we discuss ethical considerations that are generally applicable to all types of Genetic Testing, whether in a research or clinical setting. While we are of the view that healthcare professionals may be entrusted with the ethical conduct of Genetic Testing, the increasing commercialisation and ease of access to certain Genetic Testing may lead to compromising situations for members of the public. In this respect, we are particularly concerned with non-consensual Genetic Testing. This and other related issues are discussed in Part IV. In Parts V and VI, we consider the more specific ethical considerations that are applicable to human genetics research and Clinical Genetic Testing respectively.
- 3.2 In the conduct of Genetic Testing, the following ethical principles articulated in our earlier reports should continue to apply:
- (a) Respect for the welfare, safety, religious and cultural perspectives and traditions of individuals;
  - (b) Free and informed consent;
  - (c) Respect for vulnerable persons; and
  - (d) Privacy and confidentiality.

#### ***Respect for Welfare, Safety, Religious and Cultural Perspectives and Traditions***

- 3.3 Where Genetic Testing is conducted primarily for a clinical purpose, research considerations should not compromise or prejudice the primary purpose. If there is a possibility that the sample taken for clinical purposes may be used for research, this must be made known to the patient and his or her free and informed consent must be obtained. The more specific recommendations in our *Human Tissue Research* report for donations of human tissue for research to be made as gifts will then apply.<sup>7</sup>
- 3.4 In a multi-cultural and multi-religious society, healthcare professionals and researchers must be sensitive to the religious and cultural perspectives and traditions of individuals. For instance, certain cultures may be particularly sensitive to the presence of a hereditary disorder in a member of the family. Any communication of this nature should be carefully managed. Similarly, in selecting a population group to be screened, it is important to avoid stigmatisation of the entire group.

**Recommendation 2: Genetic Testing should be conducted in a manner that is respectful of the welfare, safety, religious and cultural perspectives and traditions of individuals.**

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“**Donations to be Outright Gifts.** Gifts of tissues should be accepted only on the basis that the donor renounces any property rights or claims to the tissue that they choose to donate. Donors should be informed of this principle, and if they do not agree, then their donation should not be accepted.” *Human Tissue Research* (2002), Recommendation 1D.

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***Free and Informed Consent: Freedom of Consent and the Right to Information***

- 3.5 The requirement of free and informed consent to be obtained before Genetic Testing arises from the broader societal value of respect for persons. It is generally accepted that the individual is free to decide whether to undergo any Genetic Testing, regardless of it being done in the context of screening, diagnosis or research.
- 3.6 Consent is effective only if the person giving the consent is aware of the circumstances, conditions and consequences for which it was given. How an individual may be appropriately informed prior to giving consent to testing depends on the situation in which consent is sought and the comprehensibility of the language used in the interactive process. In addition, the individual should be given sufficient time to understand the information provided and to decide whether or not to undergo Genetic Testing.
- 3.7 We propose that information to be provided to individuals before any Genetic Testing should include:
- (a) purpose of the test;
  - (b) procedure;
  - (c) discomforts and risks (if any) of the test to both the individual and the family;
  - (d) accuracy or predictive value of the test;
  - (e) implications (including social risks) of the test result (negative and positive) for the individual and his or her family members;
  - (f) treatment or management options;
  - (g) alternatives to Genetic Testing and their pros and cons;
  - (h) whether unexpected findings resulting from the test should be disclosed and the likely extent of the disclosure; and
  - (i) that the confidentiality of the test result would be maintained.
- 3.8 In some instances, healthcare personnel or scientists may want to store specimens provided for clinical testing for possible future uses in research. In such cases, informed consent for the future use of tissue specimens for research is required in addition to the consent to undergo Genetic Testing. The World Health Organization (WHO) stated that: “People should be informed of possible future uses of the specimens, whether identifiers will be retained, and if so, whether individuals will be re-contacted about new developments concerning their health care.”<sup>8</sup> We agree with this statement.

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<sup>8</sup> WHO, *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetics Services* (1998), Section 7.

- 3.9 In addition to the information in paragraph 3.7 that is to be provided to individuals before Genetic Testing, participants in Genetic Testing for research should be provided with the following additional information:
- (a) the experimental nature and purpose of the study;
  - (b) why the individual is invited to participate, and that participation is voluntary;
  - (c) the uncertainty of the results of the test for prediction and accurate genetic counselling;
  - (d) the possible benefits to others and to science;
  - (e) the confidentiality of records identifying the tested individual;
  - (f) who to contact for questions about research or in the event of a research injury;
  - (g) the right of the individual to withdraw from the research at any time;
  - (h) that refusal to consent, or withdrawal from the research at any time, will not compromise the quality of care that will be given to the individual and the family; and
  - (i) possible commercial uses.

**Recommendation 3: Genetic Testing should be voluntary and conducted only after free and informed consent has been obtained. Consent must be based on sufficient information, which includes the nature, purpose, risks and implications of the test. Consent should also be obtained for future clinical and/or research use of tissue specimens.**

- 3.10 A difficult situation may arise when an individual refuses to disclose a test result that may be medically beneficial to a third person. For instance, a genetic relative of the tested individual may benefit from knowing that the latter has a high risk of developing a genetic disorder such as colon cancer. The relative may then decide to undergo Genetic Testing, which may allow him or her to adopt beneficial practices, such as making lifestyle changes or going for regular medical check-ups. Such a scenario would encroach on the ethical principle of free and informed consent. Generally, an individual's request for the confidentiality of his or her test result to be maintained should be respected, and the test result is not to be disclosed without the individual's consent. It is nevertheless important that attending healthcare professionals point out clearly, through appropriate counselling, the important positive and negative consequences of disclosing the test result, although the final decision must rest with the tested individual. However, we emphasise that the ethical principle of privacy and confidentiality of an individual is not an absolute right. We address in greater detail the circumstance where disclosure may be made without consent of the individual in our discussion on the ethical principle of privacy and confidentiality below.

- 3.11 Where an individual has agreed to undergo Genetic Testing, this individual should be informed of the test result without undue delay unless he or she has clearly indicated the wish not to know after appropriate counselling. However, in cases where newborn babies and children are tested for treatable conditions, the test results should be disclosed to their parents or guardians. In addition, a healthcare professional may decide to postpone disclosure of the test result if the individual is not in a suitable condition to receive such information. This may arise when the test result reveals a condition that cannot be medically treated or alleviated. In research involving Genetic Testing, researchers should inform the individual prior to participation in the research whether the Genetic Information so derived will be disclosed to him or her.

**Recommendation 4: An individual should be informed of the test result without undue delay unless he or she has clearly indicated the wish not to know. However, the test results of newborn babies and children for treatable conditions should be disclosed. In research involving Genetic Testing, researchers should inform the individual prior to participation in the research whether the Genetic Information so derived will be disclosed to him or her.**

#### *Respect for Vulnerable Persons*

- 3.12 There are certain categories of persons where special procedures should be in place to ensure their voluntary and safe participation in Genetic Testing and to safeguard their welfare. Generally, it is inappropriate for such vulnerable persons to be involved in research. Exceptions can be made when the outcome of the research is greatly or critically dependent on their participation and when there is no appropriate alternative test population. In such cases, special safeguards should be assured to the greatest extent possible. We consider three categories of vulnerable persons in particular: children and adolescents, the mentally impaired and persons in dependent relationships.

##### *Children and Adolescents*

- 3.13 Genetic Testing of children and adolescents raises a number of difficult ethical and legal issues. Children and adolescents are dependent on their parents and guardians for survival and are limited in their ability to protect their own interests. As a result, it is generally recognised that all persons responsible for the care of children or adolescents should only act in the latter's best interest.
- 3.14 We appreciate that "best interest" is dependent on the specific circumstances and conditions of a child or adolescent. When considering whether the child or adolescent's best interest is met by Genetic Testing, it should be considered in the context of the family. Physicians should always consider, together with the parents or legal guardians, any possible harm before recommending Genetic Testing. However, the "best interest" approach is not an absolute one. In this regard, we note the recommendation of the European Society of Human Genetics (ESHG), indicating that Genetic Testing is permitted where it is necessary for the child's or adolescent's own health, or where the information would be imperative to diagnose the existence of

genetic disease in family members.<sup>9</sup> Similar recommendations have been made by the Council of Europe and the UK HGC.<sup>10 11</sup>

- 3.15 Genetic Testing is recommended or required in certain cases, for conditions where preventive intervention or treatment is available and beneficial in childhood or adolescence. However, the informed consent of the parent or legal guardian of the child or adolescent should be obtained. In addition, the child or adolescent should be involved in the consent process as comprehensively as possible.
- 3.16 The ability of a child or an adolescent to comprehend the purpose and implications of Genetic Testing will differ from one child or adolescent to another. Therefore, the extent of involvement of a child or adolescent should be considered on a case-by-case basis, through the process of genetic counselling. An older child or adolescent who is sufficiently mature, should be involved in the consent process and his or her wish to undergo or to refuse Genetic Testing should be respected. While we recognise the general perception that a person reaches maturity when he or she attains the age of 21 years, we consider a child or adolescent to be mature if he or she is capable of understanding the purpose and implications of Genetic Testing. We consider the capacity of a child or an adolescent to participate in the consent process to be dependent on his or her level of maturity rather than some arbitrary age. In this connection, we note and agree with the WHO's statement: "An adequate explanation for a child's assent should describe the potential harms and benefits of testing in a simple manner appropriate to the child's age."<sup>12</sup>
- 3.17 Carrier Testing should generally be deferred until the child is mature or required to make reproductive decisions. He or she should then be fully informed of the benefits, risks and implications of the test. Predictive Testing in children for late-onset diseases where there is no available preventive intervention or treatment, or where the intervention or treatment is only available during adulthood, should likewise be deferred. However, there may be exceptional situations where Carrier and Predictive Testing may be considered in children. For instance, the parents of a child at risk may find it extremely difficult to bear the psychological burden of not knowing the genetic status of their child. We consider that in such circumstances, psychological and emotional burdens may prevent or have a negative impact on the provision of the best possible care to the child or the adolescent. A conceivable event is when parents overreact to the possibility of their child developing the disease. The physician should take into consideration unique family circumstances and have the discretion to decide, together with the parents, if it is in the best interest of the child or adolescent to conduct Genetic Testing. For mature children or adolescents, we reiterate that their decision to undergo or refuse Genetic Testing should be respected. We emphasise that in such circumstances, genetic counselling is particularly important.

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<sup>9</sup> European Society of Human Genetics, *Provision of Genetic Services in Europe: Current Practices and Issues* (2001).

<sup>10</sup> Council of Europe, *Recommendation No. R(92)3 on Genetic Testing and Screening for Health Care Purposes* (1992).

<sup>11</sup> HGC, *Inside Information: Balancing Interests in the Use of Personal Genetic Data* (2002).

<sup>12</sup> WHO, *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetics Services* (1998), Section 7.

**Recommendation 5: We do not recommend the broad use of Genetic Testing on children and adolescents. Confirmatory Testing and Predictive Testing for genetic conditions where preventive intervention or treatment is available and beneficial in childhood are recommended. Carrier Testing should generally be deferred till the child is mature or when required to make reproductive decisions. Predictive Testing should generally be deferred where there is no preventive intervention or treatment, or where intervention or treatment is only available and beneficial during adulthood. However, in exceptional circumstances, parents and the physician should have the discretion to decide regarding Carrier and Predictive Testing, and counselling should be an intrinsic part of the testing process.**

*The Mentally Impaired*

- 3.18 Additional safeguards should also be considered for persons lacking the competence to agree to Genetic Testing. The ESHG identifies such persons as those suffering from mental disorders and adults placed under limited guardianship. Clinical Genetic Testing should only be permitted where it is necessary for their own health or where the information would be imperative to diagnose the existence of genetic disease in family members.<sup>13</sup> In cases where mentally impaired persons are the most suitable candidates to undergo Genetic Testing for research, special safeguards should be in place to ensure that free and informed consent of persons having legal charge over them is obtained. In addition, the welfare and safety of the mentally impaired research subject must be ensured at all times and to the furthest extent possible.
- 3.19 In Singapore, the Supreme Court of Judicature Act empowers the High Court to appoint and control guardians and keepers of “idiots, mentally disordered persons and persons of unsound mind”.<sup>14</sup> Hence, the High Court has the power to appoint a legal guardian who may provide consent on behalf of a person lacking mental competence where it is appropriate to do so. We also note the recommendation in the NMEC Gene Technology Guidelines that, in the case of an individual 21 years or older but mentally incapable of making a decision, a parent or guardian may consent on his behalf. In the main, we are of the view that Genetic Testing should not be conducted on a person who is mentally impaired unless consent has been obtained from a person who is legally authorised to decide on behalf of the mentally impaired.

*Persons in Relationship of Dependence*

- 3.20 Persons in dependent relationships require special consideration in the consent process. For example, prisoners who have been incarcerated may be under duress or some form of undue influence to give consent to those with authority over them, or they may hold some perception, which may or may not be real, that they have ‘no choice’ but to consent. Similarly, students or employees may be under duress or feel that they are under duress to agree to Genetic Testing. This category of dependent persons further includes poorly educated individuals, who are unable to fully understand what they are consenting to (due to language barriers for instance).

<sup>13</sup> European Society of Human Genetics, *Provision of Genetic Services in Europe: Current Practices and Issues* (2001), at Recommendation 14.

<sup>14</sup> *Supreme Court of Judicature Act* (Cap 322), Section 17(e).



- 3.21 In cases of dependent relationships, it is important to ensure that consent is both informed and freely given. The Nuffield Council on Bioethics stated that special care is necessary when seeking consent from prisoners, student volunteers and individuals who do not speak English.<sup>15</sup> Similarly, it would be unacceptable for those in positions of power to engage in actions that either coerce individuals into taking genetic tests or inhibit individuals from taking the same for fear of social or economic disadvantage as stated by the Human Genetics Society of Australasia.<sup>16</sup> We agree with these statements. Where there are reasons to believe that a person agrees to Genetic Testing for fear of losing healthcare benefits, this misconception should be corrected. One way to do this is to expressly indicate when obtaining consent that however a person decides, any healthcare, employment, welfare, or other benefits that are currently provided or in prospect, will not be jeopardised.

**Recommendation 6: Genetic Testing involving vulnerable persons should be conducted only if appropriate free and informed consent has been obtained. In the case of persons in special relationships, extra care should be taken to ensure that the consent is freely given. Clinical Genetic Testing should only be conducted if it is medically beneficial. Genetic Testing for research should only be conducted if the research is considered of sufficient importance and there is no appropriate alternative test population.**

### *Confidentiality and Privacy*

- 3.22 Healthcare professionals and researchers involved in Genetic Testing have an obligation to protect the confidentiality of Genetic Information. We note Article 7 of the 1997 *Universal Declaration on the Human Genome and Human Rights* of the United Nations Educational, Scientific and Cultural Organisation (UNESCO), which states: “Genetic data associated with an identifiable person and stored or processed for the purposes of research or any other purpose must be held confidential in the conditions set by law.” The WHO has similarly stated: “Genetic data should only be used to advantage and empower an individual or family, and for better treatment or prevention of disease. Data relevant to health care should be collected and kept by medical geneticists in secure confidential files.”<sup>17</sup> We agree with these statements and we are of the view that genetic test results should not be disclosed to third parties, including insurers and employers, without the free and informed consent of the individual.
- 3.23 Individuals should be provided information on how their privacy will be protected, before they consent to Genetic Testing. We agree with the HGC's position that Genetic Information should generally not be obtained, held or communicated without the free and informed consent of the individual.<sup>18</sup> Certain individuals may be unwilling to share or divulge their Genetic Information to their family members, other healthcare professionals or researchers. Hence, healthcare professionals and researchers should exercise special care in protecting the individual's privacy and the confidentiality of such information. However, we reiterate our view that the ethical principle of privacy and confidentiality is not an absolute right in itself. There may be

<sup>15</sup> Nuffield Council on Bioethics, *Genetic Screening: Ethical Issues* (1993), paragraph 4.27.

<sup>16</sup> Human Genetics Society of Australasia, *Predictive Genetic Testing and Insurance* (1999).

<sup>17</sup> WHO, *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetics Services* (1998), Executive Summary.

<sup>18</sup> HGC, *Inside Information: Balancing Interests in the Use of Personal Genetic Data* (2002), at page 42.

exceptional circumstances when Genetic Information may be disclosed notwithstanding its confidentiality or the individual's privacy. One such circumstance may be where the Genetic Information will be of direct benefit to society on the whole if its use in research is permissible. However, the reasons for the disclosure should be clearly explained to the individual concerned and his or her privacy should be safeguarded to the furthest extent possible (for instance, through anonymisation of the Genetic Information).

3.24 In addition, a situation may arise where the life of a third person will be endangered if the relevant Genetic Information is not disclosed. There is therefore a need to balance the risks of breaching confidentiality against the risks of non-disclosure. In this connection, we note and agree with NMEC's position<sup>19</sup> whereby a physician's ethical duty of confidentiality to a patient can be overridden if the following conditions are satisfied concurrently:<sup>20</sup>

- (a) Separate efforts by two healthcare professionals to elicit voluntary consent to disclosure have failed, despite the patient or client fully understanding the implications of such refusal;
- (b) There is a high probability both that harm will occur to identifiable individuals or the society at large if the information is withheld and that the disclosed information can actually be used to avert harm;
- (c) The harm that identifiable individuals (if any) would suffer would be serious; and
- (d) Appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed.

3.25 In the event that the above conditions are met, the physician should ensure that the patient concerned is aware that such a disclosure would take place and only relevant information would be disclosed.

**Recommendation 7: Genetic test results should not be disclosed to third parties, including employers and insurers, without the free and informed consent of the individual.**

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<sup>19</sup> NMEC Gene Technology Guidelines, Section 2.4.1.

<sup>20</sup> A similar position was recommended by the US President's Commission for the Study of Ethical Problems in Medicine and Medical and Behavioral Research (1983) and supported by the WHO (1998), the American Society of Human Genetics (1998) and the Institute of Medicine (1994).

#### IV. Public Access to Genetic Testing

- 4.1 In Singapore, as in many other countries, access to Genetic Testing is mainly through healthcare professionals or healthcare institutions. Healthcare professionals are also responsible for interpreting the results of genetic tests, providing pre-test and post-test counselling to the patient regarding the value and implications of the test, the significance of the test results and, if need be, treatment and other follow-up actions.
- 4.2 Generally, an individual will not obtain direct access to Genetic Testing. However, recent developments in the public availability of Genetic Testing services indicate that it is possible for an individual to conduct Genetic Testing either on himself or herself, or on another person, in Singapore or overseas.

##### *Direct Supply of Genetic Testing to the Public*

- 4.3 Since the publication of the NMEC Gene Technology Guidelines, there have been important changes in the biomedical landscape in Singapore and elsewhere, especially in genetic testing devices and services. A conventional demand-supply evaluation is illustrative. On the demand-side, the Singaporean public is, on average, gaining sophistication in knowledge of health and health-related matters. One factor that may have contributed to this social phenomenon is the increased availability of medical information from various sources, especially the Internet. When considered in light of hectic lifestyles, “face-saving” or privacy concerns and escalating healthcare costs, the prospect of a “do-it-yourself” approach to certain health and health-related matters may appear attractive. On the supply-side, advances in gene technology have simplified the usage of many devices for Genetic Testing and further enabled manufacturers to produce them at much lower cost. Considering these developments in the context of low-cost marketplaces such as the Internet, it is foreseeable that a significant number of Singaporeans may choose to by-pass medical professionals to obtain direct access to Genetic Testing for various reasons.
- 4.4 The commercialisation of Genetic Testing services and ensuing “direct supply” of Genetic Testing devices and services to the general public have become a growing concern in a number of countries. The UK HGC has recently carried out an extensive review of this development in its report *Genes Direct: Ensuring the Effective Oversight of Genetic Tests Supplied Directly to the Public* (2003). It found that devices and services for Genetic Testing are increasingly being marketed directly to the public in the UK and in some other developed countries. In such “direct supply”, the public gains access to Genetic Testing without the conventional face-to-face consultation with a medical professional so that, following a telephone call or electronic mail, an individual can post his or her tissue sample to a laboratory where the genetic analysis is performed. Alternatively, certain do-it-yourself genetic test devices can be procured over-the-counter or through the Internet. In the absence of a medical consultation, the HGC is concerned that the possible harms far outweigh the interest of an individual in obtaining information about himself or herself. Two possible “harms” from direct Genetic Testing were identified:
- (a) misinformation leading to a delay in seeking proper medical assistance or seeking unnecessary medical assistance; or

- (b) inappropriate Genetic Testing of children or other adults without proper consent.
- 4.5 We share the concerns of the HGC. If free access to Genetic Testing is allowed in Singapore, the likelihood of misinformation is high. First, there is a lack of assurance that the genetic tests or devices supplied by manufacturers are of a satisfactory quality and standard. Second, there is a high likelihood that the test result may be misinterpreted by an untrained person. The predictive nature of Genetic Information discussed in Part II of this Consultation Paper contributes to the interpretive difficulties. Third, it is unrealistic to expect suppliers of Genetic Testing kits and devices to provide long-term counselling and other support services of satisfactory standards, particularly for the diagnosis and/or prediction of serious conditions. It should be noted that even if such devices and services are not intended for the diagnosis and/or prediction of serious conditions, they might nevertheless provide Genetic Information that is indicative of the possibility of some serious condition.
- 4.6 There is a further possibility of grave harm arising from inappropriate Genetic Testing. In recent years, the supply of Genetic Testing services to establish family relationships or historical roots is a growing industry and several such services are available through the Internet. While harm is unlikely to arise where such tests are voluntarily undertaken by fully informed adults, the same cannot be said if children or unsuspecting adults are tested. The knowledge of mistaken family ties can exert a heavy psychological burden on adults, let alone children who will have to come to terms with this information without proper counselling and support. The broader impact on the relationship between the individual and his or her family members is likely to complicate matters further.
- 4.7 We envisage another possible “harm” in the potential discrimination of individuals whose Genetic Information may be acquired by third parties. While insurers or employers do not have the right to require genetic tests to be undertaken by a potential client or employee, there is presently nothing to prevent them from requiring the test results to be disclosed where available. It is arguable that disclosure of a genetic condition by a person seeking to be insured becomes necessary if he or she is aware of this condition through Genetic Testing, even if the test was conducted for some other purpose. Failure to disclose this condition may render the insurance legally ineffective, although disclosure may lead to higher premiums or preclusion from insurance coverage altogether. We will continue to review these complex issues which presently cannot be satisfactorily resolved and will consider them separately.
- 4.8 The NMEC has strongly discouraged genetic testing by manufacturers and suppliers of genetic testing kits, unless it is conducted under the direction of a physician.<sup>21</sup> However, we are of the view that a more comprehensive system of control over public access should be devised in light of recent developments in gene technology and the consequences that they entail. While it is not necessary to restrict access to all kinds of Genetic Testing, we think that it is timely to develop an appropriate regulatory framework for the oversight of Genetic Testing that is likely to cause serious harm to the public if freely accessible.

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<sup>21</sup> NMEC Gene Technology Guidelines, Section 3.2.1.

- 4.9 There is currently no specific legislation regulating access to, or supply of, Genetic Testing devices and services. The Centre for Medical Device Regulation (CMDR) of the Health Sciences Authority (HSA) has established a system for the voluntary registration of medical devices and is currently in the process of setting up a framework for the regulation of medical devices.
- 4.10 We recommend that a comprehensive regulatory framework for the direct supply of genetic tests to the public be established, taking into consideration the likely harm that may arise if access is not controlled. Genetic tests that are predictive of serious health conditions should be accessible only through qualified healthcare professionals.
- 4.11 We emphasise that genetic tests, especially those associated with possible serious health conditions, should generally be regarded as part of medical service. For a similar reason, the advertising of direct genetic tests to the public should be strongly discouraged.

**Recommendation 8: Genetic Testing should be conducted through the intermediation of a qualified healthcare professional. Accordingly, the advertising of genetic tests by manufacturers or suppliers to the public is strongly discouraged. A comprehensive regulatory framework should be established for access to Genetic Testing services. Genetic tests that provide predictive health information should not be directly offered to the public.**

***Prohibition Against Involuntary Genetic Testing***

- 4.12 It is difficult to regulate access where Genetic Testing devices and services may be easily procured via the Internet. We are concerned that such devices and services may be used on individuals without their consent as it is relatively easy for body samples to be taken from individuals without their knowledge, let alone their consent. In view of the harms that may arise from the misuse of Genetic Information, we are strongly against the taking and testing of an individual's tissues without consent. We note the HGC's recommendation that "consideration be given to the creation of a criminal offence of the non-consensual or deceitful obtaining and/or analysis of personal genetic information for non-medical purposes."<sup>22</sup> This recommendation has since been accepted by the UK legislature and enacted as law in November 2004.<sup>23</sup> We regard it as timely for Singapore to adopt a similar legislation.

**Recommendation 9: The non-consensual or deceitful obtaining of body samples for the purpose of Genetic Testing should be legally prohibited.**

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<sup>22</sup> UK HGC, *Inside Information: Balancing Interests in the Use of Personal Genetic Data* (2002), at paragraph 3.60.

<sup>23</sup> *Human Tissue Act* 2004, Section 45 (Non-consensual analysis of DNA)

## V. Specific Ethical Considerations for Human Genetics Research

- 5.1 Human genetics research is the study of genes and how they are associated with health and disease. It may involve processes leading to more effective methods for the diagnosis and treatment of genetic diseases or the development of genetic tests for clinical use. Human genetics research enhances our understanding of the genetic basis of disease and how genetic and environmental factors influence one's health. Hence, its primary objective is not to provide research participants or their families with specific information about their genetic status or health.
- 5.2 Significant research is currently taking place throughout the world to examine the genetic basis of common diseases such as cancer, heart disease and diabetes, and important discoveries are emerging. Ultimately, it is hoped that human genetics research will enable or facilitate the development of new or more reliable ways of diagnosing, preventing and treating genetic disorders effectively. The treatments envisaged extend across a broad spectrum from pharmacological, gene or cell-based therapies, to simple changes in a person's environment or lifestyle.
- 5.3 The overall ethical framework for human biomedical research has been set out in our previous reports. This framework applies to all biomedical research that involves human subjects or the use of any kind of human biological materials, including solid body tissues, organs, foetuses, blood and other bodily fluids and their derivatives, cord blood, embryos, gametes (sperm or eggs) or any part or derivative of such materials, and whether they are derived from living or cadaveric donors.
- 5.4 Human genetics research may involve research subjects, tissue samples or genetic information derived from genetic tests. As genetic materials are shared by biological relatives, genetic information derived from research using a person's tissue will have implications extending to his or her relatives. In addition to ethical considerations that apply to all research involving humans, genetic research poses unique ethical issues arising from the shared nature of genes and genetic information. The misuse of genetic information may lead to harm, including stigmatisation and unfair discrimination. Thus, privacy and confidentiality issues are important considerations for researchers involved in human genetics research.
- 5.5 In our IRB Guidelines Report, we emphasised the critical role that researchers, institutions and Institutional Review Boards (IRBs) play in ensuring the protection of the safety, health, dignity, welfare and privacy of research subjects.
- 5.6 Researchers conducting human genetics research must also observe the following:
  - (a) Obtain the approval of a research ethics committee (or IRB) before proceeding with the research;
  - (b) Seek the free and informed consent of the research subjects. Information to be provided to research subjects prior to seeking consent is outlined in Part III of this Paper. Where an attending physician is also the researcher, it may be necessary for consent to be taken separately through an independent third party to ensure the voluntary involvement of the individual. Where the research

involves human tissue that have been appropriately anonymised or can no longer be traced to an individual (such as legacy tissues), the consent requirement may be waived. However, ethics review of the research project is still required;

- (c) Protect the privacy of research participants and the confidentiality of the genetic information so derived;
- (d) When vulnerable people are involved, the principle of acting in their best interest applies; and
- (e) When the research involves using human embryos, written approval from the Ministry of Health (MOH) is required in addition to approval by the IRB. No research should be performed on any embryos more than 14 days old.

## VI. Specific Ethical Considerations for Clinical Genetic Testing

- 6.1 Clinical Genetic Testing is usually carried out as part of the health management or treatment of an individual. As such, the ethical management of Clinical Genetic Testing should not differ significantly from conventional medical service. While Genetic Information derived from Clinical Genetic Testing may be utilised in research that is independent of any human subject, such as research using genetic databases and medical registries, the ethical, legal and social issues arising from such research will be addressed in a separate paper.
- 6.2 We note and agree with the NMEC that the “introduction of a genetic test into routine clinical use must be based on evidence that the gene(s) being examined is associated with the disease in question, that the test itself has analytical and clinical validity, and that the test results will be useful to the people being tested.”<sup>24</sup> In addition, the choice of a genetic test should be based on the individual’s best interest. In the following section, we discuss ethical issues related to specific types of genetic tests.

### Section A: Specific Ethical Considerations

#### *Carrier Testing*

- 6.3 Carrier testing identifies an individual who carries a genetic abnormality that generally does not affect the person’s health but puts him or her at a higher risk of having a child with a specific serious genetic disorder. Individuals who are identified as a carrier of a disorder, such as thalassaemia or muscular dystrophy, can then be counselled about these risks and the options available to them.
- 6.4 We emphasise the importance of genetic counselling both prior to and after the test. Proper counselling can prevent confusion over the difference between being an asymptomatic carrier for a genetic disorder and being affected with the disorder. Furthermore, the risk of stigmatisation, discrimination and adverse psychological reactions may also be minimised. Genetic counselling is considered in Section C below.

#### *Preimplantation Genetic Diagnosis*

- 6.5 Preimplantation genetic diagnosis (PGD) is a procedure whereby early embryos created by *in vitro* fertilisation (IVF) are evaluated to determine the presence of one or more genetic conditions. It is then followed by the selection and implantation of unaffected embryos into the uterus. PGD was developed following the availability of IVF and new genetic testing techniques, primarily to help couples where one or both partners are known carriers of genetic disorders to have healthy children. Before this procedure was developed, PND and selective termination of an affected pregnancy were used to enable “at-risk” couples to have healthy children. With PGD, these couples have the option of starting out with unaffected pregnancies, thus avoiding the need to consider selective termination of an affected pregnancy subsequently.

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<sup>24</sup> NMEC Gene Technology Guidelines, Section 3.1.1.



- 6.6 Since 1992, when PGD was successfully applied to avoid a specific genetic defect leading to cystic fibrosis, many clinics throughout the world have begun offering PGD services. At present PGD can be used to screen for more than 100 genetic conditions, including Down's syndrome, sickle-cell anaemia, thalassaemia and Huntington's disease. It has been estimated that about 2,000 embryo-screened babies have been born throughout the world.
- 6.7 Although PGD is currently not available in Singapore as a clinical service, it is available in more than 100 clinics in many countries including the US, the UK, India, Israel, Japan and South Korea. In Cyprus and Greece, PND and PGD have been applied for the prevention of haemoglobin disorders and the number of children born with  $\beta$ -thalassaemia major has since been drastically reduced.
- 6.8 PGD has most commonly been recommended for patients with:
- (a) a child confirmed with a genetic disease and with an increased risk of having another child with the same disease;
  - (b) confirmed carrier status (in one or both partners) for a serious genetic condition; or
  - (c) advanced maternal age.
- 6.9 PGD is a technically demanding procedure. Although it presents an option for some couples to conceive a child without a genetic disease, its effectiveness and success rates, in terms of "take home" babies, are not high. Current PGD pregnancy rates are estimated at about 20%, which is similar to the rates for IVF alone. Although there are some concerns relating to the safety and long-term health consequences of PGD, there have been no reports of increased foetal malformations or other identifiable problems arising from pregnancies involving PGD-tested embryos. A recent study of the past 12 years of data from the world's three largest PGD centres, comprising 4748 PGD attempts and 754 successful pregnancies, led to the conclusion that PGD is safe.<sup>25</sup>
- 6.10 As PGD is a special form of Genetic Testing connected with IVF, it should be viewed as a technology to help couples who do not wish their children to be affected by a genetic disorder. We do not dispute the generally accepted assumption that parents will only wish to act in the best interest of their children. There is no reason to believe that this assumption should not apply generally to couples in reproductive decisions.
- 6.11 In a multi-cultural and multi-religious society, views on the ethics of PGD in Singapore are likely to be as diverse as views on human therapeutic cloning and embryonic stem cell research. Indeed, a segment of the medical community and the public may not wish to be involved in PGD, in the same way as they avoid involvement in human therapeutic cloning and embryonic stem cell research. Such conscientious objection should be respected and no one should be under a duty to

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<sup>25</sup> Y. Verlinsky et al, *Over a Decade of Experience with Preimplantation Genetic Diagnosis: A Multicenter Report*, Fertility and Sterility, Volume 82, Issue 2, Pages 292-294 (August 2004)

undergo or perform PGD. However, it should be equally open for other members of the medical community and the greater public who do not hold the same view to participate in, or have recourse to, PGD in ways that are not harmful to the moral and social fabric of Singapore on the whole.

- 6.12 Although the intent for which PGD is employed differs significantly from that in human cloning and embryonic stem cell research, the possible compromise of the sanctity of life represented in an embryo touches one of the central moral and religious concerns of these technologies. Other ethical concerns relate to the possible use of PGD for trait selection and the danger of leading society closer to eugenics. It is feared that PGD may be used to select for or against certain non-medical traits for the “enhancement” of the newborn, which thereby devalue and alter the way in which society views those who nonetheless possess the “undesirable” traits. Ethical concerns regarding the use of PGD for trait selection is aggravated by the prospect that, even if such use becomes widely and ethically acceptable, only the rich can afford to have offspring with the desirable traits in view of the high cost of PGD. As a result, society will be further stratified into the economically rich and genetically desirable at one end, and the economically poor and genetically unaltered at the other end.
- 6.13 We acknowledge these concerns and attempt to address them by drawing on the two broad guiding principles of ‘justness’ and ‘sustainability’, which were first articulated and adopted in our Human Stem Cell Report. In the first principle of ‘justness’ is the obligation to respect the common good and the fair sharing of social costs and benefits. The second principle of ‘sustainability’ reflects an obligation to respect the needs of generations yet unborn. Together, these two principles also advance the concepts of beneficence and non-maleficence. They in turn encourage the pursuit of social benefits along-side efforts to avoid or ameliorate potential harm.
- 6.14 From the experiences of countries where PGD is practiced, there are indications that this technology is helpful in addressing the reproductive needs of couples who have a known family history of a genetic disorder, are carriers of a genetic disorder, or have unexplained infertility. For instance, doctors in America have recently succeeded in using PGD to enable a woman to bear a child free of the gene mutation linked to an early-onset Alzheimer's disease that she carries. The presence of this gene mutation in an individual confers an almost 100% probability of manifesting symptoms of the disease by the age of 40 years. The experiences of countries that allow the practice of PGD also suggest that it is possible to guard against serious violations of moral and ethical standards through careful and effective regulation.
- 6.15 We are of the view that PGD should be allowed, provided that it is subject to control by a relevant authority and limited to serious medical conditions. The relevant authority should license, monitor and assess PGD to ensure that it is employed within legal and ethical limits. As such, the authority should issue regulations and guidelines for this purpose.

**Recommendation 10: Preimplantation genetic diagnosis is permissible provided that it is subject to control by a relevant authority and limited to serious medical conditions. The relevant authority should license, monitor and assess preimplantation genetic diagnosis to ensure that it is employed within legal and ethical limits.**

- 6.16 We do not consider it to be acceptable at the present time to use PGD in trait selection on non-medical grounds. A child who is selected for a particular trait such as greater mental or physical potential thought to be in some manner superior may experience increased pressure to fulfil that genetic “potential” in his or her parents’ expectations. The situation is worsened if the child fails to attain these “superior” mental and/or physical qualities for which he or she was genetically selected. In both situations, the proper relationship between parent and child is undermined – that is, the ideal that parental love should not be dependent on a child having characteristics that the parents hoped for, but rather as individuals in their own right. Allowing parents to exercise their preference in making such a ‘selection’ may introduce an element of control over the result of conception, thus making the “experience of parenthood very different from the present situation in which... parents are happy just to take their child as they find them.”<sup>26</sup> We note that some have argued that such concerns are unjustified. In their opinion, expanding control over human reproduction may be thought of as merely an extension of the parental responsibility to care for their offspring. The reasons behind a couple’s choice to have children are often personal and should not be open to public scrutiny. We do not agree with this view. Personal interest must always be balanced against public interest in any kind of society. In this case, there is public interest in maintaining a stable relationship between parents and their children, and this interest far outweighs the desire of parents to select for certain traits in their children for non-medical reasons. There may be situations where a couple may wish to implant an affected embryo for “lifestyle” reasons. In a recent case in the US, a deaf couple has deliberately conceived a deaf child because they do not consider deafness as a disability. We are of the view that such use of PGD is unfair to the child and is, accordingly, unacceptable and should be prohibited.
- 6.17 It is technically possible to use PGD for sex selection. Couples may desire this for medical reasons, since certain genetic disorders are sex-linked and only affect persons of a particular gender, for example, Duchenne muscular dystrophy is X-linked and affects only males. Sex selection may also be desired for non-medical reasons, such as balancing the gender ratio in a family, personal preference, or certain social, cultural, religious or economic motivations. We agree with the position of the International Bioethics Committee of the UNESCO that sex selection for non-medical reasons is generally unethical. Such selection tends to promote gender stereotyping and discrimination.

**Recommendation 11: Use of preimplantation genetic diagnosis for sex selection and the selection of certain desired traits for non-medical reasons should be prohibited.**

- 6.18 It is beyond our remit and premature at the present time to determine the extent that PGD should be made available to couples who are unable to afford this means of assisted conception. It is more appropriate for the relevant authority to deliberate on this issue, taking into account the economic consequences, at a time it determines to be appropriate.

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<sup>26</sup> Nuffield Council on Bioethics, *Genetics and Human Behaviour: The Ethical Context* (2002), at page 154.

### *Preimplantation Tissue Typing*

- 6.19 The UK is one of a few countries that have moved beyond the impasse of ethical debate in relation to human embryo research. The establishment of the Human Fertilisation and Embryology Authority (HFEA) under the Human Fertilisation and Embryology Act of 1990 (the 1990 Act) is a result of several years of discussion and deliberation on this subject. The HFEA licenses and monitors IVF clinics and the creation and handling of human embryos for research. At the time the 1990 Act was passed, PGD was only an experimental procedure. By the turn of this century, PGD has become an acceptable method employed to avoid the birth of children with genetic disorders. In recent years, PGD has been used in combination with tissue typing, which not only allows couples to have a healthy child, but also enables the selection of a potential tissue donor for a sick sibling. Preimplantation tissue typing (PTT) is described by the HFEA as “a new technique which allows the selection of embryos in order to bring about the birth of a child who can provide a matched tissue donation to an existing sibling, either as the sole clinical objective or in combination with [PGD] to avoid a serious genetic condition in the resulting child.”<sup>27</sup> We find the experience of the HFEA with PTT to be instructive.
- 6.20 In 2001, the HFEA adopted a cautious approach and permitted PTT on a case-by-case basis under the following conditions:<sup>28</sup>
- (a) the affected child's condition is severe or life-threatening and of sufficient seriousness to justify the use of PGD;
  - (b) the embryos created for PTT are themselves at risk from the condition affecting the existing child;
  - (c) all other possibilities of treatment and sources of tissue for the affected child have been explored;
  - (d) parents are not the intended recipient;
  - (e) the intention is to obtain only cord blood for the purposes of treatment and not other tissues or organs;
  - (f) couples receive appropriate counselling;
  - (g) families encouraged to participate in follow-up studies and PGD clinics are to provide detailed information regarding treatment cycles and outcomes; and
  - (h) the created embryos are not genetically modified to provide a match.
- 6.21 However, in July 2004, the HFEA extended the rules to allow embryos not at risk of a genetic disorder to be tested for their compatibility as tissue donors for a seriously ill sibling. The HFEA requires that such cases demonstrate “a genuine need for potentially life-saving tissue and a likelihood of therapeutic benefit for an affected

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<sup>27</sup> HFEA Report: *PreImplantation Tissue Typing* (2004) at page 1.

<sup>28</sup> HFEA Report: *PreImplantation Tissue Typing* (2004) at page 2.

child.”<sup>29</sup> This extension was made after the HFEA had carefully considered the medical, psychological and emotional implications for children and their families, and the safety of the technique performed in the past three years.

- 6.22 Ethical concerns have been expressed over PTT in that children may be used as a means to an end rather than having children for no other purpose. We note that such concerns are not supported by evidence. It has been argued that parents who conceive a child to save a life may be on higher moral ground than those who procreate as an unanticipated consequence of sexual pleasure or for some selfish purpose.
- 6.23 We have earlier expressed our view that the conduct of PGD should be allowed in Singapore provided that proper and effective safeguards are in place. In light of the UK’s experience with PTT, we consider PTT to be generally acceptable provided that it is subject to regulation by a relevant authority and evaluated on a case-by-case basis. We want to emphasise that PTT should be a measure of last resort. The relevant authority should provide clear guidelines on the eligibility of families for PTT. In this connection, we are of the view that such families must have the capabilities to ensure that the welfare of both the child conceived by way of PTT and the sick sibling are not compromised. In addition, we agree with the HFEA that follow-up studies on the psychological, social and other longer-term implications in these families should be encouraged.

**Recommendation 12: Preimplantation tissue typing, whether as the sole objective or in conjunction with preimplantation genetic diagnosis to avoid a serious genetic disorder, is permissible but should be licensed and evaluated on a case-by-case basis.**

### *Germline Genetic Modification*

- 6.24 Germline genetic modification is a type of gene technology that involves the alteration of a person’s genetic makeup in a manner that is permanent and can be transmitted to his or her offspring. We note that germline genetic modification may also be brought about inadvertently in gene therapy or through other experimental techniques.
- 6.25 While the technologies capable of rendering germline genetic modification do not fall within our definition of Genetic Testing, we are of the view that clinical practice of germline genetic modification should not be allowed at this time. Germline genetic modification is at present still experimental and will require substantial research to establish its feasibility and safety in clinical application. In addition, the potentially great impact on future generations presents serious ethical concerns. We will monitor progress in germline genetic modification and reassess its clinical applicability at an appropriate time in the future.

**Recommendation 13: Clinical practice of germline genetic modification should not be allowed at this time.**

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<sup>29</sup> HFEA Report: *Preimplantation Tissue Typing* (2004) at page 10.

### ***Prenatal Genetic Diagnosis***

- 6.26 Prenatal genetic diagnosis (PND) provides important information to couples who are at increased risk of having a baby with a genetic disorder. This information may help them decide whether or not to terminate the pregnancy and if they decide not to, the information may help them prepare for the birth of a child with a disability. The information may also be useful for the professional team to prepare for a difficult delivery. The risk factors of having a baby with a genetic disorder include:
- (a) advanced maternal age;
  - (b) family history of a serious heritable medical condition;
  - (c) one or both parents are “carriers” of mutation(s) in the same gene;
  - (d) abnormal screening test results such as ultrasound or first and second trimester screening tests; and
  - (e) history of a previous child affected by a serious growth, developmental or health problem.
- 6.27 Prenatal screening precedes PND and provides prospective parents and healthcare professionals with information regarding the health of the developing foetus. Prenatal screening procedures include:
- (a) determining whether there is a history of infertility, miscarriages, abnormal children, or a family history of genetic diseases;
  - (b) maternal serum screening tests, which are done either in the first or second trimester. These tests measure circulating levels of certain blood proteins or other metabolites where abnormal levels may indicate possible genetic and/or structural defects in the baby; and
  - (c) ultrasound scans of the foetus, usually at 12 and 22 weeks of pregnancy to detect structural abnormalities, which may indicate possible genetic defects in the baby.
- 6.28 In Singapore, prenatal screening in conjunction with pre- and post-test counselling is part of the routine prenatal care and specific diagnostic tests are performed when indicated. PND can be carried out for various genetic conditions, including Down’s syndrome, thalassaemia and haemophilia. If prenatal screening tests indicate that the foetus is likely to be affected with a disorder, PND will be offered to verify the presence or absence of a genetic disorder.
- 6.29 The range of available prenatal genetic tests is increasing as more knowledge is gained about genetic disorders through research. PND may require obtaining tissue specimens from the foetus. Acquiring these specimens involves an invasive procedure and hence poses a risk of miscarriage. It is therefore important that patients are fully

informed of this and other risks, and their consent is obtained prior to the tests being carried out.

- 6.30 If PND indicates that the foetus is or will likely be affected with a genetic disorder, the couple should be counselled about the disorder and its implications, in order to make an informed decision as to whether or not to continue with the pregnancy.
- 6.31 PND for late-onset diseases poses difficult ethical problems. If parents are strongly against abortion, the information derived from the PND provides no benefits to them or the child and may even cause the child to suffer from stigmatisation and discrimination by family and society. Hence, we propose that performing a test for late-onset diseases on a foetus should be discouraged. However, if parents are undecided and would like to consider abortion, it may be appropriate to respect their autonomy.

**Recommendation 14: Prenatal genetic diagnosis should be voluntary, conducted with informed consent and with appropriate pre- and post-test counselling. The prospective parents' choice of whether a genetic disorder warrants a prenatal genetic diagnosis or termination of the pregnancy should be respected.**

- 6.32 It is possible to employ PND for gender or trait selection for non-medical purposes. For reasons similar to those that we have proffered in relation to PGD, we are of the opinion that PND for gender or trait selection (whether physical, social or psychological characteristics or normal physical variations) should not be allowed. The practice of PND is essentially confined to serious genetic disorders and we consider this to be appropriate. We recommend that appropriate professional bodies prescribe detailed ethical guidelines on the practice of PND for their members.

**Recommendation 15: Prenatal genetic diagnosis should be limited to serious genetic diseases. The use of prenatal genetic diagnosis for gender selection, apart from sex-linked disorders is unacceptable. Similarly, it is unacceptable to use prenatal genetic diagnosis for the selection of any physical, social or psychological characteristics or normal physical variations.**

**Recommendation 16: The appropriate professional bodies should prescribe detailed ethical guidelines on the practice of prenatal genetic diagnosis for their members.**

### *Predictive Testing*

- 6.33 Predictive testing identifies healthy individuals who have inherited a gene for a late-onset disease, which is a disease that normally becomes symptomatic in adulthood, although there are cases where symptoms may arise during late childhood.
- 6.34 Predictive tests can be classified into two categories based on the predictive nature of the information derived from the tests:
- (a) *Presymptomatic tests* identify healthy individuals who have inherited a defect in a specific gene for a late-onset disease which confers on the individual an almost 100% risk of developing the disease at a later stage in life. However, these tests do not provide information on the severity and onset of the disease.

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Examples of such diseases include Huntington's disease and familial adenomatous polyposis, which are due to defects in single genes.

- (b) *Susceptibility (or predisposition) tests* identify individuals who have inherited a genetic variant or variants, which may increase their risk of developing a multi-factorial disease some time in the future. Such disorders are generally due to the interaction of genes and the environment. Alzheimer's disease, diabetes and certain cancers and heart disease fall into this category. While their genetic predisposition indicates that these individuals have an increased risk of developing the disease, some individuals may ultimately not develop the disease.
- 6.35 Healthy individuals requesting for predictive testing often do so to determine their risk of developing a genetic disease or passing on the disease to their children. Hence, presymptomatic tests are usually performed on individuals with a family history of a specific genetic disease, while susceptibility tests may be performed because of a family history or as part of population screening. As our knowledge in medical genetics increases, it is likely that the number of susceptibility or predisposition tests will increase.
- 6.36 Testing for a late-onset disease before an individual develops any symptoms allows the individual to make life-style changes to either prevent the disease from developing or assist him or her in making reproductive choices to prevent transmitting the disease to the next generation. It may also allow affected individuals to take preventive measures or undergo regular examinations to achieve early diagnosis and treatment of the disease.
- 6.37 Presymptomatic testing is generally well established, both technically and in its clinical application. It should be available for adults at risk who request it, even in the absence of treatment, after proper counselling and informed consent.
- 6.38 Susceptibility testing is at the moment not in clinical practice to any extent, largely because such tests have not been sufficiently developed and validated. Therefore, susceptibility testing should not be applied clinically unless there is unequivocal empirical evidence of validity and utility.
- 6.39 Predictive Genetic Information may be burdensome or psychologically traumatic given the uncertainty of the disease. We reiterate the importance of voluntariness and free and informed consent in genetic screening and further note NMEC's recommendation: "Testing must be voluntary and patients and/or families must not be coerced into undergoing predictive testing. Regardless of the decision made, the care of the patient should not be compromised."<sup>30</sup>

**Recommendation 17: Presymptomatic testing should be available for adults at risk who request it, even in the absence of treatment, after proper counselling and informed consent.**

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<sup>30</sup> NMEC Gene Technology Guidelines, Section 2.2.1 (b).



**Recommendation 18: Susceptibility testing should not be applied clinically unless there is unequivocal empirical evidence of validity and utility.**

### *Genetic Screening*

- 6.40 The WHO defined genetic screening as “tests offered to a population group to identify asymptomatic people at an increased risk from a particular adverse outcome.”<sup>31</sup> The main purpose of genetic screening is to prevent a disease or minimise morbidity and mortality through early diagnosis and treatment.
- 6.41 Screening tests are not definitive as they are designed to identify those at risk. A confirmatory diagnostic test should be performed as soon as possible after a positive screening test, so as to minimise unnecessary anxiety or to enable measures for the prevention or treatment of the condition to be instituted without delay.
- 6.42 Generally, population genetic screening programmes are offered only when there are proven methods of treatment or prevention. Such programmes are different from other types of medical screening, as there may be risk implications for family members of the person screened.
- 6.43 In Singapore, there are several prenatal and newborn screening programmes. Many pregnant women are screened prenatally for foetuses with Down’s syndrome. All newborn babies are screened for Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency to reduce the risk of neonatal jaundice and its complications. They are also screened for congenital hypothyroidism and for hearing defects, half of the cases of which are likely to be genetic in origin. These routine newborn and prenatal screening programmes have become socially acceptable in Singapore and hence informed consent is not explicitly taken. However, with new tests being developed, leading to an expansion of screening programmes, we recommend that free and informed consent should be obtained. The process of giving information and obtaining consent should be tailored to the level of risk and benefit to the individual and the society. For newborn screening programmes which have well-established scientific and clinical validity, the process of giving information and obtaining consent should not be too complex to the extent that it discourages participation in such programmes. The healthcare professional should explain the reasons for performing the genetic tests to parents before taking a blood sample from the baby. Institutions may consider providing additional information through means such as pamphlets for mothers or large notices displayed in clinics. Testing should not proceed if parents object to the tests after being provided with adequate information.

**Recommendation 19: In genetic screening programmes, the appropriate free and informed consent should be obtained from the individual to be tested or parents (or legally designated persons) as the case may be. A confirmatory diagnostic test should be performed as soon as possible after a positive screening test, so as to minimise unnecessary anxiety or to enable measures for the prevention or treatment of the condition to be instituted without delay.**

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<sup>31</sup> WHO, *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetics Services* (1998), Section 6.

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## **Section B. Ensuring the Proper Derivation and Interpretation of Genetic Information in Clinical Genetic Testing**

- 6.44 In this Consultation Paper, our primary concern is the proper derivation and interpretation of Genetic Information in Clinical Genetic Testing. This essentially rests on the quality of the Genetic Information, which in turn is dependent on the integrity of the diagnostic chain (this includes ensuring no sample switch or sample contamination), and the test methodology. As such, the sound practices of medical laboratories are directly relevant to the quality of the Genetic Information, and are a pre-condition to accurate interpretation.
- 6.45 Accurate interpretation of Genetic Information presents one of the greatest challenges in Genetic Testing. Another challenge is the presentation of Genetic Information in a comprehensible and empathetic manner. We address this latter challenge in the section on genetic counselling. Interpretation of Genetic Information, like other medical information, is very much an art as it is a science. Skill at interpretation depends on experience as well as up-to-date knowledge of the field.
- 6.46 As with other medical information, Genetic Information is likely to have psychological impact on patients. However, this impact may be greater if the Genetic Information suggests that a patient has a predisposition to developing a serious condition some time in the future and/or the condition is likely to affect his or her genetic relatives. A predisposition indicates that the patient has a risk of developing the genetic condition, although he or she may eventually not develop the disease. Where other family members may also be at risk of developing the genetic condition, the patient will have the additional burden of having to decide if this risk should be disclosed to them. Family members who are not affected by the genetic condition may nevertheless be affected psychologically (such as the condition of “survivor’s guilt”). This is further complicated where the patient is a member of an identical twin or a triplet. Genetic Testing of the patient will at the same time reveal the genetic status of the other member(s). In this case, there may be a conflict of wishes. For instance, the patient may wish to know the Genetic Information but his or her twin may not. It is difficult to reach a common position whereby the patient’s right to know may be balanced against his or her twin’s right ‘not to know’, since both wishes should be respected. Adding to all these difficulties are broader social implications that may arise, such as reproductive choices that a patient may be faced with. Given these concerns, we are particularly mindful of the care that is required in the accurate derivation and interpretation of Genetic Information.

### ***Standards and Quality of Genetic Test Providers***

- 6.47 As Genetic Information has far reaching implications, it is important to ensure its accuracy. The accuracy of a test is dependent on the integrity of the diagnostic chain and the test methodology. These aspects should be carefully monitored to ensure an acceptable level of confidence as to the technical accuracy of test results. Generally, genetic tests are performed at laboratories selected by healthcare professionals. However, an individual may approach laboratories directly for testing to be done. We are concerned that such direct access may not be in the best interest of the individual as there is no assurance of the quality of the test result.

- 6.48 Medical laboratories in Singapore are required to obtain a license from the MOH. Apart from minimum operational standards that the MOH prescribes, there are no generally binding standards for Genetic Testing that is conducted by medical laboratories. There is however a system of voluntary accreditation for medical laboratories. Accreditation is often very helpful in providing greater assurance as to the overall competence of the testing laboratory, as well as the accuracy of the Genetic Information thereby derived.
- 6.49 In the US, the Clinical Laboratory Improvement Amendments of 1988 establishes quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of the test results. In addition, professionals involved in Genetic Testing are usually certified by the American Board of Medical Genetics (ABMG) and/or are members of the American College of Medical Genetics (ACMG). ABMG and ACMG also regularly issue policy statements on important issues in Genetic Testing. Similarly in the UK, all laboratories providing genetic testing services need to be appropriately accredited and they take part in internal and external quality assurance programmes. Furthermore, it has been recommended that genetic testing be undertaken only by laboratories closely linked with other genetic services.<sup>32</sup> The Australian NHMRC stated that Clinical Genetic Testing should be performed only by accredited laboratories.<sup>33</sup> Laboratories are required to be particularly sensitive to the possibility of error in the performance of genetic test.
- 6.50 Currently, the Singapore Accreditation Council (SAC) conducts general accreditation of medical laboratories. Although accreditation is not mandatory, the SAC actively encourages medical laboratories to be accredited. The SAC accredits medical laboratories as part of the Singapore Laboratory Accreditation Scheme (SINGLAS), which is essentially based on standards that are internationally accepted. SAC-SINGLAS is internationally recognised via mutual recognition arrangements such as the Asia-Pacific Laboratory Accreditation Cooperation, the International Laboratory Accreditation Cooperation and European Cooperation for Accreditation. It establishes best practices and standards for laboratories, including qualification requirements for the laboratory director and other technical personnel. In addition, SINGLAS also has specific criteria for accreditation in specialty areas such as molecular pathology and cytogenetics. Other than the SAC, accreditation of medical laboratories in Singapore has also been conducted by the College of American Pathologists (CAP), and jointly by the SAC and the CAP under the SAC-CAP Laboratory Accreditation Programme.
- 6.51 We propose that all laboratories conducting Clinical Genetic Tests should be accredited by an accreditation body designated by the relevant authority, based on standards as it considers appropriate. This is necessary to maintain a high quality of Genetic Information thereby derived, which is in turn fundamental in safeguarding the welfare of tested individuals.

**Recommendation 20: All laboratories conducting Clinical Genetic Tests should be accredited by an accreditation body designated by the relevant authority, based on standards it considers appropriate.**

<sup>32</sup> UK Advisory Committee on Genetic Testing, *Report on Genetic Testing for Late-onset Disorders* (1998) at pages 19 and 20.

<sup>33</sup> NHMRC, *Ethical Aspects of Human Genetic Testing: an Information Paper* (2000).

### ***Results Interpretation***

- 6.52 There are several factors that affect the accurate interpretation of Genetic Information. These include (a) integrity of the diagnostic chain, (b) reliability of test methods, (c) technical competence of laboratory technicians, (d) ability of the individual to understand, and (e) up-to-date knowledge of the interpreter. We believe that proper accreditation of medical laboratories should address factors (a) to (c). However, factors (d) and (e) will depend to a larger extent on the interpreter of the Genetic Information.
- 6.53 The interpretation of genetic test results is complex and dependent on many factors including the nature of the disease, the modality of testing, and the health status of the patient. As we have discussed, healthcare professionals are to ensure that sound interpretation is provided to patients, and so healthcare professionals should be appropriately qualified or sufficiently experienced. Misinterpretation of results or misdiagnosis may lead to psychological trauma, and unnecessary or inappropriate therapeutic interventions or changes to lifestyle for the patient and his or her family.
- 6.54 It should also be highlighted that genetic counselling should be provided in a timely manner. As far as practicable, there should be no delay in counselling following the disclosure of the test result to the patient, so as to help the patient cope with any resultant psychological impact or emotional stress. Given these, together with the myriad of medical, psychological, social, financial and legal implications that may arise, sound and effective pre- and post-test counselling is particularly critical and should always be timely and integral to the practice of Genetic Testing.

**Recommendation 21: Interpretation of genetic test results should only be performed by healthcare professionals who are appropriately qualified or have sufficient experience. Genetic counselling should immediately follow the disclosure of the test result, particularly if the test result is not favourable.**

### **Section C. Genetic Counselling**

- 6.55 We have emphasised at various points in this Consultation Paper the importance of genetic counselling in the conduct of Genetic Testing. Genetic counselling should seek to achieve the following objectives:
- (a) provide sufficient and unbiased information, as well as appropriate support, to enable full and informed choices to be exercised; and
  - (b) assist the patient and his or her family members cope with the situation.
- 6.56 In genetic counselling, information provided should be adequate and comprehensible to the patient. The patient should always be given sufficient time to consider the available options and the opportunity to clarify doubts. In addition, counselling should be conducted in an empathetic manner and should be non-directive, especially if the condition is one where treatment is presently not available. Whenever practicable, counselling should be done in a face-to-face meeting.

- 6.57 We have indicated that free and informed consent is dependent on the information that is provided to patients before Genetic Testing, and the manner in which such information is conveyed. For this reason, we consider counselling to be intrinsic to the consent process. Taking into account the recommendations provided by the NMEC on this matter, we recommend that the following considerations be taken into account in pre-test genetic counselling:
- (a) nature of the condition to be tested;
  - (b) potential consequences of not being tested;
  - (c) foreseeable consequences as a result of testing, including implications for family members, and available support;
  - (d) test reliability and clinical validity, emphasising that not all mutations are detectable, that some mutations are of uncertain significance, and that results indicate probability, not certainty, of developing the disease;
  - (e) the nature and efficacy of any interventions that might follow after the genetic testing, including the quality of evidence concerning the efficacy of treatments, or other strategies for avoiding the consequences of mutations that might be detected;
  - (f) type of sample required, test procedure and possible risks;
  - (g) turnaround time and how the results will be conveyed to the patient;
  - (h) treatment or management options; and
  - (i) alternatives to Genetic Testing and their pros and cons.
- 6.58 Where appropriate, it may be beneficial to also take into consideration the following in pre-test genetic counselling:
- (a) possible third parties' interest in the patient's Genetic Information and the likely consequences;
  - (b) further use of Genetic Information and test samples, and their management;
  - (c) possibility of unexpected findings (such as parentage discrepancy even though the test is not a parentage test) and whether the patient will want to know such findings; and
  - (d) assure patient of confidentiality of test result, but explain circumstances that might require disclosure of the patient's test result (if necessary).

**Recommendation 22: Genetic counselling should be offered to all individuals prior to and after they undergo Genetic Testing.**

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**Recommendation 23: Genetic counselling should generally be conducted in a non-directive manner and should provide sufficient information and appropriate support to the individual and his or her family members.**

*Post-test Follow-up*

- 6.59 We are of the view that follow-up support should be provided to patients in the form of post-test counselling. Patients will often have queries on the result of their genetic tests and the implications. Healthcare professionals should attempt to address these queries in post-test counselling. In particular, we recommend that the following considerations be undertaken:
- (a) discussion on the implications of the genetic test result, whether the result is a positive, negative or inconclusive one;
  - (b) treatment or management, and/or support options;
  - (c) possible implications for family members;
  - (d) address psychological, social and ethical issues or concerns;
  - (e) requirement or obligation to disclose the Genetic Information to a third party (if any); and
  - (f) management of Genetic Information.
- 6.60 Genetic Information may reveal cases that require long term follow-up attention. In such cases, the genetic counsellor concerned is expected to:
- (a) conduct periodic review of management plan;
  - (b) monitor patient's adherence to the plan;
  - (c) clarify issues;
  - (d) give psychological support; and
  - (e) inform patient of relevant developments in medicine.
- 6.61 In certain cases involving children tested positive for a serious genetic condition, it may be prudent to discuss the implications of the test result with the parents in the absence of the child. This is to allow parents to ask questions freely and to minimise any risk of misunderstanding on the part of the child.

*Professional Diversification and Development*

- 6.62 Currently in Singapore, there is no uniform practice or standards applicable to genetic counselling, which is usually carried out by physicians. However, genetic counselling is a time consuming process. Thus, it may not be practical for genetic counselling to be solely conducted by physicians. Furthermore, in light of rapid development in

medical genetics, specialised knowledge may be required. This may mean that certain individuals who are not physicians may be better skilled at conducting genetic counselling. Such individuals may be medical geneticists, nurses or other healthcare therapists. Individuals involved in genetic counselling must be committed and prepared to invest the time and should possess up-to-date knowledge of gene technology. However, it should be noted that the responsibility for overseeing the case, including counselling, rests ultimately on physicians, as they carry ultimate clinical responsibility for patients.

- 6.63 The relevant authority should consider providing professional training in medical genetics and counselling to scientific and healthcare professionals working in this field.

**Recommendation 24: Individuals involved in genetic counselling should possess up-to-date knowledge of medical genetics and should be appropriately trained in both medical genetics and counselling.**

## VII. Summary of Recommendations

### *Genetic Information*

#### **Recommendation 1:**

Genetic Information derived from Clinical Genetic Testing should be confined to a healthcare context, owing to its complex nature and need for professional input. Accordingly, it should be regarded as medical information and the highest ethical standard should be applied in its derivation, management and use.

### *General Ethical Considerations*

#### **Recommendation 2:**

Genetic Testing should be conducted in a manner that is respectful of the welfare, safety, religious and cultural perspectives and traditions of individuals.

#### **Recommendation 3:**

Genetic Testing should be voluntary and conducted only after free and informed consent has been obtained. Consent must be based on sufficient information, which includes the nature, purpose, risks and implications of the test. Consent should also be obtained for future clinical and/or research use of tissue specimens.

#### **Recommendation 4:**

An individual should be informed of the test result without undue delay unless he or she has clearly indicated the wish not to know. However, the test results of newborn babies and children for treatable conditions should be disclosed. In research involving Genetic Testing, researchers should inform the individual prior to participation in the research, whether the Genetic Information so derived will be disclosed to him or her.

### *Genetic Testing of Vulnerable Persons*

#### **Recommendation 5:**

We do not recommend the broad use of Genetic Testing on children and adolescents. Confirmatory Testing and Predictive Testing for genetic conditions where preventive intervention or treatment is available and beneficial in childhood are recommended. Carrier Testing should generally be deferred till the child is mature or when required to make reproductive decisions. Predictive Testing should generally be deferred where there is no preventive intervention or treatment, or where intervention or treatment is only available and beneficial during adulthood. However, in exceptional circumstances, parents and the physician should have the discretion to decide regarding Carrier and Predictive Testing, and genetic counselling should be an intrinsic part of the testing process.

#### **Recommendation 6:**

Genetic Testing involving vulnerable persons should be conducted only if appropriate free and informed consent has been obtained. In the case of persons in special relationships, extra care should be taken to ensure that the consent is freely given. Clinical Genetic Testing should only be conducted if it is medically beneficial. Genetic Testing for research should only be conducted if the research is considered of sufficient importance and there is no appropriate alternative test population.



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### ***Privacy and Public Access to Genetic Testing***

#### **Recommendation 7:**

Genetic test results should not be disclosed to third parties, including employers and insurers, without the free and informed consent of the individual.

#### **Recommendation 8:**

Genetic Testing should be conducted through the intermediation of a qualified healthcare professional. Accordingly, the advertising of genetic tests by manufacturers or suppliers to the public is strongly discouraged. A comprehensive regulatory framework should be established for access to Genetic Testing services. Genetic tests that provide predictive health information should not be directly offered to the public.

#### **Recommendation 9:**

The non-consensual or deceitful obtaining of body samples for the purpose of Genetic Testing should be legally prohibited.

### ***Preimplantation Genetic Testing***

#### **Recommendation 10:**

Preimplantation genetic diagnosis is permissible provided that it is subject to control by a relevant authority and limited to serious medical conditions. The relevant authority should license, monitor and assess preimplantation genetic diagnosis to ensure that it is employed within legal and ethical limits.

#### **Recommendation 11:**

Use of preimplantation genetic diagnosis for sex selection and the selection of certain desired traits for non-medical reasons should be prohibited.

#### **Recommendation 12:**

Preimplantation tissue typing, whether as the sole objective or in conjunction with preimplantation genetic diagnosis to avoid a serious genetic disorder, is permissible but should be licensed and evaluated on a case-by-case basis.

### ***Germline Genetic Modification***

#### **Recommendation 13:**

Clinical practice of germline genetic modification should not be allowed at this time.

### ***Prenatal Genetic Diagnosis***

#### **Recommendation 14:**

Prenatal genetic diagnosis should be voluntary, conducted with informed consent and with appropriate pre- and post-test counselling. The prospective parents' choice of whether a genetic disorder warrants a prenatal genetic diagnosis or termination of the pregnancy should be respected.

**Recommendation 15:**

Prenatal genetic diagnosis should be limited to serious genetic diseases. The use of prenatal genetic diagnosis for gender selection, apart from sex-linked disorders is unacceptable. Similarly, it is unacceptable to use prenatal genetic diagnosis for the selection of any physical, social or psychological characteristics or normal physical variations.

**Recommendation 16:**

The appropriate professional bodies should prescribe detailed ethical guidelines on the practice of prenatal genetic diagnosis for their members.

***Predictive Testing*****Recommendation 17:**

Presymptomatic testing should be available for adults at risk who request it, even in the absence of treatment, after proper counselling and informed consent.

**Recommendation 18:**

Susceptibility testing should not be applied clinically unless there is unequivocal empirical evidence of validity and utility.

***Genetic Screening*****Recommendation 19:**

In genetic screening programmes, the appropriate free and informed consent should be obtained from the individual to be tested or parents (or legally designated persons) as the case may be. A confirmatory diagnostic test should be performed as soon as possible after a positive screening test, so as to minimise unnecessary anxiety or to enable measures for the prevention or treatment of the condition to be instituted without delay.

***Standards of Genetic Test Providers*****Recommendation 20:**

All laboratories conducting Clinical Genetic Tests should be accredited by an accreditation body designated by the relevant authority, based on standards it considers appropriate.

**Recommendation 21:**

Interpretation of genetic test results should only be performed by healthcare professionals who are appropriately qualified or have sufficient experience. Genetic counselling should immediately follow the disclosure of the test result, particularly if the test result is not favourable.

***Genetic Counselling*****Recommendation 22:**

Genetic counselling should be offered to all individuals prior to and after they undergo Genetic Testing.

**Recommendation 23:**

Genetic counselling should generally be conducted in a non-directive manner, and should provide sufficient information and appropriate support to the individual and his or her family members.

*Professional Development*

**Recommendation 24:**

Individuals involved in genetic counselling should possess up-to-date knowledge of medical genetics and should be appropriately trained in both medical genetics and counselling.

**CONSULTATION PAPER ON “ETHICAL, LEGAL AND SOCIAL ISSUES IN  
GENETIC TESTING AND GENETICS RESEARCH”  
5 APRIL 2005**

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102	Dr Teo Cheng Peng	Chairman/Medical Director	StemCord Pte Ltd
103	A/Prof Philip Choo	Chairman Medical Board	Tan Tock Seng Hospital
104	Master Lee Zhi Wang	President	Taoist Mission (Singapore)
105	Dr Ang Poon Liat	Chairman Medical Board	Thomson Medical Centre
106	A/Prof Loke Kah Yin	Volunteer Paediatrician	Turner Syndrome Support Group
107	Mr Rustom Ghadiali	President	Zoroastrian Association of Singapore



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**WRITTEN RESPONSES TO THE CONSULTATION PAPER ON “ETHICAL,  
LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETICS  
RESEARCH”**

1. The Cancer Institute
2. The Catholic Medical Guild of Singapore
3. Centre for Research on Islamic and Malay Affairs, Association for Muslim Professionals
4. College of Family Physicians Singapore
5. Faculty of Medicine, National University of Singapore
6. Gleneagles CRC Pte. Ltd.
7. Graduates’ Christian Fellowship
8. Institute of Bioengineering and Nanotechnology
9. Institute of Mental Health
10. KK Women’s and Children’s Hospital
11. The Law Society of Singapore
12. Life Insurance Association
13. Majlis Ugama Islam Singapura (Islamic Religious Council of Singapore)
14. National Council of Churches of Singapore
15. National Dental Centre
16. National Heart Centre
17. National Kidney Foundation
18. National Medical Ethics Committee (NMEC)
19. National Skin Centre
20. Obstetrical & Gynaecological Society of Singapore
21. Office of Life Sciences, National University of Singapore
22. Singapore Nursing Board
23. Society of Bioscience & Technology
24. Tan Tock Seng Hospital
25. U.S. Department of Health and Human Services
26. Dr Alvin Wong, Consultant, Department of Haematology Oncology, National University Hospital

*Email Responses:*

1. Dr Peter Ang, Consultant, Department of Medical Oncology, National Cancer Centre
2. Aviva Ltd
3. Chief Actuary's Office, Great Eastern Life Assurance Co Ltd
4. Consumers Association of Singapore
5. School of Biological Sciences, Nanyang Technological University



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May 30, 2005

Associate Professor Terry Kaan  
Chairman  
Human Genetics Subcommittee  
Bioethics Advisory Committee

Dear *Terry*,

**FEEDBACK ON CONSULTATION PAPER**

We have reviewed the Consultation Paper entitled "Ethical, Legal and Social Issues in Genetic Testing and Genetics Research", and found that the paper is very comprehensive and detailed. It is a well thought out paper, which covers all the important aspects of the issues discussed.

With kindest regards

*John*

Professor John Wong  
Director  
The Cancer Institute  
National Healthcare Group

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27 May 2005

Dear Sirs,

**CONSULTATION PAPER ON ETHICAL, LEGAL AND SOCIAL ISSUES IN  
GENETIC TESTING AND GENETIC RESEARCH**

We write in response to the request by the BIOETHICS ADVISORY COMMITTEE (BAC) for feedback on the consultation paper entitled, **ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETIC RESEARCH**

We understand that members of the BAC have devoted significant time and effort in coming up with such a paper, guided by a voice of conscience which you hold so true and dear.

**PREMISE FOR OUR FEEDBACK**

1. There is an eternal, universal and objective law that binds all of humankind.
2. As humans, beings endowed with reason and free will, we bear responsibility for our decisions and actions. We are impelled by our nature and bound by a moral obligation to seek the truth of this law.
3. We do not create this law. We can only discover it with our powers of intellect and will, through due process of practical reasoning. Once we have discovered this truth, we are bound to adhere to it and direct our whole lives in accordance with its demands.
4. Among the first principles of this law is that we should do good, to seek the good of each human person, and to avoid intending or doing harm to him. It is upon this basic principle that our response is based.

5. Science and technology are valuable resources for man when placed at his service and when they promote his integral development and the common good. But without conscience, science can only lead to man's ruin.

### **GENERAL FEEDBACK TO THE PAPER**

We are of the opinion, that this latest paper, sadly, like the previous papers mentioned on page 1 of the consultation, continues to ignore or disregard the humanness and dignity of the human embryo and foetus.

Although the BAC has in the past professed a special respect for human embryos and foetuses this respect nonetheless falls grossly short of acknowledging their absolute right to life, by virtue of their scientifically undisputed position as fellow members of the human race.

This considerably undermines the value of the programme that is being promoted.

Perhaps a good way of illustrating our view is to use a modern day analogy – the consultation paper proposes a well-intentioned program for health care and health promotion that is also intentionally corrupted with a virus or subroutine that attacks life.

In other words, some of the means used are not worthy of the lofty ends sought.

Because ethics is the philosophy of right human behaviour, it must recognise human rights and the dignity of human sexuality and human reproduction and take into account the sanctity of life of *all* humans (the first human right) and not just of some.

It must distinguish between the '*moral good*' and the '*useful good*', and not use any human being as a commodity with a purely utilitarian end. This it fails to achieve.

For the record, we wish to repeat the relevant comments in our response to the Ministry of Health in Nov 2003 on the **REGULATION OF BIOMEDICAL RESEARCH BILL 2003** regarding the recognition of the fertilised ovum as a human individual and the demands of this knowledge on us to act morally.

### **THE FERTILISED OVUM IS A HUMAN BEING FROM FERTILISATION.**

Our objection to mishandling of the early human is fundamental and is not in the first instance a religious one but proceeds from a process of reason that is in turn informed by scientific knowledge.

The living human embryo is - from the moment of the union of the gametes at fertilisation - a human subject with a well defined human identity by virtue of his possessing a human genome and an innate power to begin his own coordinated, continuous and gradual development, such that at no stage can he be considered as a simple mass of cells<sup>1</sup>.

From the moment of his conception, the human embryo is an individual with his personal set of chromosomes, his personal genetic make-up, already embedded in his being. This personal identity is unique to him. He is in fact a human individual with a personal identity. He is a human person. How can a human individual *not* be a human person?

As a human individual the embryo has the right to his own life, and therefore every intervention which is not in favour of the embryo is an act that violates that right.

The false notion that the embryo in the first 14 days of life is a mass of primitive cells is an unscientific error promoted by the UK Warnock Committee since 1984. This was rejected by both houses of Parliament in the UK until the fictitious “pre-embryo” was declared in 1986, paving the way to the manipulation, killing and cannibalisation of the embryo in the first 14 days.

No clump of primitive cells could ever become a man. And advances in knowledge of the human genome continue to add scientific strength to the belief that the fertilised ovum is far from being “unspecialised,” “unprogrammed” or “primitive.”

Every medical student is taught that “human development begins at fertilization when a male gamete or sperm (spermatozoon) unites with a female gamete or oocyte (ovum) to form a single cell - a zygote. This highly specialized, totipotent cell marked the beginning of each of us as a unique individual.” (Keith L. Moore and T.V.N. Persaud, *The Developing Human: Clinically Oriented Embryology*, 5<sup>th</sup> edition).

Jerome Lejeune in fact called the fertilised ovum the “most specialised cell under the sun”, specialised from the point of view that no other cell will ever have the same instruction program in the life of the individual being created<sup>2</sup>.

Like a computer program on a disk written to run a corporation, the instructions of the fertilised ovum are specialised to produce an adult human being. These instructions are progressively given up as each cell division produces daughter cells with less and less adaptability as they differentiate into organs and tissues such as heart, muscle, blood or brain cells while leaving a diminishing but viable number of ‘organ’ or ‘adult’ stem cells.

Neither can it be said that the embryo has no brain or is brain dead - the brain cannot create itself or revive itself if it is dead. Indeed, no self-fulfilling declaration that any human tissue or organ is “not yet developed” can negate or excuse the destruction of the early human’s ongoing genetic Master Plan that is developing it.

Provision in the law for allowing killing in the first 14 days on the premise that the embryo has no pain or sentience thus has no moral support in science. The same reason could in fact be given to legalise date rape of an unconscious person.

No value system or religious perspective, culture or personal circumstance can ignore these scientific facts. The creation of human embryos is the story of the beginning of human life - a life that is not just a religious issue, because an embryo is a human being regardless of religion.

**A GOOD END DOES NOT MAKE RIGHT AN ACTION WHICH IN ITSELF IS WRONG.**

The inherent concern for the life of victims of debilitating disease cannot serve as moral justification for the destruction of the life of human embryos.

Any act, guideline or law that deliberately threatens the right of innocent human life cannot claim to be acting in the interest of the common good, one which not only takes into account the good of society as a whole but at the same time that of its individual members.

A *good act*, such as performing a safe pre-natal test on an embryo or foetus, cannot be done with the wrongful intention of aborting the child if the test is abnormal.

Neither can *good intentions*, such as valid scientific and medical purposes, justify unjust acts. If they did, what would we call these *unjust acts* - *good* things to do?

To thus misrepresent “evil” as “good” opens the door to every unjust action, since no one does anything without a good reason. Inevitably, this leads to the corruption of conscience and to the increasing inability to make moral choices.

Society then becomes more and more callused in the means employed to create a more ‘perfect’ world, their moral degeneration no doubt expedited by greater technological capabilities without a commensurate increase of ethical knowledge and development of ethical strength.

Neither does informed consent, when giving *carte blanche* to procedures that kill humans, have any bearing on this issue, since no one may freely dispose of the physical integrity or life of the embryo - patient autonomy notwithstanding. Informed consent cannot sanction killing and must not be included in these proposals as a licence for killing.

We must also avoid relativism in ethics. The idea that there is no objective morality is untenable - if relativism is the starting point, then relativism being what it is, would beget more relativism, and so on *ad infinitum*. Everyone would claim to be right in his own decision.

Regulations and legal safeguards have no meaning in containing or limiting evil. In the second reading of the Abortion Act 1969, the then Minister for Health spoke of the "...typical way in which the opponents go about attacking the Bill by basing their arguments on false presumptions. Another good example of presuming falsely is that, time and again, they have insisted even in the face of facts that the Bill will allow abortions on demand. However, let me state once again that an elaborate Bill such as the one before us has been made to contain all the safeguards which are necessary ..."

Barely 4 years later, the Law on Abortion was expanded to allow abortion on demand. Abortion is now being carried out on grounds that are a far cry from the lofty reasons put forward at its inception, and reversal of the law is unlikely in the foreseeable future.

The challenge should be to find *ethical* solutions to medical diseases. The advancement of the life sciences should serve a commensurate effort to discover these solutions and not more ‘convenient’ but ethically dubious methods.

Ethical principles cross cultural and religious borders. One must believe that there *are* values ingrained in the very nature of man himself or else admit that we are a society composed of individuals who are *essentially* different, one from another. If the latter were the case, then even Hitler could have claimed justification for his atrocities in pursuit of a “purer” society.

But we know it is not so. As already mentioned, there is a law ingrained in the human heart that binds us all together, a law that tells us what is objectively right or wrong, a law whose first principle is to do good and to avoid evil.

### **SPECIFIC POINTS IN THE CONSULTATION**

#### **A. PREIMPLANTATION GENETIC DIAGNOSIS (PGD)**

1. This clearly illustrates the Pandora's box opened by IVF, of which the wrongful components are beyond the scope of this response. The ability to unjustly manipulate human life in this way has already been anticipated by the inherent processes of IVF<sup>3</sup>.
2. The act of choosing to develop one embryo to birth while destroying the others tells us that *there is* human life in the embryo per se, and that it is promoted in one but eliminated in the others.
3. In a society where a specific gene defect is of sufficiently high prevalence, pre-nuptial testing for the carrier status is an option that can be studied. But only if the information is used to decide on marriage itself or to prepare for the birth of a child with a disability.
4. As medical science advances, one should expect (or at least work towards) the improvement in prognosis for serious conditions.
  - a. This *has* happened in thalassaemia major<sup>4,5</sup> due to major advancements in transfusion medicine and iron chelation therapy. Even curative transplantation with resultant transfusion independence is now a distinct possibility, with cord blood from unrelated donors expanding the sources of haematopoietic stem cells<sup>6,7</sup>
  - b. In X-linked severe combined immunodeficiency we could be close to an unprecedented breakthrough<sup>8</sup> although there are safety<sup>9</sup> and ethical issues in gene therapy to sort out.

Instead of investing resources in PGD, healthcare bodies should concentrate efforts to the development of ethical solutions for medical conditions.

5. With PGD, we already place one foot over the threshold of eugenics into trait selection.
  - a. What is considered a "serious medical condition" warranting PGD? Do we not foresee this definition changing time and again in the near future? Will obesity be a "serious medical condition" since the obese may have shorter life spans? Or will embryos with the 'autistic' or 'depression' gene be eliminated since the quality of life of such people is deemed by some to be poor? The Committee rightly alludes to this danger<sup>10</sup>.
  - b. It is key that the Committee acknowledges children as "individuals in their own right"<sup>11</sup>, as this forms the basis for not exercising an artificial "control over the result of conception"<sup>12</sup>.
  - c. Regulatory bodies are not a solution for ethical decision making if they yield to socially or medically utilitarian demands.

#### **B. PREIMPLANTATION TISSUE TYPING (PTT)**

1. The ethical principles governing the licitness of PGD (vis a vis to treat rather than to kill) are also applicable to PTT.
2. In addition, PTT is an even more direct manifestation of the philosophy of having children not for their own sake, but for a primary utilitarian end. The "evidence" asked for by the Committee regarding concerns over children being used as a means to an end<sup>13</sup> seems to be contained within the very recommendation given for this section

itself<sup>14</sup>. The principles underlying PTT certainly do not convey a “higher moral ground”.

#### C. GERMLINE GENETIC MODIFICATION

1. The Committee has rightly alluded to ethical concerns concerning this.
2. In addition, with regard to gene therapy in general, while safety issues are yet to be resolved, other ethical issues include the use of cell lines developed from aborted foetal tissue. These cell lines are commonly used in the generation of viral vectors used in gene therapy. The Committee should bear in mind that there the use of these embryonic cell lines (e.g. the human embryonic retinal cell line PER.C6<sup>15</sup>) is not ethically acceptable to many.

#### D. PRENATAL GENETIC DIAGNOSIS (PND)

1. The ethics of abortion precede the evaluation of PND. If the basic principles on this are not understood, then an ethical discussion on PND is also flawed.
2. PND in itself need not be morally wrong. As pointed out by the Committee, the information may help the couple prepare for the birth of a child with a disability, and be useful for the professional team to prepare for a difficult delivery etc<sup>16</sup>.
3. However, PND or prenatal screening with an intention or likelihood of abortion if the test is unfavourable is wrong.
4. Counselling related to PND should include arguments that favour promoting life, even though the child may be handicapped or diseased.
  - a. There are numerous examples of couples who do not regret having children with Down’s Syndrome, “happy just to take their child as they find them”<sup>17</sup>. The handicapped child promotes bonding in the family, helps in the nurturing and maturation of human values of the other children who are normal, and brings the spouses closer together in their common love for the child who needs it most.
  - b. Adoption of a handicapped child should be an option for consideration. Many generous families have done so to their greater benefit.
  - c. The couple should be given adequate assurance of basic medical treatment if so required, and the various social and financial support systems should be made known to them.
5. The Committee rightly tends to discourage testing for late-onset disease. One can again fear and foresee the potential for the definition of “late-onset” to be conveniently manipulated.

### **THE CULTURE OF DEATH**

It is unfortunate that the practice of medical ethics has deteriorated significantly over the past fifty years or so from one that accorded absolute respect for life to one that has confused killing with healing.

There is now a culture of death, a growing network of conspiracy against human life that Pope John Paul II first drew attention to in his encyclical, *Evangelium Vitae*<sup>18</sup> published on 25 Mar 1995, “It is expanding and has reached broad sectors of public opinion, a real network of complicity against life that reaches out to include international institutions, foundations and associations.”



He wrote, "Whatever is opposed to life itself, ... murder, genocide, abortion, euthanasia, or wilful self-destruction, ... whatever violates the integrity of the human person, ... mutilation, torments inflicted on body or mind, attempts to coerce the will itself; ... whatever insults human dignity, ... subhuman living conditions, arbitrary imprisonment, deportation, slavery, prostitution, the selling of women and children; ... where people are treated as mere instruments of gain rather than as free and responsible persons; ... poison human society, .. [and] do more harm to those who practise them than to those who suffer from the injury."

The BAC has in the past correctly averred that reproductive cloning, "goes against the moral idea that a human being is not to be treated as a means to an end, but only as an end."

But, citing patient autonomy and preventing or curing disease, it continues to propose and support the conditions that lead to, or the actual use of, abortion or biomedical methods that manipulate or create human beings, only to destroy them later for their stem cells or for not having the right genotype or tissue type.

Can it be surprising then that the proliferation of clinical and research ethics committees practising this relative and flexible form of ethics can co-exist with widespread and increasing contraception, abortion, manipulation and cannibalisation of embryos, a disordered sexuality and a pandemic of AIDS?

It is educational and edifying to recall the words of former UN chief *Dag Hammarsklöld*, "You cannot play with the animal in you without becoming wholly animal, play with falsehood without forfeiting your right to truth, play with cruelty without losing your sensitivity of mind."

Ethics must be for all and not just for some.

### **SICK BABIES SHOULD NOT BE KILLED**

There is more than an ounce of truth in the observation that babies nowadays are "made" like products subject to supply and demand, cost and quality control and are bought and paid for. Sick babies are eliminated like defective products or their parts and tissues dissected and traded.

Others meanwhile write dismissively of "definitions of what constitutes a human being and religious beliefs"

Since 1970, Singapore mothers chose to kill half a million of their babies-in-utero younger than 24 weeks. Some were killed because they were "physically impaired" but most were not, yet qualified for death anyway. With a subtle shift of thinking their stem cells may now be cannibalised for distribution to others.

No one should solve life's problems by killing babies. And only the perverse can convince themselves that abortion prevents disability.

Anyway, do we really want a standard man or woman, rejecting all but those who fit into this model? Does happiness consist of being a clone or living in a society of clones? There *is* no ideal person. No one has or wants all the beautiful, physical or intellectual experiences

possible. Instead, people choose from these possibilities according to their own talents and opportunities to make themselves as happy as they can be.

Within very broad limits, both Prince and Pauper can be happy with their lot in life. Among these are Louis Braille, Stevie Wonder, Ray Charles, Claude Monet, Homer, John Milton and painter Lisa Fittipaldi who were all blind. Tom Whittaker, the first one-legged person to climb Mt Everest, Diana Golden, a one-legged skier, Singapore's own disabled swimmer, Theresa Goh and the faces of striving and triumph at the Special Olympics are further outstanding examples of people with courage and determination, to name just a few.

We are all better and kinder people for accepting our imperfections and our differences.

We must discard the notion that not having a skill or capacity is equivalent to not being a person. A practice that devalues (disabled) children *before* they are born cannot be separated from one that devalues them *after* they are born. People born with disabilities would be regarded as mere missed abortions until opportunities for correction come up, if not by extending the law on abortion, then later after birth.

Unfortunately, prenatal testing is increasingly the tool used to select babies who are disabled and to mark them for destruction. Prenatal care should be focused on protecting capacity, NOT highlighting deficiency or refusing to permit or assist the development of people with disabling traits.

We must promote a social model that does not eliminate the unfit and the unwanted but caters for all the human beings who actually exist, whether able-bodied or disabled, born and waiting to be born. We want an inclusive society not an elitist one. Our survival depends on it.

### **THE MENTORSHIP OF UK AND THE NAZI EUGENIC PROGRAMME**

This consultation paper, like others before it, has referred to the mentorship and experience of the United Kingdom. It does not, however, draw on the experience of the Nazi eugenic programme. We fear an unstoppable slide towards the deteriorating regard even for post-natal human life, as seen in the Netherlands in recent times<sup>19</sup>.

Like all these predecessors, however, any reference in this paper to the experimentation or disposal of humans is couched in the rosy language of medical care and eugenics.

1,863 babies were aborted in UK in 2002 for reasons of suspected "deformity" - an eight percent increase over the previous 1,722 aborted in 2001, whereas Down's Syndrome abortions were up by 17 percent from 591 in 2001 to 691 in 2002<sup>20</sup>.

In May 2004, the UK's Daily Mail revealed that British women were increasingly eliminating their unborn children because of non life-threatening deformities such as deformed feet or cleft lips and palates<sup>21</sup>.

In the same month, UK Police only opened a criminal investigation into an illegal 28-week abortion of a baby with a cleft lip and palate that occurred in 2002 after their initial refusal to act was challenged in High Court by a Rev Joanna Jepson, herself born with a jaw defect that was corrected when she was in her late teens<sup>22</sup>.

This must surely be just the tip of the iceberg. Multiple examples of such atrocities against human life will assail anyone who is concerned enough to conduct a cursory search of the news, and convince him that there is an expanding culture of death. Singapore is a part of this culture.

The worldwide regression to a stultified medical ethos is also reflected in the Netherlands, where mercy killing “for good reasons” was for decades regarded benignly by the law, well before it entered the statute books. The Government Rummelink study of 8,681 euthanasia cases in 1990 showed that 68% had not given explicit consent to being killed<sup>23</sup>.

In Germany, subtle shifts in medical thinking began with sterilisation and abortion of non-Aryans, but with the euthanasia of Gerhard Kretschmar, a 5-month baby, regressed to 8,000 children killed by euthanasia in Nazi Germany.

In all, 296 medical facilities were used to drug, gas or starve 275,000 children and adults, including residents of mental hospitals and homes for the aged, the handicapped in their own homes and children who were bed wetters or had misshapen ears or learning difficulties.

The Final Solution, the genocide of 6 million Jews and Gypsies, is well known but its origins are perhaps not well appreciated

Among the perpetrators of the massacre, a Nazi judge impugned in Nuremberg in 1945 for his role in the eugenic pogrom of millions of undesirable DNA carriers was reputed to have said, “I didn’t know it would come to that” when asked why he had acted thus. The prosecutor reportedly replied, “It came to that with your first one”.

The Straits Times of 12 May 2005 published a report on the inauguration of the monument that Germany created to atone for their human experimentation and the slaughter of millions.

Today, Germany is one of a few countries in the world that really knows the harm of human experimentation. Yet, when the President of the German Max Planck Society was questioned at a talk he gave recently on human cloning and embryonic stem cell research, he said that no one knows when a human being begins. There are none so blind as those who will not see.

If only those persons who themselves suffer from a particular genetic defect are prevented from reproducing, this still does not eliminate heterozygous carriers who will continue to transmit defects dependent on recessive genes.

Present technology is far from being able to detect all these carriers. Even if science is capable of doing this, it would mean the elimination of large numbers of people. This would probably mean also the elimination of many desirable traits from the gene pool, because the same person may carry both good and bad traits.

Thus programmes of negative eugenics based on present knowledge would never be of any benefit and might even have side effects that are worse than the remedy. Even if defective genes are eliminated from the gene pool, they are constantly being replaced by mutations caused by environmental factors.

### **THE ETHOS OF THE HEALTHCARE PROFESSIONAL VS THE MEDICAL AUTONOMY OF PEOPLE**

The success of any medical programme must surely depend entirely on the ethos of the medical fraternity not deviating from its Hippocratic ideals<sup>24</sup>.

To paraphrase Pope John Paul II in *Evangelium Vitae*<sup>25</sup>, we need the outlook of those who see life in its deeper meaning, its beauty and its invitation to freedom and responsibility; the outlook of those who discover in all things the reflection of the Creator, seeing in every person his living image.

Or in the words of *Socrates (470-399BC)*: “To a man who preserves his integrity, no real long-term harm can ever come. Real personal catastrophe consists in corruption of the soul.”

But incorporating the philosophy of manipulating, killing or cannibalising the embryo or foetus for good ends is a structural defect in the nature and the provision of healthcare.

Such a programme stakes the health providers’ goodwill, their ethical principles and the medical and legal ethos against the unethical aspects of patient autonomy and the Siren allure of a Master race.

A good doctor’s first principle is “*Primum non nocere*.” First, do no harm. Killing is doing harm. There are no two ways about it. For a healthcare worker to kill anyone, even when asked to do so, is to blur the line between caring and killing

To participate in this complicity against life places him in a dilemma of either rejecting any co-operation in killing or surrendering his integrity and professionalism – and if he chooses the latter to injure his own ethos and the ethos of the whole healthcare fraternity.

This cannot have a happy resolution. Would anyone like to consult a doctor whom he can’t be sure will try to cure him or at the least excuse, neglect him or even kill him?

### **CONSCIENTIOUS OBJECTION**

Respecting the legitimate autonomy of patients has its counterpart in appreciating and respecting the autonomy of healthcare workers and also of university students, who should not be browbeaten into compromising their conscience and their ethos or penalised in any way for refusing to cooperate in anything that is morally repugnant to them.

Doing so may force a legitimate reaction from health care personnel who do not wish to cooperate in what is plainly morally illicit. For example, there are anaesthetists who will refuse to provide anaesthesia for women undergoing abortions. Housemen, too, try to avoid the obstetrics and gynaecology posting for fear of running into moral complications.

Special provision should also be made for doctors who are serving their 5-year bond of employment in public hospitals and institutions. Such doctors owe their service but not their souls.

This is not merely in the area of assisting at an abortion. Conscientious objection includes participating in any testing or procedure that is likely to lead to abortion and in referring such a person to another for this purpose.

For example, prenatal screening (PND) with an intention to abort if the test is unfavourable is morally wrong and a conscientious objector may not cooperate in this evil or refer such a person for an abortion.

With respect to PND, the rights of conscientious objectors have to be safeguarded by law. There should be measures that aid in protecting the consciences of such objectors.

For example, if it is mandated that all Thalassaemia carriers be notified to the National Thalassaemia Registry, there should at least be an optional clause on the form which states “this physician is a conscientious objector to abortion and to genetic testing with a view to abortion” or the equivalent.

In a society divided on the issue of abortion, such measures are *the least* that can be done in fairness to those who are upholding the principle of human life.

### **CONCLUSION**

The Catholic Church has no objections to Genetic Screening and Genetic Counselling that respect the rights, the dignity, the privacy and confidentiality of the individual.

It has been the constant teaching of the Catholic Church that human life begins at conception and every human life is precious regardless of the state of perfection.

Genetic Screening must not be used for eugenic purpose where only the perfect are entitled to life. Genetic screening should not and must not lead to more destruction of life.

As such, we oppose all forms of destruction of life (including that of human embryos) based on any genetic defects. Any procedure, including pre-implantation diagnosis (PGD) and pre-implantation tissue testing (PTT) must seek the well-being of the individual tested, that is, with the intention to treat if any abnormality is found, without disproportionate risk to him or her. If they are used to seek out those who have a genetic defect with the intention of afterwards eliminating them, then such procedures are morally illicit and should not be done. Prenatal diagnosis (PND) should not be done with a view to abortion.

We are against all forms of stigmatisation and discrimination of individuals, families, groups of people or even an entire race based on the negative results derived from genetic screening.

The Church is also against any form of testing or intervention that puts any human life at a disproportionate risk.

The question therefore is not about genetic screening but about the consequences of the genetic information obtained. The Church is totally against using that information to destroy life, to discriminate or to stigmatise.

The information may be supplied only to help people make responsible personal decisions. It certainly is a right for a child to be free from every defect that medicine has the power to prevent or to correct, using reasonable means under the given circumstances.

It is contradictory, however to believe that this right is protected by destroying the child who has not been saved from the defect. Parents may have the responsibility not to generate such children but having generated them, they also have then the responsibility to care for them.

They cannot lighten their burden by destroying an unborn child any more than an infant or adolescent. If parents prove mistaken in their decision, society can and should assume the responsibility for adequate care of such children, a burden that is not too great compared to many other health problems.

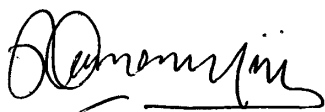
The Catholic Church provides genetic counselling and will also promote it without encouraging abortion or the destruction of any human life including the human embryo.

We supply the following recommendations:

1. Genetic Screening programs that respect the rights, the dignity, the privacy and confidentiality of every individual from conception should nevertheless be pretested by pilot projects and other studies and these programs should be constantly updated and evaluated.
2. Community participation in planning and executing these programs should be secured to educate the public as to the true significance and legitimate use of the information obtained.
3. The information obtained should be made available according to clearly stated policies known to those participating before they consent and their privacy should be carefully protected.
4. Screening programs should be voluntary. The rights of parents to make their own decisions about the use of the information in having children should be protected. That means they should not be compelled to refrain from reproduction or starting a family.
5. The general principles with regard to human experimentation should be respected.
6. The autonomy of healthcare givers and legal and scientific officers in their moral choices (that promote life and authentic human dignity) should be respected and *fully* recognised in law. There should be legal provision for conscientious objectors (to any act potentially

leading to the destruction of human life) to protect their consciences in stating and acting clearly in line with their stand.

Yours faithfully



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#### Appendix:

**Donum Vitae** (Instruction on Respect for Human Life in its Origin and on the Dignity of Procreation), Congregation for the Doctrine of the Faith, 1987.

This instruction was issued by Cardinal Joseph Ratzinger with the approval of and under the order of Pope John Paul II.

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- <sup>2</sup> Keith L. Moore and T.V.N. Persaud, “*The Developing Human: Clinically Oriented Embryology*, 5<sup>th</sup> edition.”
- <sup>3</sup> Case No E-14496, *Davis v Davis*, County Court for Blount County, Tennessee, USA: August 7, 8 & 10, 1989.
- <sup>4</sup> “In the last decades, treatment of patients with beta-thalassemia has changed considerably, with advances in red cell transfusion and the introduction of iron chelation therapy. This progress has greatly increased the probability for a thalassaemic child to reach adult age with a good quality of life. At present, the prognosis for thalassemia major patients is “open-ended”. Compliance with the conventional treatment and psychological support are critical to obtain good results. The expectancy of a long survival of good quality encourages the patients to plan their future life, having a job, a family and often children. Optimal treatment of thalassemia major is expensive and for this reason, unfortunately, available only for a minority of patients in the world. Despite the significant advances, other progresses are expected to further improve survival and quality of life. The major aim is the cure of the disease, increasing the possibility of bone marrow transplantation using HLA-matched unrelated donors, and hopefully, in the future, gene therapy. However, even the conventional treatment and in particular iron chelation is expected to improve. Efforts should be made by the Western countries, and by the international health and economic organizations to provide continuous and concrete support for achieving a high standard of management for thalassemia in all places of the world.” Abstract from Galanello R. A thalassaemic child becomes adult. *Rev Clin Exp Hematol*. 2003 Mar;7(1):4-21.
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- <sup>11</sup> Ethical, legal and social issues in genetic testing and genetics research. A consultation paper. The Bioethics Advisory Committee, Singapore. 5 April 2005. #6.16.
- <sup>12</sup> Ethical, legal and social issues in genetic testing and genetics research. A consultation paper. The Bioethics Advisory Committee, Singapore. 5 April 2005. #6.16.
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- <sup>14</sup> Ethical, legal and social issues in genetic testing and genetics research. A consultation paper. The Bioethics Advisory Committee, Singapore. 5 April 2005. Recommendation 12: Preimplantation tissue typing, whether as the sole objective or in conjunction with preimplantation genetic diagnosis to avoid a serious genetic disorder, is permissible but should be licensed and evaluated on a case-by-case basis.
- <sup>15</sup> "...So I isolated retina from a fetus, from a healthy fetus as far as could be seen, of 18 weeks old. There was nothing special with a family history or the pregnancy was completely normal up to the 18 weeks, and it turned out to be a socially indicated abortus - abortus provocatus, and that was simply because the woman wanted to get rid of the fetus... The father was not known not to the hospital anymore, what was written down was unknown father, and that was, in fact, the reason why the abortion was requested... There was permission, et cetera, and that was, however, was in 1985, ten years before this. This shows that the cells were isolated in October 1985, Leiden University in my lab. At that time already '85, I should say the cells were frozen, stored in liquid nitrogen, and in 1995 one of these was thawed for the generation of the PER.C6 cells..." See US Food and Drug Administration, Center for Biologics Evaluation and Research, Vaccines and Related Biological Products Advisory Committee meeting May 16, 2001, [http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3750t1\\_01.pdf](http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3750t1_01.pdf).
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- <sup>24</sup> "I will neither give a deadly drug to anybody who asked for it, nor will I make a suggestion to this effect. Similarly I will not give to a woman an abortive remedy. In purity and holiness I will guard my life and my art..."
- <sup>25</sup> Pope John Paul II; "*Evangelium Vitae*, 25 Mar 1995"



# Instruction on Respect for Human Life in Its Origin and on the Dignity of Procreation



## Instruction on Respect for Human Life in Its Origin and on the Dignity of Procreation

### CONTENTS OF THIS ISSUE:

*\*Instruction on Respect for Human Life in Its Origin and on the Dignity of Procreation: Replies to Certain Questions of the Day, by the Congregation for the Doctrine of the Faith.*

*"Advances in technology have now made it possible to procreate apart from sexual relations through the meeting 'in vitro' of the germ cells previously taken from the man and the woman. But (what is technically possible is not for that very reason morally admissible.) Rational reflection on the fundamental values of life and of human procreation is therefore indispensable for formulating a moral evaluation of such technological interventions," says an instruction released March 10 by the Vatican Congregation for the Doctrine of the Faith. Titled "Instruction on Respect for Human Life in Its Origin and on the Dignity of Procreation," it examines questions such as "in vitro" fertilization involving a man and woman not married to one another, as well as within marriage; experimentation on human embryos; surrogate motherhood; prenatal diagnosis and therapeutic procedures for the human embryo; infertility in marriage; and legislation related to procreation. A fundamental concern of the instruction is that human life be respected: The embryo must be treated as a person and defended in its integrity, it says. Moreover, the instruction emphasizes that "the procreation of a new person, whereby the man and the woman collaborate with the power of the Creator, must be the fruit and the sign of the mutual self-giving of the spouses, of their love and of their fidelity." The instruction takes a position against "in vitro" fertilization. But, it says, "a medical intervention respects the dignity of persons when it seeks to assist the conjugal act" — not to replace it technologically — "either in order to facilitate its performance or in order to enable it to achieve its objective once it has been normally performed." The Vatican's English text of the instruction follows.*

### FOREWORD

The Congregation for the Doctrine of the Faith has been approached by various episcopal conferences or individual bishops, by theologians, doctors and scientists, concerning biomedical techniques which make it possible to intervene in the initial phase of the life of a human being and in the very processes of procreation and their conformity with the principles of Catholic morality. The present instruction, which is the result of wide consultation and in particular of a careful evaluation of the declarations made by episcopates, does not intend to repeat all the church's teaching on the dignity of human life as it originates and on procreation, but to offer, in the light of the previous teaching of the magisterium, some specific replies to the main questions being asked in this regard.

The exposition is arranged as follows: An introduction will recall the fundamental principles of an anthropological and moral character which are necessary for a proper evaluation of the problems and for working out replies to those questions; the first part will have as its subject

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**BIOETHICS** — *continued from front page*  
respect for the human being from the first moment of his or her existence; the second part will deal with the moral questions raised by technical interventions on human procreation; the third part will offer some orientations on the relationships between moral law and civil law in terms of the respect due to human embryos and fetuses\* and as regards the legitimacy of techniques of artificial procreation.

## INTRODUCTION

### 1. Biomedical Research and the Teaching of the Church

The gift of life which God the Creator and Father has entrusted to man calls him to appreciate the inestimable value of what he has been given and to take responsibility for it: This fundamental principle must be placed at the center of one's reflection in order to clarify and solve the moral problems raised by artificial interventions on life as it originates and on the processes of procreation.

Thanks to the progress of the biological and medical sciences, man has at his disposal ever more effective therapeutic resources; but he can also acquire new powers, with unforeseeable consequences, over human life at its very beginning and in its first stages. Various procedures now make it possible to intervene not only in order to assist, but also to dominate the processes of procreation. These techniques can enable man to "take in hand his own destiny," but they also expose him "to the temptation to go beyond the limits of a reasonable dominion over nature."<sup>1</sup> They might constitute progress in the service of man, but they also involve serious risks. Many people are therefore expressing an urgent appeal that in interventions on procreation the values and rights of the human person be safeguarded. Requests for clarification and guidance are coming not only from the faithful, but also from those who recognize the church as "an expert in humanity"<sup>2</sup> with a mission to serve the "civilization of love"<sup>3</sup> and of life.

The church's magisterium does not intervene on the basis of a particular competence in the area of the experimental sciences; but having taken account of the data of research and technology, it intends to put forward, by virtue of its evangelical mission and apostolic duty, the moral teaching corresponding to the dignity of the person and to his or her integral vocation. It intends to do so by expounding the criteria of moral judgment as regards the applications of scientific research and technology, especially in relation to human life and its beginnings. These criteria are the respect, defense and promotion of man, his "primary and fundamental right" to life,<sup>4</sup> his dignity as a person who is endowed with a spiritual soul and with moral responsibility<sup>5</sup> and who is called to beatific communion with God.

The church's intervention in this field is inspired also by the love which she owes to man, helping him to recognize and respect his rights

and duties. This love draws from the fount of Christ's love: As she contemplates the mystery of the incarnate word, the church also comes to understand the "mystery of man";<sup>6</sup> by proclaiming the Gospel of salvation, she reveals to man his dignity and invites him to discover fully the truth of his own being. Thus the church once more puts forward the divine law in order to accomplish the work of truth and liberation.

For it is out of goodness — in order to indicate the path of life — that God gives human beings his commandments and the grace to observe them; and it is likewise out of goodness — in order to help them persevere along the same path — that God always offers to everyone his forgiveness. Christ has compassion on our weaknesses: He is our Creator and Redeemer. May his Spirit open men's hearts to the gift of God's peace and to an understanding of his precepts.

### 2. Science and Technology at the Service of the Human Person

God created man in his own image and likeness: "Male and female he created them" (Gn. 1:27), entrusting to them the task of "having dominion over the earth" (Gn. 1:28). Basic scientific research and applied research constitute a significant expression of this dominion of man over creation. Science and technology are valuable resources for man when placed at his service and when they promote his integral development for the benefit of all; but they cannot of themselves show the meaning of existence and of human progress. Being ordered to man, who initiates and develops them, they draw from the person and his moral values the indication of their purpose and the awareness of their limits.

It would on the one hand be illusory to claim that scientific research and its applications are morally neutral; on the other hand one cannot derive criteria for guidance from mere technical efficiency, from research's possible usefulness to some at the expense of others or, worse still, from prevailing ideologies. Thus science and technology require for their own intrinsic meaning an unconditional respect for the fundamental criteria of the moral law: That is to say, they must be at the service of the human person, of his inalienable rights and his true and integral good according to the design and will of God.<sup>7</sup>

The rapid development of technological discoveries gives greater urgency to this need to respect the criteria just mentioned: Science without conscience can only lead to man's ruin. "Our era needs such wisdom more than bygone ages if the discoveries made by man are to be further humanized. For the future of the world

\* The terms *zygote*, *pre-embryo*, *embryo* and *fetus* can indicate in the vocabulary of biology successive stages of the development of a human being. The present instruction makes free use of these terms, attributing to them an identical ethical relevance, in order to designate the result (whether visible or not) of human generation, from the first moment of its existence until birth. The reason for this usage is clarified by the text (cf. I, 1).

*Theological discussion is "still open" on some fertility techniques in which conception occurs inside the woman's body, though with medical intervention, Cardinal Joseph Ratzinger, prefect of the Congregation for the Doctrine of the Faith, said during a press conference March 10 in Rome. He said that in the absence of a church decision on the matter, individual Catholic doctors should rely on their "informed conscience" in deciding whether to perform the techniques.*

*The congregation's new instruction on bioethics and procreation rejected "in vitro" fertilization and several other fertility techniques. However, in recent years U.S. doctors have developed methods that the instruction did not specifically address.*

*One method, Gamete Intra-Fallopian Transfer or GIFT, involves extracting an ovum, placing it near sperm cells in a catheter and then inserting both into the uterus. Conception follows "in vivo," or inside the woman's body.*

*Some Catholics have judged the technique acceptable provided that masturbation is not involved in collection of the sperm. A perforated condom is used during intercourse, with the sperm retrieved from the condom afterward.*

*Ratzinger was asked whether doctors offering such methods were on morally licit grounds. He responded:*

*"When the discussion is still open and there is not yet a decision by the magisterium, the doctor is required to stay informed, according to classic theological principles and concrete circumstances" and "make a decision based on his informed conscience."*

*Jesuit Father Bartholomew Kiely, a moral theologian who helped prepare the document, said "the instruction does not pronounce a judgment on GIFT. It leaves it open*

to research by biologists and to further discussion by theologians." One main element in judging such methods, Kiely said, is whether they assist marital intercourse in attaining procreation or replace it with a laboratory technique.

Kiely said the document likewise does not make a judgment on another technique, called Low Tubal Ovum Transfer or LTOT. It was first used successfully in an Ohio Catholic hospital.

LTOT circumvents absent or blocked fallopian tubes and transfers the ova to the uterus to allow "in vivo" fertilization to take place through conjugal intercourse. It has been approved by Archbishop Daniel E. Pilarczyk of Cincinnati and theologians at Pope John Paul II Medical-Moral Research and Education Center near Boston.

LTOT, Kiely said, "seems to fall within the GIFT area, the area that is not yet defined by the document, but is left open to further research."

He said Catholics should recognize that the techniques fall in an area "that is not yet settled."

"Obviously the document couldn't go into too much detail on the medical side, because the scene literally changes from week to week," he added.

Msgr. Elio Sgreccia, an Italian ethicist who also helped prepare the document, said methods that seek to help marital intercourse attain fertility should be considered "within the range of licitness." He said that also applies to medical aid provided after the conjugal act occurs.

It is hoped that science would make available other fertility techniques that retain the conjugal act as the source of life and help it reach its full effect, Sgreccia said.

stands in peril unless wiser people are forthcoming."<sup>9</sup>

### 3. Anthropology and Procedures in the Biomedical Field

Which moral criteria must be applied in order to clarify the problems posed today in the field of biomedicine? The answer to this question presupposes a proper idea of the nature of the human person in his bodily dimension.

For it is only in keeping with his true nature that the human person can achieve self-realization as a "unified totality";<sup>9</sup> and this nature is at the same time corporal and spiritual. By virtue of its substantial union with a spiritual soul, the human body cannot be considered as a mere complex of tissues, organs and functions, nor can it be evaluated in the same way as the body of animals; rather it is a constitutive part of the person who manifests and expresses himself through it.

The natural moral law expresses and lays down the purposes, rights and duties which are based upon the bodily and spiritual nature of the human person. Therefore this law cannot be thought of as simply a set of norms on the biological level; rather it must be defined as the rational order whereby man is called by the Creator to direct and regulate his life and actions and in particular to make use of his own body.<sup>10</sup>

A first consequence can be deduced from these principles: An intervention on the human body affects not only the tissues, the organs and their functions, but also involves the person himself on different levels. It involves, therefore, perhaps in an implicit but nonetheless real way, a moral significance and responsibility. Pope John Paul II forcefully reaffirmed this to the World Medical Association when he said:

"Each human person, in his absolutely unique singularity, is constituted not only by his spirit, but by his body as well. Thus, in the body and through the body, one touches the person himself in his concrete reality. To respect the dignity of man consequently amounts to safeguarding this identity of the man '*corpore et anima unus*,' as the Second Vatican Council says (*Gaudium et Spes*, 14.1). It is on the basis of this anthropological vision that one is to find the fundamental criteria for decision making in the case of procedures which are not strictly therapeutic, as, for example, those aimed at the improvement of the human biological condition."<sup>11</sup>

Applied biology and medicine work together for the integral good of human life when they come to the aid of a person stricken by illness and infirmity and when they respect his or her dignity as a creature of God. No biologist or doctor can reasonably claim, by virtue of his scientific competence, to be able to decide on people's origin and destiny. This norm must be applied in a particular way in the field of sexuality and procreation, in which man and woman actualize the fundamental values of love and life.

God, who is love and life, has inscribed in man and woman the vocation to share in a

special way in his mystery of personal communion and in his work as Creator and Father.<sup>12</sup> For this reason marriage possesses specific goods and values in its union and in procreation which cannot be likened to those existing in lower forms of life. Such values and meanings are of the personal order and determine from the moral point of view the meaning and limits of artificial interventions on procreation and on the origin of human life. These interventions are not to be rejected on the grounds that they are artificial. As such, they bear witness to the possibilities of the art of medicine. But they must be given a moral evaluation in reference to the dignity of the human person, who is called to realize his vocation from God to the gift of love and the gift of life.

### 4. Fundamental Criteria for a Moral Judgment

The fundamental values connected with the techniques of artificial human procreation are two: the life of the human being called into existence and the special nature of the transmission of human life in marriage. The moral judgment on such methods of artificial procreation must therefore be formulated in reference to these values.

Physical life, with which the course of human life in the world begins, certainly does not itself contain the whole of a person's value nor does it represent the supreme good of man, who is called to eternal life. However it does constitute in a certain way the "fundamental" value of life precisely because upon this physical life all the other values of the person are based and developed.<sup>13</sup> The inviolability of the innocent human being's right to life "from the moment of conception until death"<sup>14</sup> is a sign and requirement of the very inviolability of the person to whom the Creator has given the gift of life.

By comparison with the transmission of other forms of life in the universe, the transmission of human life has a special character of its own, which derives from the special nature of the human person. "The transmission of human life is entrusted by nature to a personal and conscious act and as such is subject to the all-holy laws of God: immutable and inviolable laws which must be recognized and observed. For this reason one cannot use means and follow methods which could be licit in the transmission of the life of plants and animals."<sup>15</sup>

Advances in technology have now made it possible to procreate apart from sexual relations through the meeting *in vitro* of the germ cells previously taken from the man and the woman. But what is technically possible is not for that very reason morally admissible. Rational reflection on the fundamental values of life and of human procreation is therefore indispensable for formulating a moral evaluation of such technological interventions on a human being from the first stages of his development.

### 5. Teachings of the Magisterium

On its part, the magisterium of the church offers to human reason in this field too the light

of revelation: The doctrine concerning man taught by the magisterium contains many elements which throw light on the problems being faced here.

From the moment of conception, the life of every human being is to be respected in an absolute way because man is the only creature on earth that God has "wished for himself"<sup>16</sup> and the spiritual soul of each man is "immediately created" by God;<sup>17</sup> his whole being bears the image of the Creator. Human life is sacred because from its beginning it involves "the creative action of God,"<sup>18</sup> and it remains forever in a special relationship with the Creator, who is its sole end.<sup>19</sup> God alone is the Lord of life from its beginning until its end: No one can in any circumstance claim for himself the right to destroy directly an innocent human being.<sup>20</sup>

Human procreation requires on the part of the spouses responsible collaboration with the fruitful love of God;<sup>21</sup> the gift of human life must be actualized in marriage through the specific and exclusive acts of husband and wife, in accordance with the laws inscribed in their persons and in their union.<sup>22</sup>

## I

### RESPECT FOR HUMAN EMBRYOS

Careful reflection on this teaching of the magisterium and on the evidence of reason, as mentioned above, enables us to respond to the numerous moral problems posed by technical interventions upon the human being in the first phases of his life and upon the processes of his conception.

#### 1. What respect is due to the human embryo, taking into account his nature and identity?

*The human being must be respected — as a person — from the very first instant of his existence.*

The implementation of procedures of artificial fertilization has made possible various interventions upon embryos and human fetuses. The aims pursued are of various kinds: diagnostic and therapeutic, scientific and commercial. From all of this, serious problems arise. Can one speak of a right to experimentation upon human embryos for the purpose of scientific research? What norms or laws should be worked out with regard to this matter? The response to these problems presupposes a detailed reflection on the nature and specific identity — the word *status* is used — of the human embryo itself.

At the Second Vatican Council, the church for her part presented once again to modern man her constant and certain doctrine according to which: "Life once conceived, must be protected with the utmost care; abortion and infanticide are abominable crimes."<sup>23</sup> More recently, the Charter of the Rights of the Family, published by the Holy See, confirmed that "human life must be absolutely respected and protected from the moment of conception."<sup>24</sup>

This congregation is aware of the current debates concerning the beginning of human life,

concerning the individuality of the human being and concerning the identity of the human person. The congregation recalls the teachings found in the Declaration on Procured Abortion:

"From the time that the ovum is fertilized, a new life is begun which is neither that of the father nor of the mother; it is rather the life of a new human being with his own growth. It would never be made human if it were not human already. To this perpetual evidence...modern genetic science brings valuable confirmation. It has demonstrated that, from the first instant, the program is fixed as to what this living being will be: a man, this individual man with his characteristic aspects already well determined. Right from fertilization is begun the adventure of a human life, and each of its great capacities requires time...to find its place and to be in a position to act."<sup>25</sup>

"Applied biology and medicine work together for the integral good of human life when they come to the aid of a person stricken by illness and infirmity, and when they respect his or her dignity as a creature of God. No biologist or doctor can reasonably claim, by virtue of his scientific competence, to be able to decide on people's origin and destiny."

This teaching remains valid and is further confirmed, if confirmation were needed, by recent findings of human biological science which recognize that in the zygote (the cell produced when the nuclei of the two gametes have fused) resulting from fertilization the biological identity of a new human individual is already constituted.

Certainly no experimental datum can be in itself sufficient to bring us to the recognition of a spiritual soul; nevertheless, the conclusions of science regarding the human embryo provide a valuable indication for discerning by the use of reason a personal presence at the moment of this first appearance of a human life: How could a human individual not be a human person? The magisterium has not expressly committed itself to an affirmation of a philosophical nature, but it constantly reaffirms the moral condemnation of any kind of procured abortion. This teaching has not been changed and is unchangeable.<sup>26</sup>

Thus the fruit of human generation from the first moment of its existence, that is to say, from the moment the zygote has formed, demands the unconditional respect that is morally due to the human being in his bodily and spiritual totality. The human being is to be respected and treated as a person from the moment of conception and therefore from that same moment his rights as a person must be recognized, among which in the first place is the inviolable right of every innocent human being to life.

*"I look forward to joining with others in our society to work for legislation that will protect the rights" spoken of in the instruction of the Congregation for the Doctrine of the Faith on bioethics and procreation, Cardinal Joseph Bernardin of Chicago, chairman of the U.S. bishops' Committee for Pro-Life Activities said in a statement March 10. His statement appears below:*

*"In its Instruction on Respect for Human Life in Its Origin and on the Dignity of Procreation, the Congregation for the Doctrine of the Faith has addressed several important contemporary medical and moral issues. The instruction reaffirms principles of the nature of the human person and the relationship of human procreative and natural love.*

*"Its approval of certain forms of prenatal diagnosis of the fetus, of therapeutic treatment of the fetus and of certain artificial means of assisting the natural act of marital intercourse to be fertile is welcomed.*

*Similarly, its reasoned rejection of improper experimentation on human embryos, of surrogate motherhood, of 'in vitro' fertilization and of artificial insemination will provide Catholics and other people of good will with criteria for making sound moral judgments.*

*"I look forward to joining with others in our society to work for legislation that will protect the rights of which the instruction speaks.*

*Moreover, we must continue to minister to those who suffer the pain of infertility in marriage and to cooperate with the medical sciences as they seek appropriate remedies for infertility."*

Archbishop John May of St. Louis, president of the National Conference of Catholic Bishops, also welcomed the new instruction. In a statement March 10 he said: "On behalf of the National Conference of Catholic Bishops, I welcome the Instruction on Respect for Human Life in Its Origin and on the Dignity of Procreation. I am grateful to the Congregation for the Doctrine of the Faith for presenting a clear and compelling exposition of Catholic teaching in its application to contemporary concerns of life and death significance." Said May: "The instruction demonstrates that the church's moral teaching has much to contribute to a clear elucidation of the moral dimensions of experimentation and practices in the field of bioethics. I hope that, as a result of this instruction, such considerations will be given appropriate attention by scientists, researchers, ethicists and all concerned."

This doctrinal reminder provides the fundamental criterion for the solution of the various problems posed by the development of the biomedical sciences in this field: Since the embryo must be treated as a person, it must also be defended in its integrity, tended and cared for, to the extent possible, in the same way as any other human being as far as medical assistance is concerned.

## 2. Is prenatal diagnosis morally licit?

*If prenatal diagnosis respects the life and integrity of the embryo and the human fetus and is directed toward its safeguarding or healing as an individual, then the answer is affirmative.*

For prenatal diagnosis makes it possible to know the condition of the embryo and of the fetus when still in the mother's womb. It permits or makes it possible to anticipate earlier and more effectively, certain therapeutic, medical or surgical procedures.

Such diagnosis is permissible, with the consent of the parents after they have been adequately informed, if the methods employed safeguard the life and integrity of the embryo and the mother, without subjecting them to disproportionate risks.<sup>27</sup> But this diagnosis is gravely opposed to the moral law when it is done with the thought of possibly inducing an abortion depending upon the results: A diagnosis which shows the existence of a malformation or a hereditary illness must not be the equivalent of a death sentence. Thus a woman would be committing a gravely illicit act if she were to request such a diagnosis with the deliberate intention of having an abortion should the results confirm the existence of a malformation or abnormality. The spouse or relatives or anyone else would similarly be acting in a manner contrary to the moral law if they were to counsel or impose such a diagnostic procedure on the expectant mother with the same intention of possibly proceeding to an abortion. So too the specialist would be guilty of illicit collaboration if, in conducting the diagnosis and in communicating its results, he were deliberately to contribute to establishing or favoring a link between prenatal diagnosis and abortion.

In conclusion, any directive or program of the civil and health authorities or of scientific organizations which in any way were to favor a link between prenatal diagnosis and abortion, or which were to go as far as directly to induce expectant mothers to submit to prenatal diagnosis planned for the purpose of eliminating fetuses which are affected by malformations or which are carriers of hereditary illness, is to be condemned as a violation of the unborn child's right to life and as an abuse of the prior rights and duties of the spouses.

## 3. Are therapeutic procedures carried out on the human embryo licit?

As with all medical interventions on patients, *one must uphold as licit procedures carried out on the human embryo which respect the life and integrity of the embryo and do not in-*

*volve disproportionate risks for it, but are directed toward its healing, the improvement of its condition of health or its individual survival.*

Whatever the type of medical, surgical or other therapy, the free and informed consent of the parents is required, according to the deontological rules followed in the case of children. The application of this moral principle may call for delicate and particular precautions in the case of embryonic or fetal life.

The legitimacy and criteria of such procedures have been clearly stated by Pope John Paul II: "A strictly therapeutic intervention whose explicit objective is the healing of various maladies such as those stemming from chromosomal defects will, in principle, be considered desirable, provided it is directed to the true promotion of the personal well-being of the individual without doing harm to his integrity or worsening his conditions of life. Such an intervention would indeed fall within the logic of the Christian moral tradition."<sup>28</sup>

## 4. How is one to evaluate morally research and experimentation\* on human embryos and fetuses?

*Medical research must refrain from operations on live embryos, unless there is a moral certainty of not causing harm to the life or integrity of the unborn child and the mother, and on condition that the parents have given their free and informed consent to the procedure.* It follows that all research, even when limited to the simple observation of the embryo, would become illicit were it to involve risk to the embryo's physical integrity or life by reason of the methods used or the effects induced.

As regards experimentation, and presupposing the general distinction between experimentation for purposes which are not directly therapeutic and experimentation which is clearly therapeutic for the subject himself, in the case in point one must also distinguish between experimentation carried out on embryos which are still alive and experimentation carried out on embryos which are dead. *If the embryos are living, whether viable or not, they must be respected just like any other human person; experimentation on embryos which is not directly therapeutic is illicit.*<sup>29</sup>

No objective, even though noble in itself such as a foreseeable advantage to science, to other human beings or to society, can in any way justify experimentation on living human embryos

\* Since the terms *research* and *experimentation* are often used equivalently and ambiguously, it is deemed necessary to specify the exact meaning given them in this document.

1) By *research* is meant any inductive-deductive process which aims at promoting the systematic observation of a given phenomenon in the human field or at verifying a hypothesis arising from previous observations.

2) By *experimentation* is meant any research in which the human being (in the various stages of his existence: embryo, fetus, child or adult) represents the object through which or upon which one intends to verify the effect, at present unknown or not sufficiently known, of a given treatment (e.g., pharmacological, teratogenic, surgical, etc.).

or fetuses, whether viable or not, either inside or outside the mother's womb. The informed consent ordinarily required for clinical experimentation on adults cannot be granted by the parents, who may not freely dispose of the physical integrity or life of the unborn child. Moreover, experimentation on embryos and fetuses always involves risk, and indeed in most cases it involves the certain expectation of harm to their physical integrity or even their death.

To use human embryos or fetuses as the object or instrument of experimentation constitutes a crime against their dignity as human beings having a right to the same respect that is due to the child already born and to every human person.

The Charter of the Rights of the Family published by the Holy See affirms: "Respect for the dignity of the human being excludes all experimental manipulation or exploitation of the human embryo."<sup>10</sup> The practice of keeping alive human embryos *in vivo* or *in vitro* for experimental or commercial purposes is totally opposed to human dignity.

In the case of experimentation that is clearly therapeutic, namely, when it is a matter of experimental forms of therapy used for the benefit of the embryo itself in a final attempt to save its life and in the absence of other reliable forms of therapy, recourse to drugs or procedures not yet fully tested can be licit.<sup>11</sup>

*The corpses of human embryos and fetuses, whether they have been deliberately aborted or not, must be respected just as the remains of other human beings.* In particular, they cannot be subjected to mutilation or to autopsies if their death has not yet been verified and without the consent of the parents or of the mother. Furthermore, the moral requirements must be safeguarded that there be no complicity in deliberate abortion and that the risk of scandal be avoided. Also, in the case of dead fetuses, as for the corpses of adult persons, all commercial trafficking must be considered illicit and should be prohibited.

##### 5. How is one to evaluate morally the use for research purposes of embryos obtained by fertilization "in vitro?"

Human embryos obtained *in vitro* are human beings and subjects with rights: Their dignity and right to life must be respected from the first moment of their existence. *It is immoral to produce human embryos destined to be exploited as disposable "biological material."*

In the usual practice of *in vitro* fertilization, not all of the embryos are transferred to the woman's body; some are destroyed. Just as the church condemns induced abortion, so she also forbids acts against the life of these human beings. *It is a duty to condemn the particular gravity of the voluntary destruction of human embryos obtained "in vitro" for the sole purpose of research, either by means of artificial insemination or by means of "twin fission."* By acting in this way the researcher usurps the place of God; and, even though he may be unaware

of this, he sets himself up as the master of the destiny of others inasmuch as he arbitrarily chooses whom he will allow to live and whom he will send to death and kills defenseless human beings.

Methods of observation or experimentation which damage or impose grave and disproportionate risks upon embryos obtained *in vitro* are morally illicit for the same reasons. Every human being is to be respected for himself and cannot be reduced in worth to a pure and simple instrument for the advantage of others. *It is therefore not in conformity with the moral law deliberately to expose to death human embryos obtained "in vitro."* In consequence of the fact that they have been produced *in vitro*, those embryos which are not transferred into the body of the mother and are called "spare" are exposed to an absurd fate, with no possibility of their being offered safe means of survival which can be licitly pursued.

##### 6. What judgment should be made on other procedures of manipulating embryos connected with the "techniques of human reproduction?"

Techniques of fertilization *in vitro* can open the way to other forms of biological and genetic manipulation of human embryos, such as attempts or plans for fertilization between human and animal gametes and the gestation of human embryos in the uterus of animals, or the hypothesis or project of constructing artificial uteruses for the human embryo. *These procedures are contrary to the human dignity proper to the embryo, and at the same time they are contrary to the right of every person to be conceived and to be born within marriage and from marriage.*<sup>12</sup> Also, *attempts or hypotheses for obtaining a human being without any connection with sexuality through "twin fission," cloning or parthenogenesis are to be considered contrary to the moral law, since they are in opposition to the dignity both of human procreation and of the conjugal union.*

*The freezing of embryos, even when carried out in order to preserve the life of an embryo — cryopreservation — constitutes an offense against the respect due to human beings* by exposing them to grave risks of death or harm to their physical integrity and depriving them, at least temporarily, of maternal shelter and gestation, thus placing them in a situation in which further offenses and manipulation are possible.

*Certain attempts to influence chromosomal or genetic inheritance are not therapeutic, but are aimed at producing human beings selected according to sex or other predetermined qualities. These manipulations are contrary to the personal dignity of the human being and his or her integrity and identity.* Therefore in no way can they be justified on the grounds of possible beneficial consequences for future humanity.<sup>13</sup> Every person must be respected for himself: In this consists the dignity and right of every human being from his or her beginning.

*For a past text of current interest, see Pope John Paul II's 1983 address to participants in the World Medical Association convention. "Genetic manipulation becomes arbitrary and unjust," he said, "when it reduces life to an object, when it forgets that it has to do with a human subject, capable of intelligence and liberty, and worthy of respect, whatever its limitations may be; or when genetic manipulation treats the human subject in terms of criteria not founded on the integral reality of the human person, at the risk of doing damage to his dignity. In this case it exposes man to the caprice of others by depriving him of his autonomy."*

*The pope continued: "All scientific and technical progress whatever must therefore keep the greatest respect for moral values, which constitute a safeguard of the dignity of the human person. And since, in the order of medical values, life is man's supreme and most radical good, there is need for a fundamental principle: First prevent any damage, then seek and pursue the good."*

*"To tell the truth, the expression 'genetic manipulation' remains ambiguous and ought to become the object of genuine moral discernment, for on the one hand it covers adventurous attempts aimed at promoting I know not what superman, and on the other hand salutary efforts aimed at correcting anomalies, such as certain hereditary maladies, not to mention beneficial applications in the fields of animal and vegetable biology which can be useful in food production. In the latter cases, some are beginning to talk of 'genetic surgery,' so as to show better that the physician intervenes, not in order to modify nature, but to help it develop along its line, that of creation, that willed by God. In working in*

◀ this obviously delicate domain, the researcher follows God's design. God willed man to be the king of creation.

"To you, surgeons, laboratory research specialists and general practitioners, God gives the honor of the cooperation of all the powers of your intelligence in the work of creation begun on the first day of the world. One may only do homage to the immense progress accomplished in this sense by medicine during the 19th and 20th centuries. But, as you see, it is more than ever necessary to overcome the division between science and ethics, to retrieve their profound unity. It is man that you are dealing with, man whose dignity is safeguarded precisely by ethics."

## II INTERVENTIONS UPON HUMAN PROCREATION

By artificial procreation or artificial fertilization are understood here the different technical procedures directed toward obtaining a human conception in a manner other than the sexual union of man and woman. This instruction deals with fertilization of an ovum in a test tube (*in vitro* fertilization) and artificial insemination through transfer into the woman's genital tracts of previously collected sperm.

A preliminary point for the moral evaluation of such technical procedures is constituted by the consideration of the circumstances and consequences which those procedures involve in relation to the respect due the human embryo. Development of the practice of *in vitro* fertilization has required innumerable fertilizations and destructions of human embryos. Even today, the usual practice presupposes a hyperovulation on the part of the woman: A number of ova are withdrawn, fertilized and then cultivated *in vitro* for some days. Usually not all are transferred into the genital tracts of the woman; some embryos, generally called "spare," are destroyed or frozen. On occasion, some of the implanted embryos are sacrificed for various eugenic, economic or psychological reasons. Such deliberate destruction of human beings or their utilization for different purposes to the detriment of their integrity and life is contrary to the doctrine on procured abortion already recalled.

The connection between *in vitro* fertilization and the voluntary destruction of human embryos occurs too often. This is significant: Through these procedures, with apparently contrary purposes, life and death are subjected to the decision of man, who thus sets himself up as the giver of life and death by decree. This dynamic of violence and domination may remain unnoticed by those very individuals who, in wishing to utilize this procedure, become subject to it themselves. The facts recorded and the cold logic which links them must be taken into consideration for a moral judgment on *in vitro* fertilization and embryo transfer: The abortion mentality which has made this procedure possible thus leads, whether one wants it or not, to man's domination over the life and death of his fellow human beings and can lead to a system of radical eugenics.

Nevertheless, such abuses do not exempt one from a further and thorough ethical study of the techniques of artificial procreation considered in themselves, abstracting as far as possible from the destruction of embryos produced *in vitro*.

The present instruction will therefore take into consideration in the first place the problems posed by heterologous artificial fertilization (II, 1-3),\* and subsequently those linked with homologous artificial fertilization (II, 4-6).\*\*

Before formulating an ethical judgment on each of these procedures, the principles and

values which determine the moral evaluation of each of them will be considered.

### A. Heterologous Artificial Fertilization

#### 1. Why must human procreation take place in marriage?

*Every human being is always to be accepted as a gift and blessing of God. However, from the moral point of view a truly responsible procreation vis-a-vis the unborn child must be the fruit of marriage.*

For human procreation has specific characteristics by virtue of the personal dignity of the parents and of the children: (The procreation of a new person, whereby the man and the woman collaborate with the power of the Creator, must be the fruit and the sign of the mutual self-giving of the spouses, of their love and of their fidelity.) *The fidelity of the spouses in the unity of marriage involves reciprocal respect of their right to become a father and a mother only through each other.*

(The child has the right to be conceived, carried in the womb, brought into the world and brought up within marriage: It is through the secure and recognized relationship to his own parents that the child can discover his own identity and achieve his own proper human development.)

The parents find in their child a confirmation and completion of their reciprocal self-giving. (The child is the living image of their love, the permanent sign of their conjugal union, the living and indissoluble concrete expression of their paternity and maternity.)<sup>19)</sup>

By reason of the vocation and social responsibilities of the person, the good of the children and of the parents contributes to the good of civil society; the vitality and stability of society require that children come into the world within a family and that the family be firmly based on marriage.

\* By the term *heterologous artificial fertilization* or *procreation*, the instruction means techniques used to obtain a human conception artificially by the use of gametes coming from at least one donor other than the spouses who are joined in marriage. Such techniques can be of two types:

a) *Heterologous "in vitro" fertilization and embryo transfer*: the technique used to obtain a human conception through the meeting *in vitro* of gametes taken from at least one donor other than the two spouses joined in marriage.

b) *Heterologous artificial insemination*: the technique used to obtain a human conception through the transfer into the genital tracts of the woman of the sperm previously collected from a donor other than the husband.

\*\* By *artificial homologous fertilization* or *procreation*, the instruction means the technique used to obtain a human conception using the gametes of the two spouses joined in marriage. Homologous artificial fertilization can be carried out by two different methods:

a) *Homologous "in vitro" fertilization and embryo transfer*: the technique used to obtain a human conception through the meeting *in vitro* of the gametes of the spouses joined in marriage.

b) *Homologous artificial insemination*: the technique used to obtain a human conception through the transfer into the genital tracts of a married woman of the sperm previously collected from her husband.



The tradition of the church and anthropological reflection recognize in marriage and in its indissoluble unity the only setting worthy of truly responsible procreation.

**2. Does heterologous artificial fertilization conform to the dignity of the couple and to the truth of marriage?**

Through *in vitro* fertilization and embryo transfer and heterologous artificial insemination, human conception is achieved through the fusion of gametes of at least one donor other than the spouses who are united in marriage. *Heterologous artificial fertilization is contrary to the unity of marriage, to the dignity of the spouses, to the vocation proper to parents, and to the child's right to be conceived and brought into the world in marriage and from marriage.*<sup>34</sup>

Respect for the unity of marriage and for conjugal fidelity demands that the child be conceived in marriage; the bond existing between husband and wife accords the spouses, in an objective and inalienable manner, the exclusive right to become father and mother solely through each other.<sup>37</sup> Recourse to the gametes of a third person in order to have sperm or ovum available constitutes a violation of the reciprocal commitment of the spouses and a grave lack in regard to that essential property of marriage which is its unity.

"Human embryos obtained 'in vitro' are human beings and subjects with rights: Their dignity and right to life must be respected from the first moment of their existence. It is immoral to produce human embryos destined to be exploited as disposable 'biological material.'"

Heterologous artificial fertilization violates the rights of the child; it deprives him of his filial relationship with his parental origins and can hinder the maturing of his personal identity. Furthermore, it offends the common vocation of the spouses who are called to fatherhood and motherhood: It objectively deprives conjugal fruitfulness of its unity and integrity; it brings about and manifests a rupture between genetic parenthood, gestational parenthood and responsibility for upbringing. Such damage to the personal relationships within the family has repercussions on civil society: What threatens the unity and stability of the family is a source of dissension, disorder and injustice in the whole of social life.

*These reasons lead to a negative moral judgment concerning heterologous artificial fertilization: Consequently, fertilization of a married woman with the sperm of a donor different from her husband and fertilization with the husband's sperm of an ovum not coming from his wife are morally illicit. Furthermore, the artificial fertilization of a woman who is unmarried or a*

*widow, whoever the donor may be, cannot be morally justified.*

The desire to have a child and the love between spouses who long to obviate a sterility which cannot be overcome in any other way constitute understandable motivations; but subjectively good intentions do not render heterologous artificial fertilization conformable to the objective and inalienable properties of marriage or respectful of the rights of the child and of the spouses.

**3. Is "surrogate" motherhood morally licit?**

*No, for the same reasons which lead one to reject heterologous artificial fertilization: For it is contrary to the unity of marriage and to the dignity of the procreation of the human person.*

Surrogate motherhood represents an objective failure to meet the obligations of maternal love, of conjugal fidelity and of responsible motherhood; it offends the dignity and the right of the child to be conceived, carried in the womb, brought into the world and brought up by his own parents; it sets up, to the detriment of families, a division between the physical, psychological and moral elements which constitute those families.

**B. Homologous Artificial Fertilization**

Since heterologous artificial fertilization has been declared unacceptable, the question arises of how to evaluate morally the process of homologous artificial fertilization: *in vitro* fertilization and embryo transfer and artificial insemination between husband and wife. First a question of principle must be clarified.

**4. What connection is required from the moral point of view between procreation and the conjugal act?**

a) The church's teaching on marriage and human procreation affirms the "inseparable connection, willed by God and unable to be broken by man on his own initiative, between the two meanings of the conjugal act: the unitive meaning and the procreative meaning. Indeed, by its intimate structure the conjugal act, while most closely uniting husband and wife, capacitates them for the generation of new lives according to laws inscribed in the very being of man and

\* By *surrogate mother* the instruction means:

a) The woman who carries in pregnancy an embryo implanted in her uterus and who is genetically a stranger to the embryo because it has been obtained through the union of the gametes of "donors." She carries the pregnancy with a pledge to surrender the baby once it is born to the party who commissioned or made the agreement for the pregnancy.

b) The woman who carries in pregnancy an embryo to whose procreation she has contributed the donation of her own ovum, fertilized through insemination with the sperm of a man other than her husband. She carries the pregnancy with a pledge to surrender the child once it is born to the party who commissioned or made the agreement for the pregnancy.

*In a 1978 statement, Bishop Walter Sullivan of Richmond, Va., raised questions about "in vitro" fertilization when the Eastern Virginia Medical School in Norfolk, Va., announced plans to open a "test-tube-baby" clinic. Sullivan spoke of a cultural schizophrenia in which research into test-tube babies is announced while, at the same time "through legal abortion we deny life to 50,000 healthy babies each year."*

*After raising a number of questions about "in vitro" fertilization, Sullivan said: "We live in an age which has great benefits but which also mechanizes family life, depersonalizes human relationships, disintegrates marriage and marital intimacy. Is the announcement of the Norfolk test-tube clinic but another step in the dehumanizing process by which the person becomes nothing more than a product in a 'create-and-discard' society?"*

*His statement appeared in Origins, vol. 8, pp. 422f.*

**QUOTE FROM A PAST  
TEXT OF CURRENT  
INTEREST:**

*"The concept of surrogate motherhood as a legal wrong is firmly grounded in the public policy of this state for a myriad of reasons, but most significantly because it exploits a child as a commodity and exploits a woman as a 'babymaker.' In the former situation it promotes injustice, and in the latter it utterly disregards social responsibility.*

*"Children are a gift of God. As such they can never be treated as chattels or commercial pawns or as commodities to be produced as service rendered in exchange for a service fee. The practice of surrogate motherhood is an affront to the human dignity of a child. This human dignity is not only recognized but protected by the state under the doctrine of 'parens patriae,' a doctrine that is traceable to our heritage at common law. In conformity with this doctrine the New Jersey adoption laws not only prohibit the payment or the receiving of money or any valuable consideration in exchange for the placement of a child for adoption, but also make the material assistance of an agent, finder or intermediary a criminal act. The entire concept of surrogate motherhood reduces the creation of a child, a human being, to the level of a commercial transaction. The womb is leased to produce rather than to love a child into existence. When the natural mother surrenders her child for financial remuneration, she is exploiting the most precious thing she can bring into existence, her own child.*

*"The rights of the child itself are also violated. Every child has a right to true parents. Surrogate mothering confuses the relationship by introducing a second mother. The natural attachment a woman has with the child*

of woman."<sup>33</sup> This principle, which is based upon the nature of marriage and the intimate connection of the goods of marriage, has well-known consequences on the level of responsible fatherhood and motherhood. "By safeguarding both these essential aspects, the unitive and the procreative, the conjugal act preserves in its fullness the sense of true mutual love and its ordination toward man's exalted vocation to parenthood."<sup>34</sup>

The same doctrine concerning the link between the meanings of the conjugal act and between the goods of marriage throws light on the moral problem of homologous artificial fertilization, since "it is never permitted to separate these different aspects to such a degree as positively to exclude either the procreative intention or the conjugal relation."<sup>35</sup>

Contraception deliberately deprives the conjugal act of its openness to procreation and in this way brings about a voluntary dissociation of the ends of marriage. Homologous artificial fertilization, in seeking a procreation which is not the fruit of a specific act of conjugal union, objectively effects an analogous separation between the goods and the meanings of marriage.

Thus fertilization is licitly sought when it is the result of a "conjugal act which is *per se* suitable for the generation of children, to which marriage is ordered by its nature and by which the spouses become one flesh."<sup>36</sup> But from the moral point of view procreation is deprived of its proper perfection when it is not desired as the fruit of the conjugal act, that is to say, of the specific act of the spouses' union.

b) The moral value of the intimate link between the goods of marriage and between the meanings of the conjugal act is based upon the unity of the human being, a unity involving body and spiritual soul.<sup>37</sup> Spouses mutually express their personal love in the "language of the body," which clearly involves both "spousal meanings" and parental ones.<sup>38</sup> The conjugal act by which the couple mutually express their self-gift at the same time expresses openness to the gift of life. It is an act that is inseparably corporal and spiritual. It is in their bodies and through their bodies that the spouses consummate their marriage and are able to become father and mother. In order to respect the language of their bodies and their natural generosity, the conjugal union must take place with respect for its openness to procreation; and the procreation of a person must be the fruit and the result of married love. The origin of the human being thus follows from a procreation that is "linked to the union, not only biological but also spiritual, of the parents, made one by the bond of marriage."<sup>39</sup> Fertilization achieved outside the bodies of the couple remains by this very fact deprived of the meanings and the values which are expressed in the language of the body and in the union of human persons.

c) Only respect for the link between the meanings of the conjugal act and respect for the unity of the human being make possible procreation in conformity with the dignity of the per-

son. In his unique and irrepeatable origin, the child must be respected and recognized as equal in personal dignity to those who give him life. The human person must be accepted in his parents' act of union and love; the generation of a child must therefore be the fruit of that mutual giving<sup>40</sup> which is realized in the conjugal act wherein the spouses cooperate as servants and not as masters in the work of the Creator, who is love.<sup>41</sup>

In reality, the origin of a human person is the result of an act of giving. The one conceived must be the fruit of his parents' love. He cannot be desired or conceived as the product of an intervention of medical or biological techniques; that would be equivalent to reducing him to an object of scientific technology. No one may subject the coming of a child into the world to conditions of technical efficiency which are to be evaluated according to standards of control and dominion.

*The moral relevance of the link between the meanings of the conjugal act and between the goods of marriage, as well as the unity of the human being and the dignity of his origin, demand that the procreation of a human person be brought about as the fruit of the conjugal act specific to the love between spouses.* The link between procreation and the conjugal act is thus shown to be of great importance on the anthropological and moral planes, and it throws light on the positions of the magisterium with regard to homologous artificial fertilization.

#### 5. Is homologous "in vitro" fertilization morally licit?

The answer to this question is strictly dependent on the principles just mentioned. Certainly one cannot ignore the legitimate aspirations of sterile couples. For some, recourse to homologous *in vitro* fertilization and embryo transfer appears to be the only way of fulfilling their sincere desire for a child. The question is asked whether the totality of conjugal life in such situations is not sufficient to ensure the dignity proper to human procreation. It is acknowledged that *in vitro* fertilization and embryo transfer certainly cannot supply for the absence of sexual relations<sup>42</sup> and cannot be preferred to the specific acts of conjugal union, given the risks involved for the child and the difficulties of the procedure. But it is asked whether, when there is no other way of overcoming the sterility which is a source of suffering, homologous *in vitro* fertilization may not constitute an aid, if not a form of therapy, whereby its moral licitness could be admitted.

The desire for a child — or at the very least an openness to the transmission of life — is a necessary prerequisite from the moral point of view for responsible human procreation. But this good intention is not sufficient for making a positive moral evaluation of *in vitro* fertilization between spouses. The process of *in vitro* fertilization and embryo transfer must be judged in itself and cannot borrow its definitive moral quality from the totality of conjugal life of which

it becomes part nor from the conjugal acts which may precede or follow it.<sup>48</sup>

It has already been recalled that in the circumstances in which it is regularly practiced *in vitro* fertilization and embryo transfer involves the destruction of human beings, which is something contrary to the doctrine on the illicitness of abortion previously mentioned.<sup>49</sup> But even in a situation in which every precaution were taken to avoid the death of human embryos, homologous *in vitro* fertilization and embryo transfer dissociates from the conjugal act the actions which are directed to human fertilization. For this reason the very nature of homologous *in vitro* fertilization and embryo transfer also must be taken into account, even abstracting from the link with procured abortion.

Homologous *in vitro* fertilization and embryo transfer is brought about outside the bodies of the couple through actions of third parties whose competence and technical activity determine the success of the procedure. Such fertilization entrusts the life and identity of the embryo into the power of doctors and biologists and establishes the domination of technology over the origin and destiny of the human person. Such a relationship of domination is in itself contrary to the dignity and equality that must be common to parents and children.

Conception *in vitro* is the result of the technical action which presides over fertilization. *Such fertilization is neither in fact achieved nor positively willed as the expression and fruit of a specific act of the conjugal union. In homologous "in vitro" fertilization and embryo transfer, therefore, even if it is considered in the context of de facto existing sexual relations, the generation of the human person is objectively deprived of its proper perfection: namely, that of being the result and fruit of a conjugal act in which the spouses can become "cooperators with God for giving life to a new person."*<sup>50</sup>

These reasons enable us to understand why the act of conjugal love is considered in the teaching of the church as the only setting worthy of human procreation. For the same reasons the so-called "simple case," i.e., a homologous *in vitro* fertilization and embryo transfer procedure that is free of any compromise with the abortive practice of destroying embryos and with masturbation, remains a technique which is morally illicit because it deprives human procreation of the dignity which is proper and connatural to it.

Certainly, homologous *in vitro* fertilization and embryo transfer fertilization is not marked by all that ethical negativity found in extraconjugal procreation; the family and marriage continue to constitute the setting for the birth and upbringing of the children. Nevertheless, in conformity with the traditional doctrine relating to the goods of marriage and the dignity of the person, *the church remains opposed from the moral point of view to homologous "in vitro" fertilization. Such fertilization is in itself illicit and in opposition to the dignity of procreation and of the conjugal union, even when everything is done to avoid the death of the human embryo.*

Although the manner in which human conception is achieved with *in vitro* fertilization and embryo transfer cannot be approved, every child which comes into the world must in any case be accepted as a living gift of the divine Goodness and must be brought up with love.

#### 6. How is homologous artificial insemination to be evaluated from the moral point of view?

*Homologous artificial insemination within marriage cannot be admitted except for those cases in which the technical means is not a substitute for the conjugal act but serves to facilitate and to help so that the act attains its natural purpose.*

"Certainly, homologous 'in vitro' fertilization and embryo transfer fertilization is not marked by all that ethical negativity found in extraconjugal procreation; the family and marriage continue to constitute the setting for the birth and upbringing of the children. Nevertheless, in conformity with the traditional doctrine relating to the goods of marriage and the dignity of the person, the church remains opposed from the moral point of view to homologous 'in vitro' fertilization. Such fertilization is in itself illicit."

The teaching of the magisterium on this point has already been stated.<sup>51</sup> This teaching is not just an expression of particular historical circumstances, but is based on the church's doctrine concerning the connection between the conjugal union and procreation and on a consideration of the personal nature of the conjugal act and of human procreation. "In its natural structure, the conjugal act is a personal action, a simultaneous and immediate cooperation on the part of the husband and wife, which by the very nature of the agents and the proper nature of the act is the expression of the mutual gift which, according to the words of Scripture, brings about union 'in one flesh.'"<sup>52</sup> Thus moral conscience "does not necessarily proscribe the use of certain artificial means destined solely either to the facilitating of the natural act or to ensuring that the natural act normally performed achieves its proper end."<sup>53</sup> If the technical means facilitates the conjugal act or helps it to reach its natural objectives, it can be morally acceptable. If, on the other hand, the procedure were to replace the conjugal act, it is morally illicit.

Artificial insemination as a substitute for the conjugal act is prohibited by reason of the voluntarily achieved dissociation of the two meanings of the conjugal act. Masturbation, through which the sperm is normally obtained, is another sign of this dissociation: Even when it is done for the purpose of procreation the act remains deprived of its unitive meaning: "It lacks the sexual relationship called for by the moral order, namely the relationship which realizes 'the full sense of mutual self-giving and human procreation in the context of true love.'"<sup>54</sup>

*in whose creation she has participated is denied. The process destroys the parent-child bond and is a grave injustice to the child.*

*"The concept exploits women as a part of a 'human machine.' The surrogate mother uses her womb for a commercial use. When her days are accomplished and her contract labor is finished, she is made to surrender an integral part of her life, her child, and with it to surrender any natural claim or bond to the child. She has allowed herself to be used for financial gain and all that remains is the money — and the broken bond and, perhaps, some broken dreams. The probability cannot be ignored that this concept may also put undue pressure upon poor women to use their bodies to support themselves or their families. It would not be unfair to say that the concept of surrogate motherhood would not be the subject of discussion today if money was not involved; money for the mother, money for the clinics that invented the concept and money for the legal community which has mapped out the particulars of its operation.*

*"Nor should one disregard the fact that the concept of surrogate motherhood is morally wrong. It is morally wrong because it violates the biological and spiritual unity of the husband and wife, and the dignity of the person of the child as an object for which the parties negotiate....*

*"The practice of surrogate motherhood is a threat to the stability of the family. Rather than experiencing a child as a bond between a husband and wife, a child born of a surrogate arrangement can easily be a divisive force. The potential psychological impact of the stress caused by the acts of conception, pregnancy, delivery, surrender of the child and the acceptance by another of the child, involving an individual outside of the mar-*

riage relationship, cannot be underestimated. Nor can we underestimate the impact on the family structure within the family of the surrogate mother. The interest of siblings must be considered. How do they react to the fact that their baby brother or sister has been given to a stranger?...

"To some minds, this transfer of a child from a surrogate mother to a biological father and his spouse might appear to be no different from adoption. One could argue that in a surrogate situation the child has some genetic relationship to the father while in an adoption no such relationship exists. The differences, however, are vast and are rooted in biology as well as the moral and ethical standards of the human community. A child is placed for adoption because of the circumstances of the mother which prevent her from caring for the child. Her concern for the child's welfare seeks a permanent and stable home for her offspring. In a surrogate situation, a child is deliberately conceived with the intention of transferring all responsibility for the child to others, contrary to ethical norms and without regard for the best interest for the child.

"The concept of surrogate motherhood can only be described as a concept that is a legal outrage and a moral disaster."

—From a letter from the New Jersey Catholic Conference to a New Jersey Senate committee considering legislation to legalize and regulate surrogate parenthood, in the current volume, pp. 551f.

### 7. What moral criterion can be proposed with regard to medical intervention in human procreation?

The medical act must be evaluated not only with reference to its technical dimension, but also and above all in relation to its goal, which is the good of persons and their bodily and psychological health. The moral criteria for medical intervention in procreation are deduced from the dignity of human persons, of their sexuality and of their origin.

*Medicine which seeks to be ordered to the integral good of the person must respect the specifically human values of sexuality.<sup>55</sup> The doctor is at the service of persons and of human procreation. He does not have the authority to dispose of them or to decide their fate.* A medical intervention respects the dignity of persons when it seeks to assist the conjugal act either in order to facilitate its performance or in order to enable it to achieve its objective once it has been normally performed.<sup>56</sup>

On the other hand, it sometimes happens that a medical procedure technologically replaces the conjugal act in order to obtain a procreation which is neither its result nor its fruit. In this case the medical act is not, as it should be, at the service of conjugal union, but rather appropriates to itself the procreative function and thus contradicts the dignity and the inalienable rights of the spouses and of the child to be born.

The humanization of medicine, which is insisted upon today by everyone, requires respect for the integral dignity of the human person first of all in the act and at the moment in which the spouses transmit life to a new person. It is only logical therefore to address an urgent appeal to Catholic doctors and scientists that they bear exemplary witness to the respect due to the human embryo and to the dignity of procreation. The medical and nursing staff of Catholic hospitals and clinics are in a special way urged to do justice to the moral obligations which they have assumed, frequently also, as part of their contract. Those who are in charge of Catholic hospitals and clinics and who are often religious will take special care to safeguard and promote a diligent observance of the moral norms recalled in the present instruction.

### 8. The suffering caused by infertility in marriage.

*The suffering of spouses who cannot have children or who are afraid of bringing a handicapped child into the world is a suffering that everyone must understand and properly evaluate.*

On the part of the spouses, the desire for a child is natural: It expresses the vocation to fatherhood and motherhood inscribed in conjugal love. This desire can be even stronger if the couple is affected by sterility which appears incurable. Nevertheless, marriage does not confer upon the spouses the right to have a child, but only the right to perform those natural acts which are per se ordered to procreation.<sup>57</sup>

*A true and proper right to a child would be contrary to the child's dignity and nature. The*

*child is not an object to which one has a right nor can he be considered as an object of ownership: Rather, a child is a gift, "the supreme gift"<sup>58</sup> and the most gratuitous gift of marriage, and is a living testimony of the mutual giving of his parents. For this reason, the child has the right as already mentioned, to be the fruit of the specific act of the conjugal love of his parents; and he also has the right to be respected as a person from the moment of his conception.*

Nevertheless, whatever its cause or prognosis, sterility is certainly a difficult trial. The community of believers is called to shed light upon and support the suffering of those who are unable to fulfill their legitimate aspiration to motherhood and fatherhood. Spouses who find themselves in this sad situation are called to find in it an opportunity for sharing in a particular way in the Lord's cross, the source of spiritual fruitfulness. Sterile couples must not forget that "even when procreation is not possible, conjugal life does not for this reason lose its value. Physical sterility in fact can be for spouses the occasion for other important services to the life of the human person, for example, adoption, various forms of educational work and assistance to other families and to poor or handicapped children."<sup>59</sup>

Many researchers are engaged in the fight against sterility. While fully safeguarding the dignity of human procreation, some have achieved results which previously seemed unattainable. Scientists therefore are to be encouraged to continue their research with the aim of preventing the causes of sterility and of being able to remedy them so that sterile couples will be able to procreate in full respect for their own personal dignity and that of the child to be born.

## III MORAL AND CIVIL LAW

### The Values and Moral Obligations That Civil Legislation Must Respect And Sanction in This Matter

The inviolable right to life of every innocent human individual and the rights of the family and of the institution of marriage constitute fundamental moral values because they concern the natural condition and integral vocation of the human person; at the same time they are constitutive elements of civil society and its order.

For this reason the new technological possibilities which have opened up in the field of biomedicine require the intervention of the political authorities and of the legislator, since an uncontrolled application of such techniques could lead to unforeseeable and damaging consequences for civil society. Recourse to the conscience of each individual and to the self-regulation of researchers cannot be sufficient for ensuring respect for personal rights and public order. If the legislator responsible for the common good were not watchful, he could be deprived of his prerogatives by researchers claiming to

govern humanity in the name of the biological discoveries and the alleged "improvement" processes which they would draw from those discoveries. "Eugenism" and forms of discrimination between human beings could come to be legitimized: This would constitute an act of violence and a serious offense to the equality, dignity and fundamental rights of the human person.

The intervention of the public authority must be inspired by the rational principles which regulate the relationships between civil law and moral law. The task of the civil law is to ensure the common good of people through the recognition of and the defense of fundamental rights and through the promotion of peace and of public morality.<sup>69</sup> In no sphere of life can the civil law take the place of conscience or dictate norms concerning things which are outside its competence. It must sometimes tolerate, for the sake of public order, things which it cannot forbid without a greater evil resulting. However, the inalienable rights of the person must be recognized and respected by civil society and the political authority. These human rights depend neither on single individuals nor on parents; nor do they represent a concession made by society and the state: They pertain to human nature and are inherent in the person by virtue of the creative act from which the person took his or her origin.

Among such fundamental rights one should mention in this regard: a) every human being's right to life and physical integrity from the moment of conception until death; b) the rights of the family and of marriage as an institution and, in this area, the child's right to be conceived, brought into the world and brought up by his parents. To each of these two themes it is necessary here to give some further consideration.

In various states certain laws have authorized the direct suppression of innocents: The moment a positive law deprives a category of human beings of the protection which civil legislation must accord them, the state is denying the equality of all before the law. When the state does not place its power at the service of the rights of each citizen, and in particular of the more vulnerable, the very foundations of a state based on law are undermined. The political authority consequently cannot give approval to the calling of human beings into existence through procedures which would expose them to those very grave risks noted previously. The possible recognition by positive law and the political authorities of techniques of artificial transmission of life and the experimentation connected with it would widen the breach already opened by the legalization of abortion.

As a consequence of the respect and protection which must be ensured for the unborn child from the moment of his conception, the law must provide appropriate penal sanctions for every deliberate violation of the child's rights. The law cannot tolerate — indeed it must expressly forbid — that human beings, even at the

embryonic stage, should be treated as objects of experimentation, be mutilated or destroyed with the excuse that they are superfluous or incapable of developing normally.

The political authority is bound to guarantee to the institution of the family, upon which society is based, the juridical protection to which it has a right. From the very fact that it is at the service of people, the political authority must also be at the service of the family. Civil law cannot grant approval to techniques of artificial procreation which, for the benefit of third parties (doctors, biologists, economic or governmental powers), take away what is a right inherent in the relationship between spouses; and therefore civil law cannot legalize the donation of gametes between persons who are not legitimately united in marriage.

"Scientists therefore are to be encouraged to continue their research with the aim of preventing the causes of sterility and of being able to remedy them so that sterile couples will be able to procreate in full respect for their own personal dignity and that of the child to be born."

Legislation must also prohibit, by virtue of the support which is due to the family, embryo banks, post-mortem insemination and "surrogate motherhood."

*It is part of the duty of the public authority to ensure that the civil law is regulated according to the fundamental norms of the moral law in matters concerning human rights, human life and the institution of the family. Politicians must commit themselves, through their interventions upon public opinion, to securing in society the widest possible consensus on such essential points and to consolidating this consensus wherever it risks being weakened or is in danger of collapse.*

In many countries the legalization of abortion and juridical tolerance of unmarried couples make it more difficult to secure respect for the fundamental rights recalled by this instruction. It is to be hoped that states will not become responsible for aggravating these socially damaging situations of injustice. It is rather to be hoped that nations and states will realize all the cultural, ideological and political implications connected with the techniques of artificial procreation and will find the wisdom and courage necessary for issuing laws which are more just and more respectful of human life and the institution of the family.

*The civil legislation of many states confers an undue legitimation upon certain practices in the eyes of many today; it is seen to be incapable of guaranteeing that morality which is in conformity with the natural exigencies of the human person and with the "unwritten laws" etched by the Creator upon the human heart. All men of good will must commit themselves, particularly within their professional field and in the exercise of their civil rights, to ensuring the*

*For a past text of current interest in Origins, see "The Ethics of Experiments on Human Embryos," by Cardinal Basil Hume, OSB, of Westminster, England, in vol. 14, pp. 145f. Among his points, Hume supported a proposal by a government committee headed by Dame Mary Warnock regarding regulation of infertility research. Said Hume: "There is considerable merit in the committee's recommendation that a statutory authority be set up with real power to regulate and monitor all future services and research in the field of human infertility through legal and ethical safeguards. Catholics will expect the churches to be invited to nominate representatives to this body."*

*But Hume criticized the committee's recommendation that researchers be allowed to experiment with human embryos for up to 14 days after fertilization. He said that Catholics are not alone in the concern "that what may be at issue in experimentation involving the destruction of human embryos is their moral status as human individuals even at such an early stage of existence."*

Shortly before his election as Pope John Paul I in 1979, Cardinal Albino Luciani discussed the birth of Leslie Brown, the world's first test-tube baby, in an interview with an Italian magazine.

Luciani said he feared the advent of test-tube babies could present "grave risks" to humankind. Speaking "as a journalist" and not a bishop, Luciani said he could share "only in part the enthusiasm of those who applaud the scientific and technical progress after the birth of the English baby."

The possibility of having children through a test tube, "though it may not provoke disasters, at least presents grave risks," he said. Luciani wondered if the new technology would increase the risk of deformed children.

"If this is so, will not the scientist faced with new problems look like 'the sorcerer's apprentice' unleashing mighty forces without being able to hold them back or dominate them?" he asked. Science risks giving rise to a "baby factory," given today's "hunger for money and no-holds-barred attitude to morality."

However, Luciani expressed "most cordial wishes to the baby" and said he could not condemn her parents if they acted in good faith. But he also expressed agreement with Pope Pius XII, who had said if science helps only to accomplish the marital act or to continue a marital act already initiated, then there is no problem. But if science seeks "to exclude or substitute" the marital act, "the act is not licit since God has bound the transmission of human life to the conjugal sex act."

reform of morally unacceptable civil laws and the correction of illicit practices. In addition, "conscientious objection" vis-a-vis such laws must be supported and recognized. A movement of passive resistance to the legitimation of practices contrary to human life and dignity is beginning to make an ever sharper impression upon the moral conscience of many, especially among specialists in the biomedical sciences.

#### CONCLUSION

The spread of technologies of intervention in the processes of human procreation raises very serious moral problems in relation to the respect due to the human being from the moment of conception, to the dignity of the person, of his or her sexuality and of the transmission of life.

With this instruction the Congregation for the Doctrine of the Faith, in fulfilling its responsibility to promote and defend the church's teaching in so serious a matter, addresses a new and heartfelt invitation to all those who, by reason of their role and their commitment, can exercise a positive influence and ensure that in the family and in society due respect is accorded to life and love. It addresses this invitation to those responsible for the formation of consciences and of public opinion, to scientists and medical professionals, to jurists and politicians. It hopes that all will understand the incompatibility between recognition of the dignity of the human person and contempt for life and love, between faith in the living God and the claim to decide arbitrarily the origin and fate of a human being.

In particular, the Congregation for the Doctrine of the Faith addresses an invitation with confidence and encouragement to theologians, and above all to moralists, that they study more deeply and make ever more accessible to the faithful the contents of the teaching of the church's magisterium in the light of a valid anthropology in the matter of sexuality and marriage and in the context of the necessary inter-disciplinary approach. Thus they will make it possible to understand ever more clearly the reasons for and the validity of this teaching. By defending man against the excesses of his own power, the church of God reminds him of the reasons for his true nobility; only in this way can the possibility of living and loving with that dignity and liberty which derive from respect for the truth be ensured for the men and women of tomorrow. The precise indications which are offered in the present instruction therefore are not meant to halt the effort of reflection, but rather to give it a renewed impulse in unrenounceable fidelity to the teaching of the church.

In the light of the truth about the gift of human life and in the light of the moral principles which flow from that truth, everyone is invited to act in the area of responsibility proper to each and, like the Good Samaritan, to recognize as a neighbor even the littlest among the children of men (cf. Lk. 10:29-37). Here Christ's words find a new and particular echo:

"What you do to one of the least of my brethren, you do unto me" (Mt. 25:40).

During an audience granted to the undersigned prefect after the plenary session of the Congregation for the Doctrine of the Faith, the supreme pontiff, John Paul II, approved this instruction and ordered it to be published.

Given at Rome, from the Congregation for the Doctrine of the Faith, Feb. 22, 1987, the feast of the chair of St. Peter, the apostle. ■

Cardinal Joseph Ratzinger  
Prefect

Archbishop Alberto Bovone  
Secretary

#### Footnotes

<sup>1</sup> Pope John Paul II, Discourse to those taking part in the 81st Congress of the Italian Society of Internal Medicine and the 82nd Congress of the Italian Society of General Surgery, Oct. 27, 1980: AAS 72 (1980) 1126.

<sup>2</sup> Pope Paul VI, Discourse to the General Assembly of the United Nations, Oct. 4, 1965: AAS 57 (1965) 878; encyclical *Populorum Progressio*, 13: AAS 59 (1967) 263.

<sup>3</sup> *Ibid.*, Homily During the Mass Closing the Holy Year, Dec. 25, 1975: AAS 68 (1976) 145; Pope John Paul II, encyclical *Dives in Misericordia*, 30: AAS 72 (1980) 1224.

<sup>4</sup> Pope John Paul II, Discourse to those taking part in the 35th General Assembly of the World Medical Association, Oct. 29, 1983: AAS 76 (1984) 390.

<sup>5</sup> Cf. Declaration *Dignitatis Humanae*, 2.

<sup>6</sup> Pastoral constitution *Gaudium et Spes*, 22; Pope John Paul II, encyclical *Redemptor Hominis*, 8: AAS 71 (1979) 270-272.

<sup>7</sup> Cf. *Gaudium et Spes*, 35.

<sup>8</sup> *Ibid.*, 15; cf. also *Populorum Progressio*, 20; *Redemptor Hominis*, 15; Pope John Paul II, apostolic exhortation *Familiaris Consortio*, 8: AAS 74 (1982) 89.

<sup>9</sup> *Familiaris Consortio*, 11.

<sup>10</sup> Cf. Pope Paul VI, encyclical *Humanae Vitae*, 10: AAS 60 (1966) 487-488.

<sup>11</sup> Pope John Paul II, Discourse to the members of the 35th General Assembly of the World Medical Association, Oct. 29, 1983: AAS 76 (1984) 393.

<sup>12</sup> Cf. *Familiaris Consortio*, 11, cf. also *Gaudium et Spes*, 50.

<sup>13</sup> Congregation for the Doctrine of the Faith, Declaration on Procured Abortion, 9, AAS 66 (1974) 736-737.

<sup>14</sup> Pope John Paul II, Discourse to those taking part in the 35th General Assembly of the World Medical Association, Oct. 29, 1983: AAS 76 (1984) 390.

<sup>15</sup> Pope John XXIII, encyclical *Mater et Magistra*, III: AAS 53 (1961) 447.

<sup>16</sup> *Gaudium et Spes*, 24.

<sup>17</sup> Cf. Pope Pius XII, encyclical *Humani Generis*: AAS 42 (1950) 575; Pope Paul VI, *Professio Fidei*: AAS 60 (1968) 436.

<sup>18</sup> *Mater et Magistra*, III; cf. Pope John Paul II, Discourse to priests participating in a Seminar on "Responsible Procreation," Sept. 17, 1983, *Insegnamenti di Giovanni Paolo II*, VI, 2 (1983) 562: "At the origin of each human person there is a creative act of God: No man comes into existence by chance; he is always the result of the creative love of God."

<sup>19</sup> Cf. *Gaudium et Spes*, 24.

<sup>20</sup> Cf. Pope Pius XII, Discourse to the St. Luke Medical-Biological Union, Nov. 12, 1944: *Discorsi e Radiomessaggi VI (1944-1945)* 191-192.

<sup>21</sup> Cf. *Gaudium et Spes*, 50.

<sup>22</sup> Cf. *ibid.*, 51: "When it is a question of harmonizing married love with the responsible transmission of life, the moral character of one's behavior does not depend only on the good intention and the evaluation of the motives: The objective criteria must be used, criteria drawn from the nature of the human person and human acts, criteria which respect

the total meaning of mutual self-giving and human procreation in the context of true love."

<sup>11</sup> *Gaudium et Spes*, 51.

<sup>12</sup> Holy See, Charter of the Rights of the Family, 4: L'Osservatore Romano, Nov. 25, 1983.

<sup>13</sup> Congregation for the Doctrine of the Faith, Declaration on Procured Abortion, 12-13.

<sup>14</sup> Cf. Pope Paul VI, Discourse to participants in the 23rd National Congress of Italian Catholic Jurists, Dec. 9, 1972: AAS 64 (1972) 777.

<sup>15</sup> The obligation to avoid disproportionate risks involves an authentic respect for human beings and the uprightness of therapeutic intentions. It implies that the doctor "above all...must carefully evaluate the possible negative consequences which the necessary use of a particular exploratory technique may have upon the unborn child and avoid recourse to diagnostic procedures which do not offer sufficient guarantees of their honest purpose and substantial harmlessness. And if, as often happens in human choices, a degree of risk must be undertaken, he will take care to assure that it is justified by a truly urgent need for the diagnosis and by the importance of the results that can be achieved by it for the benefit of the unborn child himself" (Pope John Paul II, Discourse to participants in the Pro-Life Movement Congress, Dec. 3, 1982: *Insegnamenti di Giovanni Paolo II*, V, 3 (1982) 1512). This clarification concerning "proportionate risk" is also to be kept in mind in the following sections of the present instruction, whenever this term appears.

<sup>16</sup> Pope John Paul II, Discourse to the participants in the 35th General Assembly of the World Medical Association, Oct. 29, 1983: AAS 76 (1984) 392.

<sup>17</sup> Cf. *Ibid.*, Address to a meeting of the Pontifical Academy of Sciences, Oct. 23, 1982: AAS 75 (1983) 37: "I condemn, in the most explicit and formal way, experimental manipulations of the human embryo, since the human being, from conception to death, cannot be exploited for any purpose whatsoever."

<sup>18</sup> Charter of the Rights of the Family, 4b.

<sup>19</sup> Cf. Pope John Paul II, Address to the participants in the Pro-Life Movement Congress, Dec. 3, 1982: *Insegnamenti di Giovanni Paolo II*, V, 3 (1982) 1511: "Any form of experimentation on the fetus that may damage its integrity or worsen its condition is unacceptable, except in the case of a final effort to save it from death." Congregation for the Doctrine of the Faith, Declaration on Euthanasia, 4: AAS 72 (1980) 550: "In the absence of other sufficient remedies, it is permitted, with the patient's consent, to have recourse to the means provided by the most advanced medical techniques, even if these means are still at the experimental stage and are not without a certain risk."

<sup>20</sup> No one, before coming into existence, can claim a subjective right to begin to exist; nevertheless, it is legitimate to affirm the right of the child to have a fully human origin through conception in conformity with the personal nature of the human being. Life is a gift that must be bestowed in a manner worthy both of the subject receiving it and of the subjects transmitting it. This statement is to be borne in mind also for what will be explained concerning artificial human procreation.

<sup>21</sup> Cf. Pope John Paul II, Discourse to those taking part in the 35th General Assembly of the World Medical Association, Oct. 29, 1983: AAS 76 (1984) 391.

<sup>22</sup> Cf. *Gaudium et Spes*, 50.

<sup>23</sup> Cf. *Familiaris Consortio*, 14.

<sup>24</sup> Cf. Pope Pius XII, Discourse to those taking part in the Fourth International Congress of Catholic Doctors, Sept. 29, 1949: AAS 41 (1949) 559. According to the plan of the Creator, "a man leaves his father and his mother and cleaves to his wife, and they become one flesh" (Gn. 2:24). The unity of marriage, bound to the order of creation, is a truth accessible to natural reason. The church's tradition and magisterium frequently make reference to the Book of Genesis, both directly and through the passages of the New Testament that refer to it: Mt. 19:4-6; Mk. 10:5-8; Eph. 5:31. Cf. Athenagoras, *Legatio pro christianis*, 33: PG 6, 965-967; St. Chrysostom, *In Matthaem homiliae*, LXII, 19, 1: PG 58 597; St. Leo the Great, *Epist. ad Rusticum*, 4: PL 54, 1204; Innocent III, *Epist. Gaudemus in Domino*: DS 778; Council of Lyons II, IV Session: DS 860; Council of Trent, XXIV Session: DS 1798, 1802; Pope Leo XIII, encyclical *Arcanum Divinae Sapientiae*: AAS 12 (1879-1880) 388-391; Pope Pius

XI, encyclical *Casti Connubii*: AAS 22 (1930) 546-547; *Gaudium et Spes*, 48; *Familiaris Consortio*, 19; Code of Canon Law, Canon 1056.

<sup>25</sup> Cf. Pope Pius XII, Discourse to those taking part in the Fourth International Congress of Catholic Doctors, Sept. 29, 1949: AAS 41 (1949) 560; Discourse to those taking part in the Congress of the Italian Catholic Union of Midwives, Oct. 29, 1951: AAS 43 (1951) 850; Code of Canon Law, Canon 1134.

<sup>26</sup> *Humanae Vitae*, 12.

<sup>27</sup> *Ibid.*

<sup>28</sup> Pope Pius XII, Discourse to those taking part in the Second Naples World Congress on Fertility and Human Sterility, May 19, 1956: AAS 48 (1956) 470.

<sup>29</sup> Code of Canon Law, Canon 1061. According to this canon, the conjugal act is that by which the marriage is consummated if the couple "have performed (it) between themselves in a human manner."

<sup>30</sup> Cf. *Gaudium et Spes*, 14.

<sup>31</sup> Cf. Pope John Paul II, General Audience Jan. 16, 1980: *Insegnamenti di Giovanni Paolo II*, III, 1 (1980) 148-152.

<sup>32</sup> *Ibid.*, Discourse to those taking part in the 35th General Assembly of the World Medical Association, Oct. 29, 1983: AAS 76 (1984) 393.

<sup>33</sup> Cf. *Gaudium et Spes*, 51.

<sup>34</sup> *Ibid.*, 50.

<sup>35</sup> Cf. Pope Pius XII, Discourse to those taking part in the Fourth International Congress of Catholic Doctors, Sept. 29, 1949: AAS 41 (1949) 560: "It would be erroneous...to think that the possibility of resorting to this means (artificial fertilization) might render valid a marriage between persons unable to contract it because of the *impedimentum impotentiae*."

<sup>36</sup> A similar question was dealt with by Pope Paul VI, *Humanae Vitae*, 14.

<sup>37</sup> Cf. *supra*: I, 1ff.

<sup>38</sup> *Familiaris Consortio*, 14: AAS 74 (1982) 96.

<sup>39</sup> Cf. Response of the Holy Office, March 17, 1897: DS 3323; Pope Pius XII, Discourse to those taking part in the Fourth International Congress of Catholic Doctors, Sept. 29, 1949: AAS 41 (1949) 560; Discourse to the Italian Catholic Union of Midwives, Oct. 29, 1951: AAS 43 (1951) 850; Discourse to those taking part in the Second Naples World Congress on Fertility and Human Sterility, May 19, 1956: AAS 48 (1956) 471-473; Discourse to those taking part in the Seventh International Congress of the International Society of Hematology, Sept. 12, 1958: AAS 50 (1958) 733; *Mater et Magistra*, III.

<sup>40</sup> Pope Pius XII, Discourse to the Italian Catholic Union of Midwives, Oct. 29, 1951: AAS 43 (1951) 850.

<sup>41</sup> *Ibid.*, Discourse to those taking part in the Fourth International Congress of Catholic Doctors, Sept. 29, 1949: AAS 41 (1949) 560.

<sup>42</sup> Congregation for the Doctrine of the Faith, Declaration on Certain Questions Concerning Sexual Ethics, 9: AAS 68 (1976) 86, which quotes *Gaudium et Spes*, 51. Cf. Decree of the Holy Office, Aug. 2, 1929: AAS 21 (1929) 490; Pope Pius XII, Discourse to those taking part in the 26th Congress of the Italian Society of Urology, Oct. 8, 1953: AAS 45 (1953) 678.

<sup>43</sup> Cf. Pope John XXIII, *Mater et Magistra*, III.

<sup>44</sup> Cf. Pope Pius XII, Discourse to those taking part in the Fourth International Congress of Catholic Doctors, Sept. 29, 1949: AAS 41 (1949), 560.

<sup>45</sup> Cf. *Ibid.*, Discourse to those taking part in the Second Naples World Congress on Fertility and Human Sterility, May 19, 1956: AAS 48 (1956) 471-473.

<sup>46</sup> *Gaudium et Spes*, 50.

<sup>47</sup> *Familiaris Consortio*, 14.

<sup>48</sup> Cf. *Dignitatis Humanae*, 7.

After a 1980 U.S. Supreme Court decision allowing patents on new forms of life, the general secretaries of the U.S. Catholic Conference, the National Council of Churches and the Synagogue Council of America issued a statement in which they acknowledged the "dramatic potential for improving human life" that new life forms may have, but also warned of "unforeseen ramifications" which could, at times, make the cure "worse than the original problem." In their text (*Origins*, vol. 10, pp. 99f), the general secretaries, who at that time were Bishop Thomas Kelly, OP, Claire Randall and Rabbi Bernard Mandelbaum, said that "history has shown us that there will always be those who believe it appropriate to 'correct' our mental and social structures by genetic means, so as to fit their vision of humanity. This becomes more dangerous when the basic tools to do so are finally at hand. Those who would play God will be tempted as never before."

**Feedback from the Centre for Research on Islamic and Malay Affairs of the Association of Muslim Professionals****Executive Summary of Report to BAC**

RIMA has hosted two focus group discussions (FGDs) regarding genetic testing and research. Among the participants of the discussions were professionals from the legal, teaching and biological industries. These participants were Malay/Muslims ranging from those in their early 20s to those in their early 50s. The report is not representative of the Malay/Muslim community. An appropriate way of describing the participants of the FGDs would be that they make up a cross section of the community. By virtue of this cross sectional representation, the results of the FGDs hold no authority in painting a cultural or religious background of the Malay/Muslim community.

Generally, the participants were unsure of the procedures and purposes of genetic testing and research. We undertook the task of informing them prior to gathering feedback through a listing of the break down of what genetic testing and research encompass. Subsequently, the participants became more comfortable in articulating their concerns surrounding genetic testing and research. Several of the concerns pivoted around the permissibility of some of the procedures in genetic testing and research being in line with Islamic principles. Others centred on more practical and ethical issues that reflect the concern of consumers at the receiving end of the practice of genetic testing and research in a clinical setting.

With respect to the 24 recommendations forwarded by the Bioethics Advisory Committee in its consultation paper “Ethical, Legal and Social Concerns in Genetic Testing and Research”, the participants were in general agreement that the interests of the consumers have been accounted for. The feedback they hence gave was intended to add value to the recommendations from the perspective of a cross-section of the Malay/Muslim community. Through this consultation process, the feedback is hoped to be of use in reflecting some concerns that may arise amongst the Malay/Muslim community. It has to be emphasized again though, that the report is by no means representative of the views of the Malay/Muslim community. The feedback holds no



formal authority on religious injunctions but is one which is gathered from enlightened professionals within the community.

## Report

### INTRODUCTION

As a prelude to the discussion of the “Ethical, Legal and Social Issues in Genetics Testing and Research”, our participants were given a brief description of how genetics testing and research are conducted and the purposes behind them. For a start, we identified 7 general phases in which genetics testing and research can be organized and understood. The general flow of process can be understood in phases as:

<b>Phase 1:</b>	<b>Pre- Test Counselling (R1, R2)</b>
<b>Phase 2:</b>	<b>Consent (R3, R9)</b>
<b>Phase 3:</b>	<b>Genetic Testing (R5, R6, R8, R10, R16, R17, R20)</b>
<b>Phase 4:</b>	<b>Genetic Information (R4, R7)</b>
<b>Phase 5:</b>	<b>Interpreting Genetic Information (R19, R21)</b>
<b>Phase 6:</b>	<b>Post- Test Counselling (R22, R23, R24)</b>
<b>Phase 7:</b>	<b>Application (R11, R12, R13, R14, R15, R18)</b>

Within these 7 phases that we have identified, the 24 recommendations can be accommodated. Recommendations which we feel may pertain more to a particular phase will be presented as a recommendation subsumed under that phase. Nevertheless, we encouraged participants to think about the recommendations beyond the framework that we presented them with. Some of the recommendations may pertain to more than one phase in genetic testing and research. The framework was meant to act as a means through which they may understand the concerns that surround genetics testing and research that result in the formulation of the particular recommendation.

With this framework established, we embarked on an exploratory reading of the recommendations to deliberate over its possible implications and meanings. In general, after the participants have been exposed to the 7-phased approach to genetic testing and research that we presented them with, there was a positive outlook towards genetic testing and research. The fears were naturally present, especially with regards to processes such as germline genetic modification and choosing the desired traits in offspring through pre-implantation genetic diagnosis. However, most of our participants were receptive to the development that is taking place in the realm of genetic testing and research. Their concern revolved around the protection of the individual privacy and the nature of consent. Consent can be obtained only when the individual has been made to understand the full implications, options and the possibility of future use of the specimen obtained. Also, the issue of applying genetic information was also a cause of worry among the participants, there was a view that if not regulated and monitored, genetic testing could result in unethical ends. The rest of the paper will provide an insight into the discussion that took place with regards to the 24 recommendations forwarded by the Bioethics Advisory Committee.

**Recommendation 1** was generally agreed upon. The isolated concern surfaced was whether it is advisable to set the highest ethical standards. This view is operating on the premise that restrictive guidelines which characterize medical ethics may be debilitating for development in genetics research and testing. Nevertheless, the participants trust the discretion of the board to balance the needs of genetics research and the preservation on ethical, legal and social interests.

**Recommendation 2** has been deemed to be rather vague. There were views that for Genetic Testing to be done in adherence to ethical guidelines, individuals undergoing the tests have to be informed adequately. This information has to be presented in simple terms to facilitate understanding among the common man. The full implications of the test have to be related to the individual to prepare him in every way possible. Methods of relaying information to individuals too need to be sensitive towards the patients'

backgrounds. There was also a general sentiment of dissatisfaction with the approach of counselling to be that of a “one size-fits-all formula”

**Recommendation 3** was presented as being subsumed under the second phase of genetics testing and research. The obtaining of consent ought to come after sufficient genetic counselling, informing individuals of the risks involved in the process of the tests and research. The participants were particularly concerned as to the manner in which the consent is obtained. The time frame given for the consent to be given ought to be sufficient for the individuals to deliberate sufficiently the costs and benefits of the genetic test. Also, there ought to be enough time for the individuals to seek a second or even a third opinion with regards to the impending genetic test. It was generally agreed that consent was to be obtained specifically for different tests, taking into account the duration in which the consent remains valid.

**Recommendation 4** was categorized under the phase in which genetic information is obtained. The prompt information delivery clause that was included in the recommendation was well accepted by the participants. However, there were contentions with regards to the inclusion of the phrase “treatable conditions” in the recommendation. Some of the participants felt that even for untreatable conditions, the test results still ought to be disclosed. This is so that proper care and management of the affected individual can be achieved. Also, there were suggestions of an “opt-out” clause in relaying the results of the genetic test to the individual. Everyone hence, except for those who chose to “opt-out”, would be informed of the test results, whether or not the disease is treatable.

**Recommendation 5**, categorized under genetic testing, was generally well accepted.

**Recommendation 6** also came under the genetic testing category. With regards to this recommendation, there were concerns regarding the body of authority that will determine the importance and relevance of the research and test. There were views that

there ought to be an overarching body that governs the directions of researches along ethical guidelines.

**Recommendation 7** was classified under the fourth phase where genetic information is handled. It was generally agreed upon that this was a vital recommendation as it deals with the issue of confidentiality of an individual's genetic information. There were views that there ought to be no exception for third parties whatsoever. Also, the exact process of disclosure is not outlined in the recommendation to give the participants an idea of how the disclosing of genetic information is achieved.

**Recommendation 8** was explained in terms of the third phase, which is genetic testing itself. It was generally agreed upon that the test should take place through the intermediation of a healthcare professional. The contention came when the participants came across the statement regarding the advertising of genetic tests by manufacturers or suppliers. Some felt that the term "banned" should be used to replace "strongly discouraged". There were others, however, who felt that the advertising may in fact increase awareness and put people on their toes with regards to conducting genetic testing outside the healthcare realm. The concern revolved around the concern of what kind of advertisement would be allowed and on what grounds.

**Recommendation 9** was categorized under the issue of consent. This recommendation received positive feedback.

**Recommendation 10** again was dealt with under the phase of genetic testing itself. This recommendation was well received by the participants.

**Recommendation 11** was discussed in the sphere of the last phase of genetic testing and research, the application phase. There was unanimous agreement on the participants' part that indeed, the use of preimplantation genetic diagnosis for sex selection and the selection of certain desired traits for non- medical reasons should be prohibited.

**Recommendation 12** was also deliberated upon in terms of the application phase and was again, well received.

**Recommendation 13**, also discussed in the light of the last phase, received positive feedback.

**Recommendation 14**, pondered upon in relation to the last phase received generally positive feedback. The only concern, especially amongst the experienced mothers amongst the participants, was that counselling ought to be done at this stage by trained and professional counselors.

**Recommendation 15** also came under the application phase. This recommendation was met with positive feedback in general.

**Recommendation 16** was subsumed under the third phase, the process of genetic testing itself. There were concerns regarding the drawing up of ethical guidelines based on the objectives of the testing bodies. There was a general sentiment that there ought to be a standard set of guidelines and that these separate bodies be monitored by an overarching authority.

**Recommendation 17**, also categorized under the phase of genetic testing, was also generally agreed upon.

**Recommendation 18** was deliberated in the light of the last phase, application. Similarly, this recommendation was also welcomed positively.

**Recommendation 19** was discussed in terms of the fifth phase, which is interpreting genetic information. The participants felt that the clause “legally designated persons” ought to be applied to other aspects of genetic testing and research. It was agreed upon that, through out the entire process of genetic testing, the lack of ability on the

individuals' past to make decisions of comprehend the full information or implications of the process, there should be present, a "legally designated person".

**Recommendation 20** was subsumed under the third phase and was again, agreed upon in general.

**Recommendation 21** was pondered upon in terms of the fifth phase, which is gathering genetic information. The participants felt that the guideline for this recommendation can be found in Recommendation 2 where there is emphasis on the "welfare, safety, religious and cultural perspectives and traditions of individuals" undergoing genetic testing. Also, many felt that it should be at this point where individuals making important decisions regarding genetic testing can be referred to counselors to help them make informed choices. The counsellors must be especially sensitive to the religious and cultural background of the individuals, keeping in mind their medical condition. The counsellors ought to act as a bridge between the individuals and healthcare professionals, who may tend to impose medical jargon on the common man. Therefore, it is imperative that the counsellors employ a simple and clear mode of communication along with being sensitive to the various backgrounds of individuals. This will, tie in very closely with Recommendation 22.

**Recommendation 22** was agreed upon unanimously after being deliberated on in terms of the second last phase of genetic testing, which is the "post-test counselling" phase.

**Recommendation 23**, also subsumed under post-test counselling, was received positively with particular attention to the notion of counselling to be done in a "non-directive manner".

**Recommendation 24** was also discussed under the last category of genetic testing, which is the application phase. This recommendation received amiable feedback in the light of having sensitive counsellors with a sound medical background.



## College of Family Physicians Singapore

3<sup>rd</sup> Jun 2005

Associate Professor Terry Kaan  
Chairman  
Human Genetics Subcommittee  
Bioethics Advisory Committee  
20 Biopolis Way #08-01 Centros  
Singapore 138668

### 19<sup>th</sup> Council (2003- 2005)

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Dr Tan See Leng

Dr Tan Yew Seng

Dr Wong Weng Hong

#### Honorary Editor

Dr Ng Joo Ming Matthew

Dear A/Prof Kaan

### REQUEST FOR FEEDBACK ON CONSULTATION PAPER

The College 19<sup>th</sup> Council has discussed and noted that the consultation paper has comprehensively and extensively discussed the many ethical, legal and social issues involved in genetic testing and genetic research.

The proposed recommendations will put in place safeguards to prevent abuse without stifling opportunities for patients to benefit from advances in medical genetics.

Of particular relevance to family physicians is the point made in the paper that the relevant authorities should consider providing professional training in medical genetics and counselling to scientific and healthcare professional in this field.

It is foreseeable that family physicians will be consulted for advice on medical genetics by their patients or patients' families. Thus family physicians should be on the radar screen of the relevant authorities for professional training in medical genetics and counselling.

Properly empowered the family physicians have a significant role to play in genetic counselling.

In fact the College has taken the initiative to host the World WONCA Conference in July 2007 with the theme "The Human Genome".

With best regards.

Yours sincerely

A/Prof Cheong Pak Yean  
President  
19<sup>th</sup> Council (2003-2005)  
College of Family Physicians Singapore

Faculty of Medicine  
Dean's Office



Prof John Wong  
Dean  
Faculty of Medicine

June 7, 2005

Associate Professor Terry Kaan  
Chairman  
Human Genetics Subcommittee  
Bioethics Advisory Committee  
20 Biopolis Way,  
#08-01 Centros  
Singapore 138668

Dear *Terry*,

**REQUEST FOR FEEDBACK ON CONSULATATION PAPER**

Thank you for your letter of April 4, 2005, and allowing the Faculty of Medicine, NUS, the opportunity to comment on the consultation paper entitled "Ethical, Legal and Social issues in Genetic Testing and Genetic Research".

The Faculty generally thinks that the paper is well written and covers most key areas. However, the issue of genetic testing of already harvested or stored tissues and the consent issues behind this was not addressed in the paper. We are of the opinion that this should be explicitly addressed. The issue of whether a generic consent is sufficient for tissues obtained primarily for diagnostic or therapeutic purposes is a difficult one with vast implications for translational research. It has also become increasingly easy to obtain genetic information from stored tissue.

We hope that you would find the above feedback useful.

Yours sincerely

A handwritten signature in black ink, appearing to read 'John Wong', is positioned above the typed name.

Professor John Wong  
Dean, Faculty of Medicine  
National University of Singapore





**GLENEAGLES CRC PTE. LTD.  
MEMORANDUM**

**To** : Biomethics Advisory Committee  
**From** : Prof Jeremy Chapman  
**Cc** :  
**Date** : 09 May 2005  
**Re** : Request for Feedback on Consultation Paper

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**Message**

Please find our feedback for your perusal.

**REQUEST FOR FEEDBACK ON CONSULTATION PAPER**

**BIOETHICS ADVISORY COMMITTEE**

**Professor Jeremy Chapman**

The consultation paper: Ethical, Legal and Social Issues in Genetic Testing and Genetics Research

The International Scientific Advisory Panel of Gleneagles CRC has reviewed this paper and has the following comments:

The paper provides an excellent approach to the majority of issues involved in genetics testing. Two areas of current genetic testing seem not to have been considered specifically, or are mentioned but not identified as significant.

- 1 Genetic testing for the purpose of paternity testing (2.7a)
- 2 Genetic testing for matching of individuals for transplantation of cells and organs, especially for unrelated bone marrow transplantation

In addition to these two papers, genetic testing may be used extensively in the forensic medicine field and in criminal forensics. We presume that tests for these purposes are excluded from consideration under this auspice but the paper does not make this explicit. Indeed the definition: point 2.3 states "include, but are not limited to...", suggesting that any use of genetic information could be under consideration.



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17 May 2005

Associate Professor Terry Kaan  
Chairman, Human Genetics Subcommittee  
Bioethics Advisory Committee  
20 Biopolis Way, #08-01 Centros  
Singapore 138668

Dear Prof Kaan

**CONSULTATION PAPER ON ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETICS RESEARCH**

**Introduction**

The Graduates' Christian Fellowship has been invited to give its comments to the paper on 'Ethical, Legal and Social Issues in Genetic Testing and Genetics Research',

We have divided our paper into two parts. The first segment outlines values and principles of our worldview and the outworking of these values and principles as they are translated into legislation. The second part sets out our specific recommendations to the paper and is based on the assumption that our basic premise is rejected and, therefore, seeks to preclude or mitigate the evil of certain aspects of genetic testing and genetics research.

**Part I - Values and Principles**

Human Dignity and Sanctity of Life—A bulwark of the Christian faith and that of many other religions is the respect for human life, the dignity of a human being and the sanctity of life.

Our perspective is derived from our belief that human beings are made in the image of the Almighty God.

*So God created man in his own image, in the image of God he created him; male and female he created them. (Genesis 1:27).*

Additionally, the Word of God makes it clear that life as we understand it begins at the time of conception and we say like the psalmist

- 1 -

**SECTIONAL GROUPS & MINISTRIES**

Christian Conciliation & Arbitration Ministry (CCAM) Christian Medical & Dental Fellowship (CMDF) Comparative Religion Interest Group (CRIG) Fellowship of Christian Care Professional (FCCP) Indonesian Graduates' Christian Fellowship (IGCF) Lawyers' Christian Fellowship (LCF) Links & Connections Marketplace Christian Network (MCN) New Graduates' Ministry (NGM) . Origins Interest Group (OIG) Teachers' Christian Fellowship (TCF) Technical Interest Group (TIG) UK Returnees (Chinese Overseas Christian Mission) – COCM

*“You formed my inward parts;  
You covered me in my mother’s womb.  
I will praise You, for I am  
Fearfully and wonderfully made;  
Your eyes saw my substance, being yet unformed  
And in Your book they all were written,  
The days fashioned for me,  
When as yet there were none of them.”*

So, the Holy Bible, directs our firm belief that all embryonic stem-cell experiments are forbidden as a destruction of life.

In addition, we reject the view of a dichotomous separation of the soul or spirit from the body. It is our view that as a human, we cannot separate the spirit from the body and from the soul or personhood.

*‘... the LORD God formed the man from the dust of the ground and  
breathed into his nostrils the breath of life, and the man became a living  
being.’ (Genesis 2:7)*

Man was created both matter and spirit in order to become a living being. As a human being, he or she is an integrated whole. We recognise that we do not live in a perfect world. There are some who among us were either born (perhaps now conceived, through natural or artificial means) or through debilitating illness or accidents, may seem less than human.

However, we cannot accept with good conscience attempts by those (based on the presupposition of a dualistic world view of the separation of the body and spirit) who seek to define personhood in terms of certain capacities. In exposing this presupposition, Gilbert Meilaender in his book titled ‘Bioethics’ writes,

*‘To be a person one must be conscious, self-aware, productive. The class of persons will widen or narrow depending on how many such criteria we include in our definition of personhood. But, in any case, the class of human beings will be wider than that of persons. Not all living human beings will qualify as persons on such a view – and, we must note, it is persons who are now regarded as bearers of rights, persons who can have interests that ought to be protected.’<sup>1</sup>*

Such a definition of “personhood” based on criteria established by man arbitrarily, would eliminate human beings who do not satisfy these man-made criteria. These man-made criteria have, already, in many jurisdictions, eliminated the unborn who are voiceless and helpless and may if utilitarian views prevail eventually eliminate the sick, the old and hapless who are no longer economically productive.

It is our belief that the unborn, the helpless, the sick and the aged are fully human beings to be accorded value and dignity and who are loved by the creator God. They are no less valuable than those who are “conscious, self-aware” and “productive”.

<sup>1</sup> Meilaender, Gilbert, Bioethics, 1996, Eerdmans, Grand Rapids

#### SECTIONAL GROUPS & MINISTRIES

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Francis Crick, the Nobel Laureate and biophysicist, popularly known as the “father of DNA” has estimated that ‘the amount of information contained in the chromosomes of a single fertilized human egg is equivalent to about a thousand printed volumes of books, each as large as a volume of *Encyclopaedia Britannica*.’<sup>2</sup> Judge Robert H. Bork who referred to the point made by Francis Crick stated that ‘*Such a creature is not a blob of tissue or, as the Roe opinion so infelicitously puts it, a “potential life”. As someone has said, it is a life with potential*’<sup>3</sup>

Some would argue in favour of genetic testing in a search for cures to improve the ‘quality of life’ of the sick. It is imperative that we continue to find better treatments and alleviate as much as possible the pain and suffering of the sick. However, it is also imperative that the sanctity of life needs to be preserved. Otherwise, we may be trading one life for another. We subscribe to the statement made in the Lausanne Occasional Paper No. 58, ‘*Christians however maintain that all human lives are of equal worth, yet we recognise that modern medical decisions cannot avoid some ‘quality of life’ considerations. For example, judgments that the burden of a treatment outweighs its benefits for a particular patient involve an evaluation of the patient’s quality of life. There is no obligation to extend human life by the maximum amount of time, if the patient will die soon regardless of treatment and treatment will add burden to the dying process. Both ‘sanctity of life’ and ‘quality of life’ considerations are legitimate and important, with the proviso that for Christians, quality considerations cannot justify overriding the sanctity of human life.*’<sup>4</sup>

In a consumer society in which we live, trading or the commercialization of life often creeps in it unnoticed. The advancement of technology also brings with it a variety of options that bring hope of healing. The choice of an available option comes with responsibility for the consequences of the choice, for example, once a couple have decided to go ahead with a choice of natural or artificial procreation method, we are of the opinion that the human life henceforth conceived, is a vulnerable person and needs to be protected. We should not fall into a consumer mentality by disowning our own children, like picking a defective book off the shelf and subsequently casting it aside as having ‘no commercial value’. This plain disregard of human life runs against the grain of our belief. However, we find deep sympathy for victims of rape and incest and leave the matter as their conscience or faith guides them.

**Stewardship** – is another fundamental premise which Christians are to operate and practise in the world, on behalf of God. This call is not limited to just Christians but to the entire humankind.

*‘God blessed them and said to them, “Be fruitful and increase in number; fill the earth and subdue it. Rule over the fish of the sea and the birds of the air and over every living creature that moves on the ground.” (Genesis 1:28)*

This translates into an outworking for Christians to engage the world actively and positively in all dimensions of life. They include, helping the sick and needy, protecting human, animal life and the environment, good governance, ethical conduct.

<sup>2</sup> Doris Gordon, “Abortion and Rights: Applying Libertarian Principles correctly,” *Studies in Pro-life Feminism*, Spring 1995, pp. 121, 127

<sup>3</sup> Bork, Robert H, *Slouching towards Gomorrah*, p.175

<sup>4</sup> Chia, Roland et al, 2005, *Bioethics: Obstacle or Opportunity for the Gospel?* Lausanne Occasional Paper No. 58, Lausanne Committee for World Evangelization

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*'He has showed you, O man, what is good. And what does the LORD require of you? To act justly and to love mercy and to walk humbly with your God.'* (Micah 6:8)

In the health care industry, we continue to encourage and applaud professionals, practitioners and researchers (regardless of faith and creed) to develop new methods and cures. This include preventive medicine, antenatal and post-natal diagnosis and care for babies.

Preventive medicine is key in helping diagnosis and subsequently providing a cure before a medical condition occurs such as the use of vaccines. We also find it useful in antenatal diagnosis and cure or to cope with post birth procedures or care for the babies.

However as good and responsible stewards, the end does not justify the means. Neither should we presume to take the place of God rather than simply be good stewards. For the concept of steward or regent connotes that there is privilege in service to the world, but not ownership. As human beings and society, we need to come to terms with our limitations. Going beyond our limitations will only bring tragedy, which we have witnessed throughout history.

**Pride** – can be positive affirmation of achievements and efforts. A healthy dose of pride in our life, society and community is a good thing. However, we have seen all too often that pride is precedent to many a downfall. As a Chinese saying goes, 'jiao bing bi bai'<sup>5</sup>. In this information age, we can get information of almost anything. There arises much concern about security and the subsequent use of information.

We are glad to note the attempts to safeguard information derived from genetic testing and genetics research. We have in our comments sought to tighten the procedures. Thought should be given to the dangers of hacking and unscrupulous data mining. An engineering saying goes, 'fool proof systems only prove the existence of fools'. (Unattributable). We are of the opinion that unless it is absolutely necessary, and fully supported by recommendations of qualified professionals and medical evidence, information such as DNA should not even be documented, much less distributed.

We wish to emphasize that even having knowledge of a probability of contracting a certain illness through DNA testing, without a clearly defined cure or purpose is frivolous and should not be permitted. It only adds onto the burden of scarce medical resources and the expense of taxpayers' money. What is even more unthinkable is the possibility of insurance premia or medical resources pegged to such probabilities.

## **Part II - Comments on Recommendations**

### **Genetic Information**

#### **Recommendation 1:**

*Genetic Information derived from Clinical Genetic Testing should be confined to a healthcare context, owing to its complex nature and need for professional input. Accordingly, it should*

<sup>5</sup> Jiao Bing Bi Bai – The proud army will certainly fall.

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*be regarded as medical information and the highest ethical standard should be applied in its derivation, management and use.*

Comment:

We agree and applaud the committees' recommendation that Genetic Information be limited to areas concerning of healthcare. In this regard, we are concerned that the information used will be harnessed for commercial, social engineering or discriminatory purposes. The context of healthcare should be further understood as primary relating to the individual. For example, where hereditary diseases are concerned the protection of the individual's right to privacy must be protected against the perceived social benefits of the society.

### **General Ethical Considerations**

#### **Recommendation 2:**

*Genetic Testing should be conducted in a manner that is respectful of the welfare, safety, religious and cultural perspectives and traditions of individuals.*

Comment:

We agree and applaud the committees' recommendation that Genetic Testing be conducted in accordance with religious perspectives. The consequence of this recommendation must be to allow the individual equal access to the religious perspectives. A pragmatic viewpoint which may favour economic realities or self-actualisation should not be preferred to the religious perspective that considers the individuals relationship to His or Her God. The committee should, therefore, set guidelines that would allow equal access to counsellors who promote particular religious perspective, subject, of course to such counsellors being properly qualified and allow appropriate religious material to be available in hospitals and clinics throughout Singapore.

#### **Recommendation 3:**

*Genetic Testing should be voluntary and conducted only after free and informed consent has been obtained. Consent must be based on sufficient information, which includes the nature, purpose, risks and implications of the test. Consent should also be obtained for future clinical and/or research use of tissue specimens.*

Comment:

We agree with this recommendation.

#### **Recommendation 4:**

*An individual should be informed of the test result without undue delay unless he or she has clearly indicated the wish not to know. However, the test results of newborn babies and children for treatable conditions should be disclosed. In research involving Genetic Testing, researchers should inform the individual prior to participation in the research, whether the Genetic Information so derived will be disclosed to him or her.*

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Comment:

We agree with this recommendation.

The recommendations should take into account the possibility that treatment for a particular ailment may be developed in the future and allow doctors to inform potential clients that they may wish to come back for testing. If a test is positive but no treatment is available at the time, the regulation should allow patients to be informed when a new treatment has been developed.

## **Genetic Testing of Vulnerable Persons**

### **Recommendation 5:**

*We do not recommend the broad use of Genetic Testing on children and adolescents. Confirmatory Testing and Predictive Testing for genetic conditions where preventive intervention or treatment is available and beneficial in childhood are recommended. Carrier Testing should generally be deferred till the child is mature or when required to make reproductive decisions. Predictive Testing should generally be deferred where there is no preventive intervention or treatment, or where intervention or treatment is only available and beneficial during adulthood. However, in exceptional circumstances, parents and the physician should have the discretion to decide regarding Carrier and Predictive Testing, and genetic counselling should be an intrinsic part of the testing process.*

Comment:

We agree and applaud the committees' decision not recommend the broad use of Genetic Testing on children and adolescents. The decision as to discretion in exceptional circumstance should be made collectively by the parents, the physician and the child, where he or she is matured enough to understand the circumstance, after proper counselling.

### **Recommendation 6:**

*Genetic Testing involving vulnerable persons should be conducted only if appropriate free and informed consent has been obtained. In the case of persons in special relationships, extra care should be taken to ensure that the consent is freely given. Clinical Genetic Testing should only be conducted if it is medically beneficial. Genetic Testing for research should only be conducted if the research is considered of sufficient importance and there is no appropriate alternative test population.*

Comment:

The determination of what is medically beneficial should be finally decided by the individual under the advise of the physician.

An independent committee should determine whether a particular form of research is sufficiently important to be pursued. These areas should be controlled by legislation and there should be a presumption against Genetic Testing unless it is pre-approved by the committee.

In the case of vulnerable persons, access to counselling for the guardians of these person should also be available, and recommended, in the same way as it is for the individual.

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### **Privacy and Public Access to Genetic Testing**

#### **Recommendation 7:**

*Genetic test results should not be disclosed to third parties, including employers and insurers, without the free and informed consent of the individual.*

#### Comments:

We agree with this recommendation.

We would urge the committee to propose legislation that would make it illegal to divulge such information to 3<sup>rd</sup> parties without consent of the individual. There should also be legislation that bans insurers and/or employers from requesting for genetic testing.

#### **Recommendation 8:**

*Genetic Testing should be conducted through the intermediation of a qualified healthcare professional. Accordingly, the advertising of genetic tests by manufacturers or suppliers to the public is strongly discouraged. A comprehensive regulatory framework should be established for access to Genetic Testing services. Genetic tests that provide predictive health information should not be directly offered to the public.*

#### Comments:

All Genetic Testing, without exception, should be conducted through the intermediation of a qualified healthcare professional. The conduct of Genetic Testing for matters other than related to healthcare should not be allowed and therefore the advertising of commercial genetic tests should be made illegal. Genetic Testing should not be available except in pre-approved facilities. The potential for misuse of Genetic data and Genetic profiling may give rise to a new form of discrimination. The use of Genetic Testing to satisfy human curiosity should not be permitted.

#### **Recommendation 9:**

*The non-consensual or deceitful obtaining of body samples for the purpose of Genetic Testing should be legally prohibited.*

#### Comment:

We agree with this recommendation.

### **Preimplantation Genetic Testing**

#### **Recommendation 10:**

*Preimplantation genetic diagnosis is permissible provided that it is subject to control by a relevant authority and limited to serious medical conditions. The relevant authority should license, monitor and assess preimplantation genetic diagnosis to ensure that it is employed within legal and ethical limits.*

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**Comment:**

We believe that Preimplantation Genetic Testing should not be allowed. This process involves the testing the embryos for genetic defects prior to IVF and the determination as to what constitutes an acceptable genetic profile for a child may mean the destruction of embryos and a form of human genetic manipulation.

The consultation paper itself discusses the statement “the ideal that parental love should not be dependent on a child having characteristics that the parents hoped for, but rather as individuals in their own right. Allowing parents to exercise their preference in making such a ‘selection’ may introduce an element of control over the result of conception, thus making the “experience of parenthood very different from the present situation in which... parents are happy just to take their child as they find them”. We would like to propose that this argument is heeded on every level, including whether or not the child has a potential serious health condition.

If PGT is implemented, we feel it is also important for the Committee to prescribe what constitutes serious medical condition and who decides. The parents-to-be may consider a genetic condition serious where, for example, it requires extensive treatment or one or more corrective surgeries as a baby or adult. Whereas such a ‘serious’ medical condition does not discount the person from being able contribute to and thus benefit society as a whole.

According to the consultation paper more than 100 genetic conditions can be tested now. This number can only increase. The Committee should consider whether there should be a limit on the number of embryos that can be screened, or whether the limit will base on the financial and emotional strengths of the parents-to-be.

Furthermore, the Committee should consider that some embryos are carriers of a serious medical condition, but may not manifest the symptoms themselves. We would like the recommendation to ensure that embryos are not excluded from implantation on the basis that they are carriers of inherited diseases.

**Recommendation 11:**

*Use of preimplantation genetic diagnosis for sex selection and the selection of certain desired traits for non-medical reasons should be prohibited.*

**Comment:**

We agree with this recommendation.

**Recommendation 12:**

*Preimplantation tissue typing, whether as the sole objective or in conjunction with preimplantation genetic diagnosis to avoid a serious genetic disorder, is permissible but should be licensed and evaluated on a case-by-case basis.*

**Comment:**

We are of the view that Preimplantation tissue typing should not be allowed. The selection of embryos to bring the birth of a child who can provide a matching tissue donation should not be permitted even in circumstances where a sibling is seriously ill. Whenever possible,

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parents should be encouraged to conceive naturally even for the provision of matching tissue types

### **Germline Genetic Modification**

#### **Recommendation 13:**

*Clinical practice of germline genetic modification should not be allowed at this time.*

Comment:

Germline Genetic modification should not be allowed at any time.

Recommendations 10-13 bring into focus the different religious beliefs concerning the IVF issue. We are of the view that that spiritual counselling for people of different faiths should be freely available and recommended before any IVF treatment is undertaken.

### ***Prenatal Genetic Diagnosis***

#### **Recommendation 14:**

*Prenatal genetic diagnosis should be voluntary, conducted with informed consent and with appropriate pre- and post-test counselling. The prospective parents' choice of whether a genetic disorder warrants a prenatal genetic diagnosis or termination of the pregnancy should be respected.*

Comment:

The process of counselling should include pastoral and spiritual for persons of different faiths. There should be recognition that informed consent requires education not just in areas of the physiological and psychological but must also involve the spiritual.

#### **Recommendation 15:**

*Prenatal genetic diagnosis should be limited to serious genetic diseases. The use of prenatal genetic diagnosis for gender selection, apart from sex-linked disorders is unacceptable. Similarly, it is unacceptable to use prenatal genetic diagnosis for the selection of any physical, social or psychological characteristics or normal physical variations.*

Comment:

We agree that Prenatal genetic diagnosis should be limited to serious cases. In the case of sex-lined disorders Prenatal genetic diagnosis should be limited only to cases where there is an opportunity for medical cure on good medical grounds. All other areas of Prenatal genetic diagnosis should not be permitted. As we have outlined above, we ask the Committee to define what constitutes a "serious" case.

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**Recommendation 16:**

*The appropriate professional bodies should prescribe detailed ethical guidelines on the practice of prenatal genetic diagnosis for their members.*

## Comment:

We are of strongly of the view that the recommendations outlined should be committed to legislation rather than left to be detailed in ethical guidelines.

**Predictive Testing****Recommendation 17:**

*Presymptomatic testing should be available for adults at risk who request it, even in the absence of treatment, after proper counselling and informed consent.*

## Comment:

We agree that Presymptomatic testing should not be available for healthy adults. We would urge the committee to focus on a clear and qualified definition of an “adult at risk” so as to limit the abuse of the definition to encompass non-critical illnesses.

**Recommendation 18:**

*Susceptibility testing should not be applied clinically unless there is unequivocal empirical evidence of validity and utility.*

## Comment:

Susceptibility testing should be limited to areas where the information provided can be used to support post-birth care. We cannot agree to susceptibility testing where the purpose is to decide whether to abort the baby. In respect of being able to give informed consent, it should be mandatory for hospitals to provide persons of faith with access to religious guidance and information.

**Genetic Screening****Recommendation 19:**

*In genetic screening programmes, the appropriate free and informed consent should be obtained from the individual to be tested or parents (or legally designated persons) as the case may be. A confirmatory diagnostic test should be performed as soon as possible after a positive screening test, so as to minimise unnecessary anxiety or to enable measures for the prevention or treatment of the condition to be instituted without delay.*

## Comment:

We agree with this recommendation.

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## Standards of Genetic Test Providers

### Recommendation 20:

*All laboratories conducting Clinical Genetic Tests should be accredited by an accreditation body designated by the relevant authority, based on standards it considers appropriate.*

Comment:

We agree with this recommendation.

These laboratories should be monitored by the relevant authority to ensure that the procedures are followed and testing is carried out to the highest possible standard (ie minimising the possibility of false results).

An evaluation committee should be formed that will assess the value and use of new genetic tests as and when they are developed. When accredited tests are released for use in Singapore, then designated people from each accredited laboratory should be given a standard training to ensure the highest procedural standards are implemented.

### Recommendation 21:

*Interpretation of genetic test results should only be performed by healthcare professionals who are appropriately qualified or have sufficient experience. Genetic counselling should immediately follow the disclosure of the test result, particularly if the test result is not favourable.*

Comment:

We agree with this recommendation.

Where possible, when the accuracy of the test is not assured then multiple types of testing (where available) should be recommended, especially for the serious medical conditions or in situations that are ethically controversial.

## Genetic Counseling

### Recommendation 22:

*Genetic counselling should be offered to all individuals prior to and after they undergo Genetic Testing.*

Comment:

We agree with this recommendation.

*The costs of genetic counselling should be implemented in such a way that it can be readily claimed from medical insurance (ie to be considered a normal part of the treatment not an optional extra), so that people do not refuse the option of counselling based on possible financial constraints.*

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*The Committee should consider whether a help-line, or official on-line web site, is at all feasible. This would not be a substitute for genetic counselling but may be able to encourage individuals to pursue personal counselling. This resource could also include a list of contacts to counsellors, both medical and spiritual that are trained and authorised in this field.*

**Recommendation 23:**

*Genetic counselling should generally be conducted in a non-directive manner, and should provide sufficient information and appropriate support to the individual and his or her family members.*

Comment:

We agree with this recommendation. We would further urge the committee to set criteria so that religious groups can train counsellors to attain the necessary qualifications to be certified as Genetic Counsellors.

**Professional Development**

**Recommendation 24:**

*Individuals involved in genetic counselling should possess up-to-date knowledge of medical genetics and should be appropriately trained in both medical genetics and counselling.*

Comment:

We agree with this recommendation.

Thank you.

Yours truly



for Timothy Goh  
President, Graduates' Christian Fellowship

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10 May, 2005

Associate Professor Terry Kaan  
Chairman  
Human Genetics Subcommittee  
Bioethics Advisory Committee  
20 Biopolis Way, #08-01 Centros  
Singapore 138668

Dear Prof Terry Kaan:

Refer to your letter dated on 4 April 2005 to Professor Jackie Ying, Executive Director of Institute of Bioengineering and Nanotechnology, requesting for feedback on the consultation paper from your committee, I am forwarding you our two cents worth as follows.

Dedicated to improving the health and quality of life, Institute of Bioengineering and Nanotechnology (IBN) focuses its research activities on the following 6 areas:

- Nanobiotechnology
- Delivery of Drugs, Proteins, and Genes
- Tissues Engineering
- Artificial Organs and Implants
- Medical Devices
- Biological and Biomedical Imaging

There are two aspects of our on-going studies that are related to your discussion on Genetic Testing and Genetics Research, namely the development of gene delivery vectors/systems and medical devices for genetic diagnosis.

**Gene Therapy:**

The current version of the recommendations has mainly focused on clinical genetic testing, which is indeed the most commonly used gene technology in hospitals currently. In terms of gene manipulation, we note and concur with the recommendation 13 on germline genetic modification, the clinical practice of which should not be allowed at this time. However, in view of the importance of somatic genetic modification, e.g. gene therapy, a new medical approach widely tested right now, we would appreciate hearing the views from the Bioethics Advisory Committee on what will be your recommendations and whether there is anything that is not allowed.



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Since the first clinical trial gene therapy started in 1990, many such human clinical trials are on-going right now all over the world. In USA, gene therapy is subject to greater oversight than virtually all other therapeutic technologies. The NIH guidelines require federally funded institutions and their collaborators to submit detailed information about proposed and ongoing clinical trials of gene therapy products. Much of this information must be disclosed to the public. Singapore has conducted several early-phase gene therapy studies and will for sure have more years down the road. Your recommendations would be crucial in protecting patients without impeding the development of gene therapy products.

Some of the comments from USA are copied below for your information:

“The field of gene therapy continues to focus on patients with severe and life-threatening diseases who usually have few treatment options or who have failed all available therapies. Thousands of patients have now received somatic cell (nonreproductive cell) gene therapies targeted at life-threatening genetic diseases, cancer and AIDS. We therefore recommend that the first candidates for gene therapy should be patients:

- in whom the disorder is life threatening or causes serious handicap;
- for whom treatment is at present unavailable or is unsatisfactory but for whom treatment may be beneficial.

Judgments on the ethics of gene therapy in man will initially apply to individual cases and will require assessment of factors such as safety, efficacy, alternative treatments and prognosis - in other words, the balance of risk and benefit for the patient.

In the near future, treatment by gene therapy might be justified in cases of invariably fatal or life threatening diseases for which no alternative treatment is available.”

Related to somatic genetic manipulation, stem cells have been tested for transplantation into human bodies. These stem cells could be genetically modified before the transplantation. While the related issues have probably been addressed in the sets of recommendations for stem cells application, the genetic manipulation part may need to be emphasized in your recommendations on Genetic Testing and Genetic Research.

### **Genetic Testing**

Regarding genetic tests, we would suggest the consideration of using the term of “genetic analysis” instead of “testing” in some sentences. For example, page4





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2.3(g) “Genetic testing for research” would be better illustrated by “Genetic analysis for research”.

On page 5, 2.4(a) “genetic tests are commonly accomplished by direct testing, where tests are performed on the DNA or RNA specific for a gene”. This statement is true for most of traditional genetic tests. These days, many new “genome”-based tests have been developed, for example DNA microarrays for SNPs and STRs, which would have nothing to do with genes but those non-coding sequences of human genome, meaning genetic tests could be simply based upon DNA sequence analysis. This point should probably be clarified either in 2.4(a) or 2.4 (c) linkage testing.

Also, in line with the definition on “gene technology” provided by the NMEC, we suggest using “Ethical, legal and social issues in genetic analysis and manipulation” as the title of your recommendations.

Sincerely yours,

WANG Shu, PhD  
Group Leader  
Institute of Bioengineering and Nanotechnology

cc: Prof Jackie Y. Ying, Executive Director  
Noreena AbuBakar, Director, Administration



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16 May 2005

Associate Professor Terry Kaan  
Chairman, Human Genetics Subcommittee  
BIOETHICS ADVISORY COMMITTEE  
20 Biopolis Way  
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Singapore 138668

Dear Professor Kaan

**REQUEST FOR FEEDBACK ON CONSULTATION PAPER  
"ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND  
GENETICS RESEARCH"**

Thank you for inviting my comments on the above consultation paper.

I agree with all the recommendations set forth.

Yours sincerely

A/Prof Wong Kim Eng  
Chairman, Medical Board  
IMH/WH



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20 May 2005

Associate Professor Terry Kaan  
Chairman  
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20 Biopolis Way  
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Dear Terry

**REQUEST FOR FEEDBACK ON CONSULTATION PAPER**

I refer to your Request for Feedback on Consultation Paper entitled " Ethical, Legal and Social Issues in Genetic Testing and Genetic Research". I am pleased to inform you that the feedback from our clinicians have been very favourable and agree with the 24 recommendations.

In addition, the following pointers were raised for your consideration:

1. That the results of the Genetics should not be kept in the patients casenotes as it concerns very sensitive information, as shown by the degree of discussion necessary for the implementation of such tests.
2. That Item 8) "advertising.... to the public" should be prohibited rather than being strongly discouraged, as advertisement by manufacturing companies primarily serves to increase demand for their products, and in this case for a test of highly sensitive nature.

For your perusal.

Dr Tay Eng Hseon  
Chairman Medical Board

Our Ref: LS/12/05/CSY/sha

Your Ref:

18 May 2005

Associate Professor Terry Kan  
Chairman, Human Genetics Sub-Committee  
Bioethics Advisory Committee  
20 Biopolis Way #08-01  
Centros  
Singapore 138668

Dear Sir,

**Re: Request for Feedback on Consultation Paper**

I refer to your letter of 4 April 2005 together with enclosures.

I am pleased to enclose the comments of the Law Society's Ad-Hoc Committee on Bioethics on the consultation paper on 'Ethical, Legal and Social Issues in Genetic Testing and Genetic Research'.

If you require any information or clarification, please call me at 65300215 or email me at <yasho@lawsoc.org.sg>.

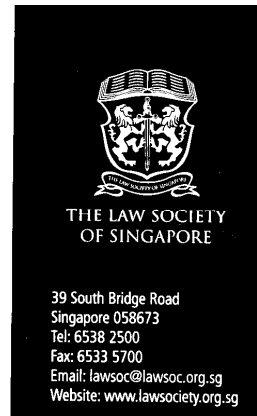
Yours faithfully



Yasho Dhoraisingam (Ms)  
Chief Executive Officer

Enc./

c.c. Ad Hoc Committee on Bioethics  
c.c. Council



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**THE BIOETHICS ADVISORY COMMITTEE'S CONSULTATION PAPER ON ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETICS RESEARCH**

**Ad hoc Committee Members:**

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Messrs Rodyk & Davidson

Members : Kuah Boon Theng,  
Legal Clinic LLC

Audrey Chiang  
Messrs KhattarWong

Mak Wei Munn  
Messrs Allen & Gledhill

We have been appointed by the Law Society of Singapore to provide our comments on the Consultation Paper by the Bioethics Advisory Committee ("BAC") on Genetic Testing and Genetic Research.

All members of this ad-hoc committee are involved in advising and representing individuals and organisations in the health care industry as part of their legal work.

This Committee has necessarily limited their comments to the legal aspects of the Consultation Paper based on the current law in Singapore. Although we have no doubt that due consideration is being given to the legislative amendments that would be necessary to regulate Genetic Testing and Genetic Research, we have also included some comments on what we view to be lacunae within the current legislative framework that should be addressed.

This Committee agrees, in general, with the recommendations of the BAC, save for comments on the following points. For convenience, we have addressed issues in the order in which they appear as recommendations in the Consultation Paper.

1. **The Role of Institutional Review Boards/ Ethics Committees**

1.1 Presently, most hospitals have Institutional Review Boards (IRBs) and Ethics Committees that approve all applications for clinical trials. Part of the approval process includes the vetting of the patient information sheets and consent forms. The IRBs review the information sheets and consent forms to ensure that sufficient information is provided to the patient in order for the patient to have sufficient

information in arriving at a decision to participate in the clinical trial. The consent form is also vetted to ensure that the patient's rights are protected. At present, it is sometimes the case that samples that are taken in the course of a specific clinical trial may be retained for purposes of genetic testing, whether presently contemplated or even for purposes to be determined in the future. There may be a variation in the amount of information being conveyed to the research subject regarding the implications of genetic testing. It is suggested that there be a requirement for all research involving Genetic Testing, whether as the main objective of the research or incidental to a clinical trial, to be subject to approval of the relevant IRBs, who can then ensure that appropriate information to the subject and suitable arrangements for genetic counselling is provided.

2. **Recommendation 3 & Paragraph 3.9**

2.1 Although the right of the individual to withdraw his consent in participating in the research study is recognised, it is not clear what the individual's rights are following the withdrawal of his participation in Genetic Testing in respect of:-

- (a) the genetic material already taken from him; and
- (b) the information/ results derived from such material.

2.2 We would suggest that there be a mechanism for the individual to withdraw from the test and at the time his consent is taken, information setting out how the individual can withdraw.

2.3 Further, information should also be provided at the outset to the individual, stating whether the individual can insist on the destruction of all material and test or research results upon his withdrawal from the research, and if not, assurances as to anonymization of the information derived from the genetic material and whether the information can be traced to the individual.

3. **Paragraph 3.11**

3.1 Paragraph 3.11 allows the healthcare professional to decide to postpone disclosure of a test result if the individual is not in a suitable condition to receive such information. This is a well recognised doctrine of therapeutic privilege.

3.2 However, we are concerned that it is suggested that the decision to disclose would depend on whether the condition can be medically treated or alleviated. It is also unclear from the Report whether this is intended to allow the doctor to merely postpone the disclosure of the information, or not to disclose the information at all on

grounds of therapeutic privilege. The disclosure (or non-disclosure) of test results is known to be based on a variety of factors and specifically referring to whether the condition is capable of being treated/alleviated would appear to give greater weight to that factor, which in our view, is unwarranted. This is because the process of pre-test genetic counselling should already have warned the individual of the possibility that the results may reveal a condition that cannot be treated or alleviated, and if the individual has consented to undergoing the genetic testing on that basis, we should feel that the results should not be withheld from him or her.

- 3.3 Furthermore, to say that the healthcare professional need not disclose test results based on present knowledge of treatment options puts the onus on healthcare professionals to subsequently review these cases. In the event treatment becomes available in the future the healthcare professional may bear the burden of tracking individuals who were previously tested, for purposes of recalling them for consultation.

4. **Consent**

- 4.1. It must be remembered that unlike consent for medical treatment, consent for clinical trials, genetic testing and research are different as there is seldom a direct benefit to the individual or any benefit that may be derived is questionable.

- 4.2 As such, greater must be taken to ensure that individuals are fully aware of all relevant information and are able to consent to participate in the proposed research.

5. **Genetic Testing on Children- Paragraphs 3.16 and 3.17**

- 5.1 Paragraphs 3.16 and 3.17 recognise that mature adolescents may be capable of making informed decisions on undergoing or refusing Genetic Testing. Paragraph 3.17 states that for mature children or adolescents, their decision to undergo or refuse Genetic Testing should be “respected”.

- 5.2 It is not clear if the decision of a mature child or adolescent can override that of a parent. This could give rise to practical difficulties if the position is not made absolutely clear.

- 5.3 There are 3 possible approaches. Firstly, obtaining consent for medical treatment is like a key- the door can be unlocked by anyone with a key, in which case, for a person below the age of 21, as long as either parent or the child gives consent, the other cannot override that consent.

- 5.4 The 2<sup>nd</sup> approach is to respect the sanctity of the body. Once a child is mature enough to make decisions regarding his own health, then his decisions alone should be the determining factor *unless* he is then deemed insufficiently mature.
- 5.5 The 3<sup>rd</sup> approach is that until the child reaches the age of majority, his wishes can be considered but ultimately, the parents decide. This does not appear to accord with the consultation paper and we assume that this is not the basis for consent to be obtained.
- 5.6 A position should be taken on whether the analogy of a key and a lock is to apply or the 2<sup>nd</sup> viewpoint is to be preferred by the Advisory Committee.
6. **Recommendation 5**
- 6.1 For Carrier and Predictive Testing, the recommendation appears to be against the idea of testing for young children. Carrier and Predictive Testing can be carried out where a mature child consents, or in exceptional circumstances for a young child, where the parents *and* the physician consent.
- 6.2 Some members of this committee are of the view that allowing for exceptional circumstances for young children may create more problems. Based on the example given, carrying out a test to address a parent's difficulty of not knowing the genetic status of the child exposes the child to even greater risk where the test results are "unfavourable". We would like the Advisory Committee to consider if testing for such reasons alone should be allowed and whether it would be better for a consistent approach to be taken instead of allowing exceptions. Where there are reasons to make exceptions, we feel that any decision should be taken together with the relevant IRB (if it involves clinical research) or Ethics Committee.
7. **Persons of Unsound Mind- Paragraph 3.18**
- 7.1 There are unaddressed issues in relation to mentally incompetent adults as the identity of a person legally authorised to consent may not be easily understood nor can that person be easily identified.
- 7.2 We recognise that in cases of "idiots, mentally disordered persons and persons of unsound mind", the Court has the power to appoint a Committee of Persons under the Mental Disorders & Treatment Act. This power also extends to persons who are comatose or suffering from other serious neurological deficit but not brain dead.



- 7.3 Leaving it to the researcher or healthcare professional to obtain consent to carry out genetic testing or research on a mentally incompetent adult from a Committee of Persons may not be workable in practice.
- 7.4 Firstly, in reality, a Committee of Persons is seldom appointed for mentally incompetent persons as relatives are seldom advised of the procedure nor are the relatives keen to apply to Court due to the costs involved. In practice, where a mentally incompetent patient requires medical treatment, treatment is still provided if it can be certified that the treatment is in that patient's interest.

If there is no Committee of Persons, no consent can be obtained, unless the researchers undertake this process of getting a legal guardian appointed for the purposes of obtaining consent.

- 7.5 Further, the medical professional/ researcher will seldom be able to obtain the consent of a responsible Committee of Persons, unless the medical professional/ researcher can show that the Genetic Testing will benefit that individual. This is because the duty of the Committee of Persons is to act in the best interest of the individual. If the Committee of Persons were to consent to the extracting genetic material from that individual for tests when the individual derives no benefit, this may be construed to be a breach of their fiduciary duty to the individual.
- 7.6 Currently, the Medical (Therapy, Education and Research) Act (Cap 175) sets out a framework whereby the relatives of a deceased can consent to the deceased's body being given to an appropriate institution for purposes under this Act and the Act sets out clearly who can consent and the order of priorities among the relatives who can give such consent. The problem is that the Act only addresses cases where the donee is dead.
- 7.7 Our suggestion is that the provisions in the Medical (Therapy, Education and Research) Act be extended to cover such cases. To protect the patient, it should be expressly provided that the patient can withdraw from the test/research should he recover his mental competence.

## 8. **Cadaveric Tissue**

- 8.1 The added benefit in extending the use of the Medical (Therapy, Education and Research) Act is that it would then deal with the use of cadavers for genetic testing and research, an issue which has not been dealt with in this Consultation Paper.

## 9. **Confidential Information- Recommendation 7 & Paragraph 3.24**

- 9.1 Given the starting premise that genetic information is to be treated like other medical information, the physician or researcher would be under a strict duty of confidentiality and the information can only be disclosed in certain well defined circumstances- usually involving the consent or implied consent of the patient.
- 9.2 Paragraph 3.24 appears to recognise the defence of public policy in allowing disclosure of confidential information. However, at present, there are no decisions by the Singapore courts on the ambit and the applicability of public policy as a defence to the disclosure of confidential information.
- 9.3 It is only the Infectious Diseases Act that mandates the disclosure of certain information by the physician for specific diseases. We suggest that genetic information be subject to the same requirements and where necessary, public disclosure for specific conditions be statutorily mandated.
10. **Pre-Natal Genetic Diagnosis- Recommendation 14**
- 10.1 It must be remembered that under the Termination of Pregnancy Act, a pregnancy can only be terminated within 24 weeks of gestation. Any guidelines or legislation in relation to foetal tests should be consistent with this timeline to allow for termination of the pregnancy.
11. **Recommendation 15**
- 11.1 Although the use of PND for gender selection or selection of other traits for non-medical purposes will be prohibited, care must be taken to ensure that creative means of subverting these prohibitions do not surface. As such, the ambit of serious genetic diseases that require PND must be clearly and expressly defined. As an example, we note that colour blindness may be considered a sex-linked disorder. To suggest that PND be conducted for such a condition and possibly allow an otherwise normal foetus to be aborted would surely not be the intended position of the Advisory Committee.
- 11.2 Even where the PND does relate to a serious disease or condition, often the results may only confirm that the foetus has a slightly higher chance of developing the disease as compared to a normal individual. We have a concern whether parents should be allowed to undergo tests and decide to abort on the basis of a slim chance of a disease occurring. This is especially acute in the case of late onset diseases.
- 11.3 Therefore, in considering whether genetic tests should be offered to parents as part of PND, the following considerations should be noted:-

- (a) the accuracy rate of the test;
- (b) likelihood of the condition manifesting itself;
- (c) when the condition is likely to manifest (i.e. how late in life);
- (d) whether the condition is treatable.

If it is felt that the option of these PND genetic tests should be offered to the parents, they should be advised of the matters in (a) to (d) above.

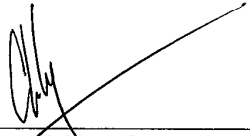
11.4 Accordingly, the severity of the condition, the accuracy of the available tests and the availability or likely availability of treatment of the disease are important considerations to be included in the Recommendation.

12. **Paragraph 6.43**

12.1 Reference is made to the statement "These routine newborn and prenatal programmes have become socially acceptable in Singapore and hence informed consent is not explicitly taken".

12.2 Our view is that, for all screening procedures, informed consent must be expressly obtained. The statement highlighted above may not or should not reflect current medical practice.

Dated this 11<sup>th</sup> day of May 2005

  
\_\_\_\_\_  
Chairman, Ad hoc Committee  
Christopher Chong



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Professor Terry Kaan  
Chairman, Human Genetics Subcommittee  
Bioethics Advisory Committee  
20 Biopolis Way  
08-01 Centros  
Singapore  
138668

11 May 2005

Dear Professor Kaan

Thank you for inviting the Association's comments upon the consultation paper on the issues raised by the developments in field of genetic science.

The paper highlights the far-reaching impact of these developments upon a wide range of social, ethical and public-policy issues. However, it is perhaps appropriate that I confine my comments to those areas which have specific relevance to life and health insurance.

In paragraph 4.7, the paper acknowledges the fears that disclosure of genetic information could lead to the emergence of a 'genetic underclass' who may find difficulty in obtaining insurance. These concerns are based more on speculation than upon fact but they do, nevertheless, need to be addressed.

In reality, there is little reason to suppose that the proportion of the population that can be accepted for insurance will suffer as a result of advances in genetic science. Historic evidence suggests that advances in medical knowledge have consistently contributed to improvements in mortality and a broadening of access to insurance. We doubt that the development of genetic science will prove to be any different. It is far more likely that a better understanding of the interaction between genetic makeup and environmental influences will, over time, improve the effectiveness of health management and, as a result, lead to further improvements in mortality. If one accepts that premise, there is a clear coincidence of interest between life insurers and society as a whole in the successful development of genetic technology.

We fully understand that the link between genetic profile and predisposition to disease is by no means straightforward - even with many of the monogenic disorders. Certainly, we have insufficient knowledge of the all-important link between multifactorial genetic defects and other behavioural and environmental factors. It may be some time before even those who are specialists in the field of genetics are able to predict, with confidence, the impact of specific genetic defects upon mortality. That being so, insurance companies do not seek, and for the

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foreseeable future would have no intention of seeking, genetic tests as a tool for screening of applications.

Nevertheless, as your paper has identified, one must draw a distinction between the active use of genetic tests as a routine underwriting tool and the more passive requirement to disclose the result of a test conducted for some entirely different purpose. We note that the dilemma that this poses has been put to one side for further study.

We certainly welcome and endorse your Recommendation 8 in which you urge discouragement of the development of genetic testing services outside of the framework of the healthcare profession. For society as a whole, the principal concerns must be for the social consequences of testing without appropriate counseling. However, an additional worry for insurers would be that the information would encourage insurance buying decisions that are inappropriate and based on unjustified fears or, worse still, taken with a view to gaining advantage from information that would not be available to the insurer.

Even where testing is carried out within the umbrella of the healthcare profession, Insurers would have concerns about the potential *longer-term* implications of being denied access to relevant medical history. The foundations of insurance are firmly rooted in pooling of risks but, at the same time, underpinned by attempts to achieve broad equity between premiums and the risk borne by the pool. Discrimination *between*, as distinct from *against*, applicants is part and parcel of the risk evaluation process. An asymmetry of information between the applicant and the insurer opens the risk of an unfair cross-subsidy between individuals presenting significantly different risk profiles. This may be manageable in the short term but could have more serious consequences if – or, more likely, when – genetic technology establishes a place in mainstream medical practice.

We are also mindful that the perceptions and definitions of what constitutes ‘genetic information’ or a ‘genetic test’ will change over time. It is recognized that many more conditions have a genetic component than was once thought to be the case. We must, therefore, expect that genetic testing techniques will be used increasingly in the diagnosis of conditions that would currently be identified by clinical means.

Thus, the industry would be very concerned if the *principle* of withholding genetic information were enshrined as a right. Nevertheless, I suggest that there is considerable scope for the Association to work with your Committee to develop interim measures which address the real concerns that you have identified. Furthermore, I would also see mutual benefits in an ongoing dialogue to ensure that, as genetic technology develops, the insurers’ response is based on sound ethical and scientific principles and, equally, that public-policy decisions on the use of genetic information do not overlook the genuine interests of insurers and the majority of their policyholders.

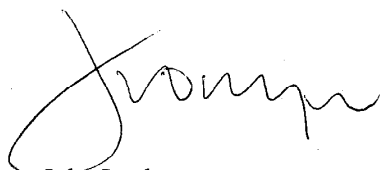
**LIFE INSURANCE  
ASSOCIATION**

I would therefore very much welcome a meeting with you and/or members of your Committee to explore ways in which the industry can work cooperatively to support your objectives.

In the meanwhile I attach a paper entitled '*Genetic Science and its Implications for Life Insurance*'. This is a paper, of which I was the principal author, published in the Transactions of the International Congress of Actuaries in 1998. It was the result of the studies of a working group formed by the Institute of Actuaries in UK to address the issues of equity and access to insurance posed by genetic developments. The opening section was designed for an audience that had little knowledge of genetics and will be of little interest to your committee members. However, you may find the discussion that follows relevant to the issues that you are debating. The science has taken several strides forward since that paper was written and I would, therefore, also commend a more recent paper by Daykin et al entitled '*Genetics and Insurance – Some Social Policy Issues*' which is published in the British Actuarial Journal 2003 Vol. 9.

I look forward to hearing from you if you feel that the Association can help you in framing your final recommendations.

Yours sincerely



John Lockyer  
Executive Director

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Trans 26th ICA, 3, 101-129

## **Genetic Science and its Implications for Life Insurance**

By J. Lockyer, P C Brett, S A Hannington, J A N Lockyer, A S Macdonald and  
J J Woods  
United Kingdom

### **Summary**

Genetic science is driven by the prospect of advances in knowledge and medical care, both positive forces. Unfortunately, insurance is widely seen as an impediment, holding back applications because of fears about the consequences for a 'genetic underclass'. It is important that the actuarial profession, the insurance industry and other interested parties reach methods of dealing with genetic information that are practical and acceptable to all parties.

First, insurers must understand the implications of genetic disorders. There range from monogenic inherited disorders with very specific outcomes (such as Huntington's disease) or with variable outcomes (such cystic fibrosis) through polygenic disorders which represent one of many influences on the outcome, to non-inherited somatic disorders (such as lead to many cancers).

Striking a balance between workable insurance practice, in which adverse selection is controlled, and acceptable public policy, in which discrimination is not extended unreasonably, will not be easy. At one extreme is the view that the scientific principle of insurance should be upheld, if the purchase of insurance is in any way voluntary. At the other is the view that insurance principles cannot override natural justice. A pragmatist might acknowledge the strengths of both arguments, and ask how much any departure from the unfettered 'right to underwrite' might cost. Little information is available to help, as yet. One study, confined to life assurance, suggests that the costs would not be large provided some limits were placed on the sums assured that could be obtained under limited underwriting. No comparable studies have been carried out for health or long term care insurance, where greater problems might be expected.

More research is needed urgently into all aspects of insurance-buying behaviour and adverse selection, as well as the implications of the purely statistical knowledge to be gained from genetic tests. Such research will not be easy, and might require the insurance industry to look beyond the statistics it gathers in the ordinary course of its business, but, in its absence, policy-makers are likely to be more strongly swayed in directions which appear to be supported by relevant research.

*Genetic science and its implications for life insurance*

## **La Génétique et ses Applications pour l'Assurance Vie**

By J Lockyer, P G Brett, S A Hannington, J A N Lockyer, A S Macdonald and J J Woods

### **Summaire**

Les généticiens sont aiguillonnés par deux forces positives : leur désir de faire avancer les connaissances et celui d'améliorer les soins médicaux. Les assureurs sont, pour leur part, souvent considérés comme des poseurs d'obstacles, freinant la transposition de ces avancées, de crainte qu'elles ne génèrent une "sous-classe génétique". Il est donc temps que les actuaires, les sociétés d'assurances et les autres groupes intéressés mettent au point des méthodes de traitement de l'information génétique qui soient praticables et susceptibles d'être acceptées par toutes les parties.

Tout d'abord, les assureurs doivent bien comprendre l'impact des différentes catégories de maladies génétiques :

- maladies héréditaires monogéniques, présentant des manifestations très spécifiques (maladie de Huntington, par ex.) ou variables (mucoviscidose)
- maladies multifactorielles (en conjugaison avec des facteurs environnementaux)
- maladies somatiques acquises (qui sont la cause de nombreux cancers, par ex.).

Il ne sera pas facile de trouver un équilibre entre des pratiques d'assurance viables permettant de contrôler l'anti-sélection et une réglementation publique acceptable selon laquelle la discrimination reste limitée. Il existe deux points de vue diamétralement opposés : certains considèrent que les principes scientifiques de l'assurance sont à appliquer puisque contracter une assurance est un acte volontaire ; d'autres estiment que les principes de l'assurance ne peuvent primer sur la justice naturelle. Une personne pragmatique peut reconnaître la solidité des deux argumentations et demander ce que coûterait l'abandon du "droit d'évaluer les risques". Pour l'heure, nous avons peu d'informations à ce sujet. Une étude, limitée à l'assurance vie, laisse entendre que les surcoûts ne seraient pas énormes à condition que l'on limite les sommes assurées au moment de la souscription. Il n'existe pas d'études similaires, ni en Maladie, ni en Dépendance, or c'est là qu'on peut s'attendre à des problèmes plus sérieux.

Il est donc urgent d'analyser plus finement ce qui pousse les gens à acheter des couvertures d'assurance, sans oublier les nombreux aspects de l'anti-sélection et l'impact des connaissances purement statistiques que l'on peut tirer des tests génétiques. Cette recherche ne sera pas facile et il se peut que les assureurs soient amenés à exploiter des statistiques dépassant le cadre de leurs affaires quotidiennes. Faute de quoi, le législateur aura plutôt tendance à retenir les conclusions prônées par ceux qui auront fait des recherches pertinentes.



*J. Lockyer et al (UK)*

## **1. Introduction**

1.1 The authors of this paper are the members of the Genetics Working Party which was established by the Life Insurance Board of the Faculty and Institute of Actuaries in the United Kingdom, the objectives of which were:

- to inform members of the profession, in general terms, about developments in genetic testing
- to discuss the philosophical issues raised
- to examine the practical implications for the life insurance market

This paper is a report on the results of the Group's studies.

1.2 A huge international research effort is currently being directed to the mapping of the human genetic code and to the parallel development of new genetic tests. The pace of these advances, allied to the perceived predictive powers of these new tests, has led to public concern about the implications of this new technology. An area that has attracted considerable comment and attention is the use of genetic information by insurance companies. In particular there is concern that, through ignorance or prejudice, people with genetic defects will not be treated fairly at the hands of the insurance industry.

1.3 This subject is very much at the forefront of the insurance industry's thinking, following the Association of British Insurers' recently published draft Code of Practice and with the Human Genetics Advisory Commission's report on the implications of genetic testing for life insurance due at the end of the year.

1.4 The view that seems to have gained popular support is that insurers should be denied access to genetic information on the grounds that its use would be discriminatory and would affect the rights of those who, through no fault of their own, may already be disadvantaged. It is therefore timely that the Genetics Working Party of the Life Insurance Board has completed this paper.

1.5 Due to the complexities of this subject, this working party has concentrated on the effects of genetics on life insurance. It is the working party's opinion that the conclusions in this paper cannot necessarily be carried over to critical illness, permanent health, long term care or private medical health insurance. For instance, critical illness policies, which pay on the diagnosis of certain conditions, are affected more by the prognostic abilities of genetic testing. The issues involved with these covers are left for a future paper.

### *Genetic science and its implications for life insurance*

1.6 It is generally accepted that, with the increased understanding of genetics, tests will be developed that will identify a person's predisposition to given genetic conditions. However, what is less certain is the predictive power of these tests or their applicability to the general population. At the one extreme there are those who argue that the sheer volume of genetic information and the complexity of the interaction with environmental factors mean that the ability to analyse and understand the full implications of an individual's genetic profile is a distant dream.

1.7 At the other extreme there are those who foresee the possibility of generally available genetic screening within a generation. The truth is probably somewhere between the two. Currently genetic tests are complex, expensive and only capable of identifying one genetic condition. As a result, they are presently used only on people with a family history of the given condition. Hence, it seems probable that generally available multiple genetic tests are at least a decade away.

1.8 Life insurance depends on the unknown, with people being prepared to insure their lives to cover the risk that misfortune may strike. The degree of certainty that genetic testing will bring to people's understanding of their future mortality poses unique and fundamental questions, especially if its use by the insurers is restricted. As mentioned above, genetic testing will have no practical effect on life insurance for a number of years. One could argue that these questions do not need to be considered just yet but public concern about this issue demands answers now.

1.9 In looking at this topic the working party was conscious that man's power to invent is matched only by his ability to underestimate the potential of what he has developed. Whatever one might say today about the impact of any scientific development will, in all probability, prove to be a gross understatement of the reality that will unfold. This being so, the working party stresses the need for the profession to revisit this topic on a regular basis and to avoid becoming locked into a position, the full implications of which cannot be fully comprehended.

1.10 The structure of the paper follows the working party's aims mentioned previously.

1.11 Chapter 2 gives a brief introduction to genetics. It explains in simple terms what genes are, how genetic conditions are inherited, what types of genetic diseases there are and finally what consequences genetic testing will have for these different types of genetic diseases. It concludes that genetic testing is likely to become a routine tool in medical practice.

*J. Lockyer et al (UK)*

1.12 The next chapter describes the political background. It starts with the 1989 resolution of the European Parliament and traces the events that have led to the response from Association of British Insurers' and the review underway by the Human Genetics Advisory Commission. It then looks at how some other governments have taken a tougher line in this respect than the British Government.

1.13 The fourth chapter looks at the philosophical issues posed by conflicting views on the rights of access to genetic information. It examines the reasons for underwriting, points out that, at present, there is no justifiable reason to require an applicant to undergo a genetic test but explores the need for disclosure of genetic tests that have taken prior to application. Finally it questions whether those with genetic disorders should be treated more favourably than someone with another form of disorder.

1.14 The final chapter looks at the necessity to come up with a practical solution which addresses public concern. Referring to the work of Macdonald it concludes that the Association of British Insurers' concessions will not lead to a large increase in the insured lives mortality experience and therefore provides a balance between the concerns of the public and the requirements of the insurers.

## **2. Understanding Genetics**

2.1 Before entering into a discussion of the significance of genetic technology, it will be helpful to define some of the key elements of the genetic lexicon.

### ***DNA***

2.2 Deoxyribonucleic acid - DNA to give it its more manageable abbreviation - consists of two intertwining strands made up of four bases; adenine (A), thymine (T), guanine (G) and cytosine (C). Each strand contains sequences of these four bases. Complementary strands pair A with T and G with C so that, for each sequence on one strand, there is a complementary sequence on the other.

2.3 The sequences of the genetic alphabet, A, T, G, and C, are arranged in 'words' of three letters. About 10% of these three letter sequences contain the instructions to produce amino acids which, in turn, combine to form proteins. The remaining combinations of the genetic alphabet along the DNA chain have no recognised function.

### *Genetic science and its implications for life insurance*

2.4 The equivalent of approximately 2 metres of DNA is packed into each human cell.

#### **Chromosomes**

2.5 Chromosomes are paired bodies, in the cell nucleus, which consist of proteins and DNA. Until the 1940s it was not known whether it was DNA or the proteins which carried the genetic code but the prevailing thought was that DNA was far too simple a molecule to carry the complex web of information required to record the blue-print for the control of life form. In 1944 Oswald Avery, a microbiologist, published an article which demonstrated that it was, in fact, DNA, and not the proteins in a chromosome, that carried the genetic code.

2.6 Cells in the human body have 23 pairs of chromosomes - 22 pairs of what are known as 'autosomes' and one pair of sex chromosomes. One chromosome from each pair comes from the mother and the other from the father - each consisting of one long DNA molecule in a tightly coiled strand. The autosomes of the two sexes look identical but the sex chromosomes are quite distinct. Females have two large 'X' chromosomes whereas males have a single 'X' chromosome and a smaller 'Y' chromosome. The 'Y' chromosome has relatively few genes - a fact which, as we shall discuss later, has implications which make males more prone to certain types of inherited diseases.

#### **Genes**

2.7 Genes have been described as beads along a string of DNA - each made up of 'sentences' arranged from 'words' from the genetic alphabet. They vary considerably in size, from a sequence of around five hundred letters to something in excess of two million.

2.8 It is estimated that there are about 100,000 genes which control the biological processes in human beings. The location of each gene is fixed and, because chromosomes are paired, genes are also paired. Each gene produces its own specific protein, which has a crucial part in controlling the processes necessary for life. If there is an error in the genetic code the specific protein produced by the affected gene will not function properly and this may cause disease.

2.9 Each cell of the body has the same DNA and therefore the same genes. However, depending upon the gene's ascribed function and the location of the cell in which it is situated, it may be active or 'switched off'.

#### **The Genome**

2.10 Originally the word genome was coined to describe the whole body of genes in cell. However, it is now recognised that 90% of the three-letter

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sequences in DNA appear to have no direct genetic function. As a result, the meaning of the word has been modified to include all DNA within a cell.

### **Basic Rules of Inheritance**

2.11 The development of genetic science has been closely linked to the study of the rules which govern inheritance. We now understand that it is genetic diversity that explains why we have individual characteristics. Many of these differences are benign but, as we shall see, there are variations in genetic structure that have more serious – even sinister – implications.

2.12 The founding father of genetics was an Austrian Benedictine monk by the name of Gregor Mendel. It was he who discovered the basic laws of inheritance in the mid 19<sup>th</sup> Century through his study of the garden pea. One of the traits which he studied was how the colour of the peas in the pod passed from one generation to the next.

2.13 He pollinated a yellow pea plant with a green pea plant as a result of which he produced plants which all had yellow peas. These yellow pea plants were then used to pollinate one another. This time the result was a mixture of plants with green and yellow peas in the ratio of one green to three yellow. This led Mendel to propose that each plant has a pair of genes which determine the colour and that, during fertilisation, the pollen and egg provide one gene each which form a pair. The genes, he proposed, were either dominant, in which case only a single copy of the gene is necessary for the trait to manifest itself, or recessive if it takes two copies of the gene for the trait to emerge.

2.14 These are the rules which, indeed, define single gene, or Mendelian disease. There was, however, a further variant which Mendel's experiment had not identified. This next step in the understanding of inheritance came at the beginning of this century and resulted from the experiments of Thomas Morgan. From his study of fruit flies he made the discovery that it was the chromosomes which are present in all cells that carry the genetic information and which, therefore, must contain the genes.

2.15 He found patterns of inheritance that could not be explained by Mendel's rules. One example was eye colour. Fruit flies have either white eyes or red eyes. Morgan found that the eye colour depended on the eye colour of each parent. When white-eyed males were crossed with red eyed females, there were both white and red-eyed offspring. However, when red eyed males were crossed with white eyed females, all of the male offspring had white eyes whilst all the females had red eyes. This led Morgan to the discovery that, in the case of the fruit fly, eye colour is inherited through the X chromosome. A daughter will inherit an X chromosome from both the

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mother and father, with the red eye gene being dominant over the white eye gene, but a son would only inherit the X chromosome from the mother and get white eyes.

2.16 It has subsequently been found that this pattern also applies to humans. The Y chromosome carries very few genes and therefore the ordinary rules of Mendelian dominance and recessivity do not apply. Any gene on the single X chromosome will show its effect in a male, whether or not it is recessive in females. This is known as sex linkage.

**Genetic Disease**

2.17 Any disease, which arises as a result of an error in the genetic code, might reasonably be termed a genetic disease. The term has commonly been held to be synonymous with the single gene or monogenic disorders. The reality is, as Dr Francis Collins of the National Center for Human Genome Research is reported to have observed, "all disease except trauma is genetic".

***Monogenic Disease***

2.18 There is a range of known disorders which arise from a mutation of a single gene. These are the monogenic disorders of which Huntington's Disease is the most commonly cited example. Huntington's is an *autosomal dominant* disease which means that the defect is in a gene located on one of the autosomes (in this case on Chromosome 4) and that it requires only one of the pair genes to be defective for the disease to manifest itself.

2.19 Autosomal recessive diseases are those which require both genes of a pair to be mutated. This will occur if the mutation is transmitted from both parents. If only one gene has the mutation, the disease will not manifest itself but could be passed on to any offspring. Cystic fibrosis is an example of such a condition.

2.20 The sex-linked diseases occur where a mutated gene located on the X chromosome causes disease in males even though the same condition is recessive in females. This occurs because no paired gene exists on the Y chromosome and thus the mutated gene effectively dominates. Examples are colour blindness, haemophilia and muscular dystrophy.

2.21 In some cases there is a straightforward correlation between the disorder and a specific genetic defect. However, the abnormalities leading to other monogenic diseases may be more difficult to unravel. Cystic Fibrosis, for example, is not characterised by a unique mutation. 70% of sufferers do share a common mutation of a particular gene but the absence of that particular abnormality does not guarantee freedom from the disease. There are over 500 known mutations which might lead to a similar outcome.

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2.22 Yet more confusingly, certain conditions can arise from mutations to one of a number of different genes. Alzheimer's disease is an example where various forms of the condition can be traced to mutations to different genes.

2.23 There is not absolute correlation between the inheritance of a genetic profile which is indicative of a monogenic condition and the incidence of disease. The likelihood that the disease will manifest itself is described by the *penetrance*. Huntington's is an example where the penetrance is at or near 100%. Not all monogenic defects confer the same degree of certainty but most carry a high probability that the condition will occur.

2.24 There is a danger that initial studies tend to overestimate the penetrance of a particular genetic abnormality. This tendency arises as a result of the fact that most studies have been conducted by observation of individuals and families where there is a history of the particular condition. It is now recognised that, in the wider population, there may be others with the same genetic mutation but who also have a compensating factor somewhere within their genetic makeup.

2.25 The monogenic disorders also vary in their *expressivity*. This term is used to express the extent to which the severity of the disease, when and if it manifests itself, may vary. Cystic fibrosis again serves as an example. The condition can present symptoms ranging from mild to severe.

#### ***Chromosomal Disorders***

2.26 Another category of genetic disease, the chromosomal disorders, arise, not from mutations, but where material is either added to or missing from a chromosome. Symptoms become apparent at an early age and, in common with many of the monogenic disorders, these conditions are only infrequently encountered amongst applicants for life insurance.

#### ***Polygenic or Multifactorial Disorders***

2.27 These are complex genetic disorders which arise from the interaction between mutations to a number of different genes and which may be strongly influenced by environmental factors.

2.28 They indicate an increased susceptibility to a particular condition rather than an omen of inevitability and, in many respects, genetics technology is merely confirming and extending through molecular biology what had been concluded from general or clinical observation. It has long been understood that the secret of a long and healthy life is careful selection of one's parents! The familial link in a number of adult disorders had been recognised without the aid of genetic science even though the cause may not

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have been understood. Despite the lack of any clear pattern of inheritance, the tendency for heart disease, obesity, hypertension, and a host of other ailments, to run in families is not a newly recognised phenomenon.

2.29 The interaction of the underlying genetic abnormalities – mutations which may affect a number of genes – and other behavioural or environmental factors is less than perfectly understood.

***Acquired Genetic Disease***

2.30 Lastly there are the acquired, or *somatic* genetic disorders. These arise where mutations occur in one or more cells which were perfectly normal at birth. The genetic makeup of a particular cell may be damaged by an external environmental factor, such as exposure to cigarette smoke or ultraviolet light or, perhaps, through a fault in the process of DNA replication. The resulting mutation then replicates itself by the normal process of cell division. The common cancers are the most obvious examples. Acquired genetic disease is not usually passed on to the next generation.

**Genetic Testing**

2.31 Genetic tests may be used to detect a range of known monogenic disorders. These tests offer the capability to identify monogenic diseases before there are any physical symptoms. This raises sensitive ethical questions because the results can have consequences, not only for the individual, but also for other members of the family and even for an unborn generation.

2.32 Tests may also be used to detect acquired or somatic diseases during their presymptomatic state. Unlike the other forms of genetic abnormality, which can be detected from any sample of DNA, somatic diseases may only be detectable from certain localised sites. In that sense, these tests may not conform to the popular conception of what is meant by a genetic test although the technology may be similar. By contrast, tests for somatic disease do not raise any new or controversial ethical issues and might reasonably be considered in the same light as any other diagnostic tool.

2.33 It is likely that tests for predisposition to multifactorial disorders will eventually become available although it may be a long way into the future before these become a reality. These tests will not be indicative of either presymptomatic illness or of any inevitability that the disease will ever occur. They will, however, give warning of a greater than normal degree of risk. In a sense, they are analogous to other known risk factors such as blood pressure, cholesterol level etc. and, in much the same way, knowledge of these predispositions will offer individuals the opportunity to adapt their lifestyle and to minimise the risk.



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2.34 It will be apparent that genetic disease is not just a limited subset of the human condition. It is now recognised that many more conditions, than was once thought to have been the case, have a genetic component and, indeed, that most non-hereditary diseases can also be traced to a genetic mutation. A huge international effort is being directed at the mapping of the human genetic code – an effort which is producing new genetic tests at a bewildering rate. It seems likely that, over time, genetic technology will emerge as a routine tool at the forefront of many, if not most, facets of medical practice.

### **3. The Political Framework**

3.1 Recognition of the extreme sensitivity of the information potentially revealed by genetic testing is leading to intense international debate in legal, political and ethical circles about the use of, and access to, genetic information.

3.2 Naturally, the issues raised extend far beyond the boundaries of direct concern to our profession but, in this section we limit commentary to those areas of the debate which have relevance to insurance.

3.3 As far back as 1989, the European Parliament adopted a resolution on the Ethical and Legal Problems of Genetic Engineering. Principle 19 of that resolution bans insurance companies from demanding a genetic test or from being informed of the result of a test which had already been carried out. Principle 20 states that an insurer has no right to be notified of all of the genetic data known to the policyholder. This resolution has no legal force in the member states. In contrast to a Directive, which demands adherence, such a resolution only encourages action.

3.4 Whilst a number of jurisdictions, both within Europe and elsewhere, have reached for the statute book, the UK Government has taken a more measured approach in the search for practical resolution of conflicting interests in the genetic debate.

3.5 One of the principal contributions to the debate in the UK has been a report produced in 1993 by the Nuffield Council of Bioethics and entitled, *Genetic Screening - Ethical Issues*. Chapter 7 of this report contains a very clear and balanced view of the issues that relate to insurance. Its recommendations can be summarised as follows:

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- That British insurance companies should adhere to their practice of not requiring genetic tests as a prerequisite of insurance cover
- That there should be discussions between Government and the insurance industry about the future use of genetic data.
- That, pending the outcome of those discussions, insurance companies should grant a temporary moratorium on the requirement for disclosure of genetic data. However, there were two important qualifications to this recommendation. Firstly, that, in the case of individuals with a known family history of genetic disease, those individuals may be asked to disclose the result of any relevant genetic tests. Secondly, that the moratorium should only apply to policies of 'moderate size' – it being left to discussion between the industry and the Government as to what that limit should be.

3.6 The House of Commons Select Committee on Science and Technology published a report on *"Human Genetics, The Science and its Consequences"* in July 1995. Whilst the full report concerns itself with a very much wider range of issues, it contains a significant section which addresses the insurance implications of genetics. In forming its opinions, the Committee had taken evidence from, amongst others, a delegation from the Association of British Insurers.

3.7 The report acknowledges that an individual with an unfavourable test result has an incentive to take out life insurance and recognises that current practice of insurers in seeking disclosure of test results is to avoid such adverse selection.

3.8 The Committee accepted that the insurance industry has, collectively, tried to deal with genetics in a responsible way but, nonetheless, registered a number of concerns:

- The Committee expressed the view that the industry had reacted with "undue complacency" in preparing for the potentially profound effects that the development of genetic science could have in the relatively short term. It recommended that the industry be given a year in which "to propose a solution acceptable to Parliament" with the threat of legislation should it fail to do so.
- that insurance implications would deter people from taking genetic tests and, by so doing, hinder research;
- that there were doubts about insurance companies abilities to interpret the results of tests, particularly in the early stages of development of genetic tests when their implications are unclear or unproven;

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- that, if one insurance company attempted to "cherry pick" by offering preferential rates to those with good genetic profiles, others would be forced to do so.

3.9 The Government of the day did not entirely accept these recommendations and, in its response, expressed the view that legislation would not be appropriate now or in the foreseeable future. Nor did it agree to the imposition of a deadline for the development of a solution to the use of genetic information. However, the Government encouraged the industry to enter into dialogue with geneticists with a view to the development of an industry-wide code of practice and hoped "to see substantial progress within 12 months".

3.10 The industry's response took a little longer than 12 months to emerge and when it came, in February 1997, was in the form of an ABI Policy Statement. The essence of this Statement was that for a two-year period:

- the ABI reaffirmed that its members would not require applicants to undergo genetic testing on application for life insurance;
- no account would be taken of the results of genetic tests, which may have been taken for other purposes, in the underwriting of new life insurance policies of sums assured up to a total of £100,000 which are directly linked to a new mortgage.
- Notwithstanding the previous undertaking, applicants would be expected to disclose the results of any earlier genetic test.
- Individual companies were left with the freedom to decide whether or not they wished to extend the concession to other types of policies.

3.11 There is little doubt that the impact of the ABI Statement was diminished by the delay in its emergence and the thin veneer of unanimity amongst the membership.

3.12 Nevertheless, the spectre of legislative interference in insurance affairs has, so far, been somewhat remote although the high profile of the genetics issue could mean that immunity from legislation could prove to be a fragile thing. Political opinion has an understandable tendency to respond to public pressure. As Theodore Roosevelt, who presumably knew about these things, was once heard to observe; "The successful politician is he who says what everybody is thinking most often and in the loudest voice." Given that we have had a change of government it is not beyond the bounds of possibility that the temperature of the political debate could be raised.

3.13 The next catalyst could prove to be a report from the Insurance Group of the Human Genetics Advisory Commission. The Human Genetics

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Advisory Commission was established as an independent group to advise both Industry and Health Ministries on developments in human genetics. The Insurance Group has been consulting with experts from within and without the insurance industry and is expected to publish its findings towards the end of 1997.

3.14 Political pressure could yet come in the form of European legislation. In February 1992, The Committee of Ministers of the Council of Europe adopted the Recommendation on Genetic Testing and Screening for Health Care Purposes. Principle 7 of this recommendation prohibits insurance companies from requiring genetic tests, or from enquiring about results of previously performed tests, as a pre-condition of an insurance policy.

3.15 Belgium was the first country to incorporate this recommendation into law. Interestingly, the prohibition is upon the *transmission* of data rather than the use of data. As a result, the onus is upon the applicant to refrain from declaring genetic data, even if it would be to his or her advantage to do so.

3.16 The Committee of Ministers has recently adopted the final version of the Convention on Human Rights and Biomedicine. The convention is now open for signature and any member state which ratifies this convention will be required to adopt its provisions into national law. Article 11 of the convention states: "*Any form of discrimination against a person on the grounds of his or her genetic heritage is prohibited.*"

3.17 Insurance, by its very nature, is discriminatory. It is therefore expected that, in due course, an explanatory report will be produced which, amongst other things, will explain the intended meaning of the word "discrimination". The supplementary report could possibly exempt insurance altogether or permit classification which is equitable or based upon reliable statistical data.

3.18 Article 12 goes on to say:  
*" Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate counselling."*

3.19 France, Austria, Norway and the Netherlands are all countries which have adopted, either voluntarily or as a result of legislative action, bans upon the use of genetic tests for insurance purposes.

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- 3.20 France adopted a law in 1994 which limited the use of genetic tests to medical purposes or scientific research. Concurrently, the French Federation of Insurance Companies announced a 5-year voluntary ban on the use of genetic information in the assessment of insurability.
- 3.21 In Austria, legislation bans the use of genetic tests by employers or insurers.
- 3.22 A law introduced in Norway in 1994 restricted the use of genetic tests to medical diagnostic and/or therapeutic purposes. It also prevents anyone from enquiring whether a genetic test has been performed other than where symptoms are present.
- 3.23 The Netherlands first introduced a 5-year moratorium in 1990. This has recently been extended indefinitely subject to a new provision that it can be cancelled with a 2-year notice period. Under this moratorium, insurers have agreed to abstain from seeking genetic tests and from using genetic information in the assessment of policies below NLG300,000 (approximately £100,000).

#### **4. Insurance Issues**

- 4.1 There is a common perception that the science of genetic testing will present the insurance industry with a powerful tool which will be used to identify those with a favourable genetic profile. These fears may have been fuelled by moves in some markets - particularly in the United States - towards 'preferred underwriting' approaches through which some companies have sought to segment the insured population into smaller, more tightly homogeneous units.
- 4.2 To some, the issue is quite fundamental. For them there is a firm belief that it is intrinsically wrong for insurers (or indeed others) to discriminate against those who have a genetic abnormality.
- 4.3 These concerns raise questions about the role which insurance should play in our society and the extent to which a private insurance industry can or should be a vehicle for the expression of public policy. In this section we examine the issue of access to insurance in the context of a voluntary private insurance sector. This is a discussion which has wider relevance but the debate will focus on the implications which are raised by the prospect of the increasing use of genetic testing in clinical practice.

*Genetic science and its implications for life insurance****The franchise to insurance***

- 4.4 Professor Wilkie (1996) recounts the history of the way in which risk classification practices have emerged. The current reality is that life insurance is accessible to a vast majority of the population. Claims are often made that 95% of life insurance applicants are accepted on 'ordinary terms'. However, the logic of this statement, although well understood by those in the industry, may not convey an entirely accurate impression to others. 'Ordinary terms' does not mean the same terms for all 95%; nor even the same terms for people of a similar age. It is more likely to imply terms which are standard for the age, sex and smoking status of the insured.
- 4.5 Furthermore, this does not imply that 95% of the population will enjoy insurance cover on normal terms since the very existence of a selection procedure means that some people in poor health will be discouraged from applying.
- 4.6 There seems little reason to suppose that the proportion of the population that will be accepted for insurance will suffer as a result of genetic advances. History has demonstrated that advances in medical knowledge have consistently contributed to improvements in longevity and a broadening of access to life insurance. The development of genetic science will not, of itself, arrest this trend. It is more likely that a better understanding of the interaction between genetic makeup and environmental influences will, over time, improve the effectiveness of health management and, as a result, lead to further improvements in mortality. This being so, there is a clear coincidence of interest between life insurance providers and society as a whole in the successful development of genetic technology.
- 4.7 Equally, it would be unduly alarmist to suggest that improvements in the ability to detect disease would result in the emergence of an 'insurance underclass'. Generally advances in diagnosis have led to better treatment and improved understanding of the risk factors. As a result, individuals who might previously have been declined or severely rated are more likely to be accepted into the insurance pool. Historically this has been the case - for example in the underwriting of diabetes and of applicants with raised blood pressure.
- 4.8 However, advancements in the diagnosis of life threatening conditions do not always go hand-in-hand with improvements in the timeliness or quality of treatment. That is not to say that such advances have no value. Their justification may be found in their epidemiological role if not in their clinical value to the individual. But, where the development of diagnostic techniques precedes advances in treatment, there is a danger that the newly acquired knowledge may affect the terms on which insurance is available. This may be so even where the individual is showing no physical signs of disease.

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4.9 One may draw examples from the tests for monogenic disorders. Such tests will be justified, even in the absence of parallel improvements in treatment, because of the implications for family planning. The same was also true of testing for HIV infection. Before multi-drug thereapies became available, the result did not change the outcome for the individual but the process of testing was clearly in the wider public interest.

***Genetic profile as an underwriting tool?***

4.10 The link between genetic profile and prediction of disease is by no means straight forward - even with many of the monogenic disorders. It remains a fact that we know little of the all-important interaction between multifactorial genetic defects - defects which might affect more than one gene - and other behavioural and environmental factors. As a result, it may be sometime before specialists in the field of genetics can predict the impact of specific genetic defects on longevity with confidence.

4.11 The equivocal value of the knowledge that might be gained means that, as yet, genetic testing appears to have little value as a tool of the life insurance underwriter. Other tests for predisposition to many of the common disorders are more readily available and better understood - blood tests, urinalyses, blood pressure readings etc. Even if that were not the case, it would be wise to heed the words of The Rt. Hon Lord Griffith (1992) "Unless there is any compelling necessity associated with the very preservation of society, I do not think that any pressure should be put upon any person to submit to a genetic test".

***Disclosure of information***

4.12 However, one must draw a distinction between the active use of genetic tests as a routine underwriting tool and the more passive requirement for disclosure of the results of tests which have been conducted for other purposes. It is the question, whether or not applicants should be absolved of any requirement to disclose the results of any such test, which poses the more pressing debate.

4.13 The concept that individuals might, with legislative sanction, withhold information which they know or suspect to be material to their risk raises interesting philosophical issues. The inherent inequality of information between insured and insurer about the nature of the risk being run meant that insurance developed as a contract of *utmost good faith* with an obligation on each party to disclose relevant information. As pointed out by Wilkie the principles of utmost good faith have been amended to put an onus on the insurer to give guidance to the applicant on what constitutes material information. Nevertheless, explicit, or even tacit, recognition of the right to

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withhold information would strike at one of the core principles upon which private insurance is based.

4.14 Lord Griffith is unequivocal about the legal position; "If an applicant for insurance has undergone a genetic test which reveals that he suffers a hereditary disorder threatening his health he must disclose it to the insurance company for it manifestly affects the risk he wishes to insure against."

4.15 Dr O'Neill (1996) argues that, notwithstanding the legal position, it is wrong, in principle, to 'discriminate' against those who are found to have a genetic abnormality. The arguments are predicated on the principle that individuals should have the right of access to life insurance if the causes of their increased risk are not of their making. In so far as none of us has control over our genetic make-up it is clearly the case that no fault can be ascribed to those who have a 'genetic disease'. But, it is also the case that, with the exception of willing exposure to known risks, such as smoking, no one can be held responsible for the causes of his own mortality.

4.16 Arguments are also put forward that the need to disclose information about genetic tests to insurers will discourage individuals from taking tests and inhibit the development of the science. However, it is difficult to untangle the extent to which these fears are unprompted or to which they are a consequence of the counselling given. Those who argue the deterrent factor might say the same of a range of other diagnostic tests which *could* have an impact on insurability. It is possible that the concerns about disclosure of genetic test results is a matter of unfamiliarity and lack of confidence in the insurers ability to understand their significance. Perhaps the same may have been said of other tests, such as blood pressure tests; ECGs; blood tests etc, in the early years of their use. There is no suggestion that the need to disclose the results of such tests now has a deleterious effect upon their use in clinical medicine.

*Questions of access and equity*

4.17 Wilkie draws a distinction between *mutuality*, where individuals contribute to the pool through a premium which relates to the risk they bring, and *solidarity* where the correlation between premium and risk no longer applies. In this case, premiums may be equal, regardless of risk, or assessed according to ability to pay.

4.18 The foundations of private insurance are rooted firmly in the pooling of risks but, at the same time, underpinned by attempts to achieve broad equity, in terms of equivalence of value, between cost and benefit. To this extent, life insurance takes on the characteristics of mutuality



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- 4.19 To support this system, insurers adopt the concept of risk classification through which individuals are categorised in broadly homogeneous groups. In motor and personal lines property insurances, the subdivision of risks has been refined to take an increasing range of factors into account. In life assurance, by contrast, the vast majority of risks are now classified by the three factors of age, sex and smoking status. For the remainder, some further adjustment in premiums may be required to reflect additional risks posed by health, occupation or leisure pursuits.
- 4.20 It is accepted that the 'equality of value' is by no means perfect and to that extent there are some concessions to 'solidarity'. The 'ordinary rates' group may encompass some quite wide variations in expected mortality. Nevertheless, the aim is to limit overt cross-subsidy between individuals presenting significantly different risk profiles. Discrimination *between* - as opposed to *against* - applicants is part and parcel of the risk evaluation process. Let us draw once again upon the wisdom of Lord Griffith: "The essential skill of an insurer is the assessment of risk to the insured. It will defeat the social purpose of insurance if this risk cannot be reasonably accurately assessed."
- 4.21 Dr O'Neill sees it differently. She argues that whilst the process of risk classification can be justified in the case of motor insurance the same arguments do not apply to life insurance. She points out that, in motor insurance, the individual can exercise control over the risk factors and, furthermore, that it is socially acceptable for bad drivers to be penalised (cf 4.15).
- 4.22 As one moves to extremes of segmentation, the principles of risk pooling and those of equality of value become somewhat at odds. The more refined risk classification becomes, the more limited will be the opportunities to spread risk.
- 4.23 It is open to debate whether, in fact, a detailed segmentation of risk, whether through the use of genetic information or otherwise, is in the interests of the industry as a whole. An individual insurer may gain some 'first mover' advantage through a more refined risk classification process which allows it to compete more effectively for the better risks. However, any significant success is likely to force an early competitive response which will make that initial advantage short lived.
- 4.24 In the process the industry may turn its back on a significant area of opportunity. With pressures upon the public purse there is an opportunity for the industry to present itself as a custodian of private welfare provision. Such ambitions are unlikely to be realised if 'cherry picking' - and in particular,

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'cherry picking' on the basis of genetic information - is seen to be the norm for the industry.

4.25 It is by no means axiomatic that a system of insurance must necessarily be based upon assumptions of equality of value. The *aggregation* of risks is consistent with the principles of risk pooling although, the greater the heterogeneity of risks, the further one moves towards to the principles of solidarity. A system which grants equality of access can work satisfactorily in circumstances where there is compulsion to participate. The system can also operate where there is consensus amongst the insureds that the cross-subsidy is reasonable or where there is ignorance of the level of cross-subsidy involved. The crucial issue is that those who are, in effect, funding the subsidy should remain motivated to join the insurance pool.

4.26 Dr Robert Pokorski (1997) observes that an insurance company could insure every one who passed by a designated point so long as the practice did not become public knowledge. It is the fact that purchasing decisions are not entirely random that makes some form of screening a necessity.

4.27 The Friendly Society movement thrived without strict adherence to principles of solidarity. However, the community of interests which underpinned their existence finds less ready acceptance amongst a generation that has grown up with the Welfare State and become unused to the concept of mutual self-help as a means to provide a safety net.

4.28 Whilst the status quo is by no means the only possible model on which insurance principles can be built, it is difficult to see how equality of access can sit comfortably with a system of insurance which is both private and voluntary. Automatic rights of access would inevitably bring changes in buying behaviour, both in the timing of purchase and the amount of insurance bought. These would have a fundamental impact upon insurance costs - involving increases for which the only source of funding would be other policyholders. The magnitude of the cross-subsidy required would lead to a spiralling of costs as those in poor health would have a greater propensity to buy life insurance protection whilst healthy lives would have little incentive to remain in the insurance pool. Indeed there would be little incentive for anyone to buy full life insurance protection until the first symptoms of malaise are felt. Up to that point accident cover would suffice.

4.29 Thus it would seem that a voluntary system can only coexist with universality of rights of access if the cross-subsidies are funded from a source outside of the insured population. Even governments might balk at underwriting such an open-ended commitment.

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***Genetic disadvantage - a case for special treatment?***

4.30 However, in the context of this paper, our concern is not merely with the merits or problems of universality of access but whether a voluntary system of insurance can operate equitably without access to genetic information. The fact remains that the present level of knowledge is such that there are only a very limited number of genetic disorders which, in the absence of other risk factors, would warrant denial of insurance or substantial rating. But, is there a case for a guarantee of special treatment?

4.31 As we shall demonstrate in the next section, it may be possible to grant *limited* rights of access to the group of asymptomatic adults who suffer from certain of the genetic disorders. Their numbers are sufficiently small in comparison to the broader policyholder base that the effect of the cross-subsidy will not be apparent or too unpalatable. However, there must be doubt whether, in a private system of insurance, it would be equitable or sustainable to guarantee access to insurance to the 'genetically' disadvantaged whilst denying a similar privilege to those suffering from a clinically diagnosed condition. Some argue that there is difference in that the former group are asymptomatic and merely have a predisposition to disease whilst the latter group may be exhibiting real signs of illness. However, it remains the case that each might have a similar predisposition to claim and it is this that is the critical criterion. Would it be right or logical, for example, to guarantee insurance to an asymptomatic 40 year old with the Huntington gene whilst denying the same cover to someone of a similar age with HIV or a history of heart disease?

4.32 Furthermore, there seems little justification in equity if access to insurance depends upon having a politically acceptable form of disadvantage. There is another group of 'disadvantaged' who also have need to make provision for their dependants and who may find themselves excluded from the insured population. These are the economically disadvantaged - those who cannot afford the premiums. It may well be the case that someone with a genetic disadvantage may be better able to pay an 'actuarially appropriate' premium than someone of lesser means. Yet, clearly, the economically disadvantaged can only be brought within the insurance net in a system based on the principles of solidarity.

***Questions of definition***

4.33 The granting of special treatment on the grounds of genetic disadvantage has a further and perhaps more fundamental difficulty which relates to the matter of definition. The perception of genetic disease is generally one of disease acquired through inherited genes. It is now recognised that many more conditions than was once thought to be the case have a genetic component. Furthermore, it has come to light that most non-hereditary diseases are also linked to genetic mutations. In the case of the

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acquired diseases, only a limited number of cells may be affected but, nonetheless, the cause may reasonably be described as being 'genetic'. What is of particular concern is the likelihood that genetic testing techniques will be used increasingly in their diagnosis.

4.34 As we have seen, there are undoubtedly those who would seek, not only to ban insurers from seeking genetic tests, but also to bar their access to results of tests that have been conducted for other purposes. It is clear that the protagonists of the case, either for or against legislation or codes of practice, need to have a very clear understanding of what is included in their interpretation of a genetic test. Unless great care is exercised, any such barriers could have consequences of much greater significance than was intended. This will be particularly true if, as seems likely, genetic testing assumes an increasing role in diagnostic medicine. It would be a pyrrhic victory indeed if protection intended for the few were to make access to insurance more difficult or less affordable for all.

## **5. Towards a Practical Response**

5.1 In the previous section we discussed some philosophical issues relating to the rights of access to insurance which would be raised by the increasing availability of genetic tests. However, the concerns about the implications of insurance for the development of genetic testing are not limited to calls for rights of access but will also include:

- fears amongst health professionals that the need to disclose genetic testing information in insurance applications will discourage the development of genetic testing.
- concerns about the confidentiality of genetic information.
- concerns about the ability of industry practitioners to interpret genetic test results

5.2 The insurance industry has its own concerns which have contributed to the apparent difficulty the industry has had in finding common ground with its critics. These concerns are:

- concessions made now could become precedents, in a field which is changing rapidly, before the full implications can be properly evaluated.
- pressure will be exerted to extend any concessions beyond the strict confines of life insurance and into critical illness and other forms of disability or health coverages.

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- a backlash from other interest groups who might argue equal rights to such a concession.
- 5.3 What practical steps might be taken to mitigate some of the public concerns without causing material damage to the integrity of the selection process or to the prudent operation of a sound insurance industry? Pokorski (1997) has argued strongly that what is at stake is not just a question of extra costs being small or large, tolerable or intolerable; it is the very scientific principle of voluntary insurance. However, it could be argued that if extra costs are regarded as containable, the purity of the principle will not be allowed to over-ride social concerns; it might therefore be unfortunate if matters were pushed to a conclusion in the context of life insurance alone. In this context, the lack of quantitative work, especially in the areas of health and long term care insurance, should be of concern.
- 5.4 There is consensus within the industry that insurers should not initiate the use of genetic tests as a means of screening proposers. It is likely that unanimity on this issue will ensue unless:
- over-the-counter tests become freely available which makes the industry open to non-disclosure or,
  - a substantial new entrant was to come to the market with the intention of 'cherry-picking' on the basis of genetic screening.
- 5.5 In either case insurers might feel compelled to respond to protect their positions.
- 5.6 One should not lose sight of the fact that, other things being equal - buying behaviour, access to traditional forms of medical and financial evidence - genetic science does not, of itself, increase the risk. The risk is of anti-selection - the risk that, human nature being what it is, buying behaviour will be influenced by the knowledge that genetic testing can bring.
- 5.7 The greater challenge is to find ways in which the need for disclosure of tests, performed for other purposes, might be limited. Various solutions have been proposed, but in the absence of much quantitative work, these run the risk of only leading to confrontations between different sets of principles.
- 5.8 At one extreme, some would argue that private insurers should not have to give way; they operate on the basis of mutuality and it would be a fundamental error (indeed, a scientific error) to make them relinquish that principle. Pokorski (1997) is one who defends the supremacy of the scientific

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principle of insurance, and the apparatus that comes with it. This is, of course, quite different from saying that private insurers could not operate on the basis of solidarity within a different framework, such as compulsory insurance.

5.9 At the other extreme, some would argue that principles of justice are supreme, and should be upheld over principles which tend to favour the interests of corporations, even such scientific principles as those that underpin insurance. See Moultrie & Thomas (1996) for a clear example of such a view, or Barr (1996) for some suggested consequences for the conduct of insurance business. These principles weigh most heavily in the provision of services which might be regarded as basic to a decent life; health care, disability income and long term care.

5.10 In the middle are those who are pulled in both directions. It is hard to argue with principles based on a strong sense of justice, but it is also hard to argue with science. To these individuals, the question is a more pragmatic one, of where to draw the line. The application of the principles of insurance, in practice, is far from exact; there is therefore little to be gained, and much that might be lost, by mounting a ferocious defence of (for example) the "right to underwrite" unless there is a clear risk of an intolerable outcome. If it is likely that the costs of some departure from the pure scientific principle are modest, then the question becomes that of seeking practical means to meet, and to allocate, these costs; for example, by various forms of retrospective pricing. Barr recognised that, if concessions are to be made to those who would otherwise be subject to rating or declinature, the cost must be borne by others, for example:

- by spreading the cost amongst the policyholders of the insurance company concerned
- by pooling risk across the policyholders of all insurance companies
- by placing the cost burden on taxpayers generally
- by the individual bearing part of the additional cost with the remainder being spread in one of the above three ways.

5.11 The extent to which any of these provides a workable solution will depend upon the safeguards that can be built in to limit the quantum of the subsidy required - which, viewed from the opposite perspective, will limit the value of the concession. But, there must come a point at which departures from the scientific principle are so significant that a stand ought to be made (recall that in 1897, the State of Indiana tried to incorporate into law some mathematical constructions which yielded a value of pi of 9.2376! (Beckman, 1971)). One danger of the pragmatic approach is that it could lead to a slippery slope; once a principle has been conceded where there is relatively

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little risk, it might fail as a defence where there is much more risk (Pokorski, 1997). The countervailing danger is that insurers' natural desires to remain in business lead them to disprove their own warnings of dire consequences, with obvious effect on their credibility.

5.12 At present, some UK life insurers have announced that they do not think that genetic testing will have a significant impact on life insurance and have eschewed any use of genetic tests. Some quantitative work, described later, tends to the same conclusion. No health or long term care insurers, as yet, have followed suit, and it is unlikely that any will. Also, moratoria have been adopted by life insurers in several countries, mostly depending on some maximum benefit. The pragmatist's line, therefore, seems to be drawn somewhere between life insurance and other forms of insurance.

5.13 In the UK, legislators and others have acknowledged the principle of private, mutual insurance, and have accepted that adverse selection is a real concern. There is, however, very little evidence of how much it would cost life insurers, and even less evidence of the cost to health and long term care insurers, so it is unclear how heavily this will weigh in the scales, under pressure to shift welfare costs. The same lack of evidence makes it difficult to assess the practicality of any of the suggested means of controlling or spreading any subsidies, and so does little to foster a meeting of minds.

5.14 Macdonald (1997), in a paper to a joint meeting of the Royal Society and the actuarial profession in the UK, developed a Markov model to illustrate the possible impact of adverse selection on life insurance. In all cases studied, the most significant impact on costs is where those anti-selecting effect policies with higher than average sums assured. For example, this factor proved to be of greater significance than the propensity to anti-select.

5.15 Macdonald acknowledges that his results are based on highly uncertain parameters and must therefore be taken as being illustrative of relativities and rough orders of magnitude rather than as an absolute statement of costs of anti-selection. However, a model of severe late-onset monogenic disorders suggest that, even with very high levels of adverse selection, the cost of including such lives in the insurance pool would be equivalent to an increase to the standard premium of between 10 and 30%, provided that the amount of insurance coverage granted is no greater than the average.

5.16 His results confirm, what may be deduced from general reasoning, that the closer the 'adverse selector' is to the likely age of onset of disease, the greater is the cost. He therefore questions whether it would be fair for

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someone who obtained genetic information at the age of 20 to defer a 'right to insure' until say, the age of 40.

5.17 Normal rules of elasticity of demand suggest that an increase in price will bring about a reduction in demand which, in practice, is likely to affect the number of healthy lives seeking insurance. This is a variable which is not built in to the model. However, if one takes the view that demand for term cover is relatively inelastic over the range hypothesised by Macdonald, this factor can be ignored.

5.18 At first sight an increase of the order 10% might appear to be a manageable and reasonable price to be paid by the many to deliver a measure of financial security to the few who might otherwise have difficulty in obtaining insurance. However, one must remember that those susceptible to late-onset monogenic disorders are a limited subset of those with some form of genetic abnormality and certainly very limited subset of the total population that might have difficulty in obtaining insurance. The cost of cross-subsidy would escalate if concessions to prudent rules of underwriting evidence were available to a wider population.

5.19 It is important to remember that Macdonald was modelling the impact of adverse selection upon life insurance. The knowledge which an individual might gain regarding his or her susceptibility to specific diseases means that the results of genetic tests would be indispensable to insurers of critical illness policies and of certain other health products.

5.20 The Association of British Insurers has been the focal point for the genetics debate by the life insurance companies over the last two years. Professor Sandy Raeburn, a leading geneticist was appointed the ABI's Genetic Adviser in October 1996. The key development was a position paper 'Developments in Genetic Science and the Insurance Industry' circulated in January 1997.

5.21 This paper proposed three options:

- Option 1 involved no concession but instead reaffirmed the policy of the industry not to require individuals to take genetic tests as a condition for insurance. Any genetic tests already taken were to be disclosed on any application for insurance.
- Option 2 contained a limited concession, insurers would not use the results of genetic tests already undertaken if the insurance was linked to a mortgage and the sum insured was limited to £75,000.



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- Option 3 was a broader concession; insurers would not take account of the results of any genetic test in deciding the terms and conditions of insurance provided the proposer was not seeking unreasonable levels of life insurance in relation to his or her circumstances.

5.22 All three options would still require the full disclosure of genetic test results but options 2 and 3 would disregard the results. The rationale for this was three fold. First, it upheld the principle of 'utmost good faith'. Second, it would enable the collation of information on proposals where genetic test results are given. This data could give an indication of the cost to the industry of any concession agreed. Third, it avoids the difficulty of explaining what does and what does not have to be disclosed.

5.23 Such an approach would leave unanswered concerns regarding the confidentiality of genetic information. There may also be room for dispute where the genetic test result confirms information gained from normal clinical evidence. In these circumstances, it may be difficult to satisfy the applicant that the results of his genetic test have been ignored.

5.24 Considering option 2 in more detail, what are the merits of this approach?

5.25 It avoids the major risk from adverse selection by linking the concession to both the presence and the quantum of the mortgage.

5.26 An asymptomatic individual with a positive test is unlikely to take out a significantly higher mortgage than he would otherwise had done - particularly as mortgages will be limited by income.

## **6. Summary and Conclusion**

6.1 Genetic science is driven by the prospect of advances in knowledge and medical care, both positive forces. Unfortunately, insurance is widely seen as an impediment, holding back applications because of fears about the consequences for a 'genetic underclass'. It is important that the actuarial profession, the insurance industry and other interested parties reach methods of dealing with genetic information that are practical and acceptable to all parties.

6.2 First, insurers must understand the implications of genetic disorders. There range from monogenic inherited disorders with very specific outcomes (such as Huntington's disease) or with variable outcomes (such as cystic fibrosis) through polygenic disorders which represent one of many

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influences on the outcome, to non-inherited somatic disorders (such as lead to many cancers).

6.3 Striking a balance between workable insurance practice, in which adverse selection is controlled, and acceptable public policy, in which discrimination is not extended unreasonably, will not be easy. At one extreme is the view that the scientific principle of insurance should be upheld, if the purchase of insurance is in any way voluntary. At the other is the view that insurance principles cannot override natural justice. A pragmatist might acknowledge the strengths of both arguments, and ask how much any departure from the unfettered 'right to underwrite' might cost. Little information is available to help, as yet. One study, confined to life assurance, suggests that the costs would not be large provided some limits were placed on the sums assured that could be obtained under limited underwriting. No comparable studies have been carried out for health or long term care insurance, where greater problems might be expected.

6.4 More research is needed urgently into all aspects of insurance-buying behaviour and adverse selection, as well as the implications of the purely statistical knowledge to be gained from genetic tests. Such research will not be easy, and might require the insurance industry to look beyond the statistics it gathers in the ordinary course of its business, but, in its absence, policy-makers are likely to be more strongly swayed in directions which appear to be supported by relevant research.

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MUI OOM/31/2

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17 May 2005

Associate Professor Terry Kaan  
 Chairman  
 Human Genetics Subcommittee  
 Bioethics Advisory Committee  
 20 Biopolis Way, #08-01 Centros  
 Singapore 138668  
 Fax : 6478 9581

Dear Prof. Terry Kaan,

**REQUEST FOR FEEDBACK ON CONSULTATION PAPER**

We refer to your letter of 4 April 2005 to Haji Mohd Alami Musa, President Muis.

2 Our general view is that the paper is well balanced and fair in its assumptions and recommendations. We agree that proper legislation should be put in place to safeguard against any misuse and abuse.

3 Looking at the specifics of the paper, we further feel that there may be some issues that may have connection with the application of our Islamic Law, which may require our Fatwa (Legal) Committee to issue its opinion on them, such as :

3.1 Recommendation 7:

“Genetic test results should not be disclosed to third parties, including employers and insurers, without the free and informed consent of the individual”.

Concern: whether immediate family who have interest such as spouses and siblings have a right to be informed.

3.2 Recommendation 12:

“Preimplantation tissue typing, whether as a sole objective or in conjunction with preimplantation genetic diagnosis to avoid a serious genetic disorder, is permissible but should be licensed and evaluated on a case-by-case basis”.



Concern: The matter requires religious opinion from Fatwa Committee

3.3 Recommendation 14:  
“Prenatal genetic diagnosis should be voluntary, conducted with informed consent and with appropriate pre- and post-test counselling. The prospective parents’ choice of whether a genetic disorder warrants a prenatal genetic diagnosis or termination of the pregnancy should be respected”.

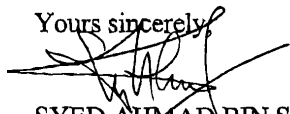
Concern: This may have bearing on the Islamic’s view on abortion.

3.4 Recommendation 17:  
Presymptomatic testing should be available for adults at risk who request it, even in the absence of treatment, after proper counselling and informed consent”.

Concern: There could be religious and social implications, such as on marriage.

5 We are therefore convening the Fatwa Committee to deliberate the above issue to offer its religious opinion on them. We expect to have them in a months’ time and will revert to you soon after that.

Yours sincerely,



SYED AHMAD BIN SYED MOHAMED  
for SECRETARY  
MAJLIS UGAMA ISLAM SINGAPURA

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16 June 2005

Associate Professor Terry Kaan  
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Dear Prof Terry Kaan,

**REQUEST FOR FEEDBACK ON CONSULTATION PAPER**

Further to our letter of 17 May 2005, we are pleased to enclose herewith the opinion of MUIS Office of Mufti which has consulted the views from Muis Fatwa Committee on the Consultation Paper on Ethical, Legal and Social Issues in Genetic Testing and Genetics Research.

2 We have no objection for the said opinion to be published by the Bioethics Advisory Committee.

Yours sincerely,

Syed Ahmad Bin Syed Mohamed  
for Secretary  
Majlis Ugama Islam Singapura

BACHumanGeneticsFatwaOOM



**Respon Jawatankuasa Fatwa  
Terhadap Saranan Jawatankuasa Penasihat Bioetika Mengenai Ujian Baka**

**Pendahuluan :**

Jawatankuasa Fatwa mengalu-alukan setiap perkembangan ilmu pengetahuan secara khusus dalam bidang sains hayat. Pendekatan ini diambil atas dasar bahawa agama Islam adalah agama yang bertunjangkan ilmu pengetahuan. Selama mana ilmu tersebut tidak menyalahi dua syarat di bawah ini, maka ianya dibolehkan iaitu :

- i. Ianya tidak ada tegahan daripada Syara' melalui nas Al-Quran atau As-Sunnah,
- ii. Ianya tidak mendatangkan mudarat kepada manusia.

Apa jua ilmu dan kajian yang mendatangkan manfaat kepada masyarakat Islam dan menolak keburukan daripada mereka, di situlah terletak syariat Allah. Imam Ibnu Al-Qayyim berkata:

فإن الشريعة مبناهما وأساسها على الحكم ومصالح العباد في المعاش والمعاد، وهي عدل كلها، ورحمة كلها، ومصالح كلها، وحكمة كلها، فكل مسألة خرجت عن العدل إلى الجور، وعن الرحمة إلى ضدها، وعن المصلحة إلى المفسدة، وعن الحكمة إلى العبث، فليست من الشريعة...<sup>1</sup>

Ertinya : “Maka sesungguhnya syariat itu terbina atas asas hukum dan maslahat manusia di dunia dan akhirat, Syariat itu keseluruhannya adalah adil, keseluruhannya adalah rahmat, keseluruhannya adalah maslahat, dan keseluruhannya adalah hikmah. Maka setiap masalah yang keluar dari keadilan kepada kezaliman, dari rahmat kepada sebaliknya, dari maslahat kepada keburukan dan dari hikmah kepada sia-sia, maka masalah itu bukan daripada Syariat...”<sup>1</sup>

Dr Ali Qurra Daghi di dalam artikel beliau mengenai perubatan baka juga berkata :

<sup>1</sup> Ibn al-Qayyim al-Jawziyyah, *I'lām al-Muwaqqi'in*, jilid 3 ms 797, Maktabah Nazar Mustafa al-Baz, Makkah – Riyadh.

فالشريعة الإسلامية مبنية على تحقيق المصالح ودرء المفسد، فأينما تكن المصلحة الحقيقية فثمَّ شرع الله تعالى. فالشريعة عدل كلها، ورحمة كلها، وخير كلها، فأى شيء فيه الضرر والقسوة، أو الظلم والجور، أو المفسدة والمضرة، فليس من هذه الشريعة.

Ertinya : “Syariat Islam terbina atas memastikan wujudnya maslahat dan menolak keburukan. Maka di mana sahaja terdapat maslahat yang pasti, maka di situlah terletaklah syariat Allah Ta’ala. Syariat itu keseluruhannya adalah adil, keseluruhannya adalah rahmat dan keseluruhannya adalah kebaikan. Maka apa-apa perkara terdapat di dalamnya bahaya, kekerasan, kezaliman, penyelewengan, keburukan dan kemudaratan, maka itu semua bukan daripada Syariat.”<sup>2</sup>

#### **Pandangan Jawatankuasa Fatwa Terhadap Kertas Saranan Jawatankuasa Penasihat Bioetika Mengenai Isu Etika Ujian Baka.**

Jawatankuasa Fatwa telah berbincang dan meneliti kandungan kertas saranan mengenai isu “Etika, Perundangan dan Sosial dalam Ujian dan Kajian Baka” (*Ethical, Legal and Social Issues in Genetic Testing and Genetics Research*) yang disediakan oleh Jawatankuasa Penasihat Bioetika, Singapura (*The Bioethics Advisory Committee*). Hasil daripada perbincangan tersebut Jawatankuasa Fatwa berpendapat bahawa secara dasar semua 24 rekomendasi yang terkandung di dalam kertas saranan rekomendasi etika perubatan ujian baka (*Genetic Testing*) boleh diterima kerana ianya tidak bercanggah dengan prinsip-prinsip Syara’ dan al-Urf. Ianya merupakan isu teknikal yang tiada menyentuh hak individu dan tiada pula unsur paksaan. Sehubungan dengan itu, Jawatankuasa Fatwa secara dasar berpendapat bahawa ujian baka ini adalah harus.

Jawatankuasa Fatwa juga telah memberikan penekanan terhadap beberapa rekomendasi yang dirasakan ada kesan terhadap pandangan agama yang perlu diperincikan dan diperjelaskan lebih lanjut. Ianya seperti berikut :

#### **Rekomendasi 3 :**

<sup>2</sup> <http://www.islamonline.net/Arabic/contemporary/2002/07/article02.shtml>



Jawatankuasa Fatwa mengalu-alukan rekomendasi ini yang antara lain menekankan bahawa ujian baka harus dijalankan secara pilihan dan tiada unsur paksaan.

**Rekomendasi 5 :**

Jawatankuasa Fatwa juga sangat mengalu-alukan dengan kandungan rekomendasi ini yang menyatakan bahawa kedua ibu-bapa tidak digalakkan melaksanakan ujian baka untuk anak-anak mereka. Ujian baka tersebut diserahkan kepada pilihan anak-anak mereka setelah mereka sampai usia matang.

**Rekomendasi 7 :**

Saranan rekomendasi ini agar natijah atau keputusan ujian baka seseorang tidak didedahkan kepada mana-mana pihak ketiga juga disetujui oleh Jawatankuasa Fatwa.

**Rekomendasi 12 :**

Jawatankuasa Fatwa berpendapat bahawa melakukan salinan tisu bagi menghasilkan rawatan pada masa depan adalah sesuatu yang harus. Sehubungan dengan itu, contoh yang diandaikan bagi pasangan yang ingin mendapatkan anak kedua yang dihasilkan daripada salinan tisu bagi tujuan merawat penyakit anak pertama mereka adalah dibolehkan, ianya termasuk salah satu daripada bab ikhtiyar mencari rawatan. Namun, perlu diambil perhatian bahawa perlaksanaannya hendaklah tidak menimbulkan kemudharatan kepada yang terlibat.

**Rekomendasi 14 & 15 :**

Daripada rekomendasi ini, timbul pertanyaan tentang hukum melaksanakan Diagnosa Baka Sebelum Bersalin (*Prenatal Genetic Diagnostic*) untuk mengetahui kecacatan kandungan dan mengenalpasti penyakit serius. Jawatankuasa Fatwa dalam hal ini berpendapat bahawa secara dasar tiada halangan bagi setiap individu untuk menjalankan *Prenatal Genetic Diagnosis*. Sekiranya keputusan atau natijah *Prenatal Genetic Diagnosis* menjelaskan terdapat kecacatan ke atas kandungan atau menghidapi penyakit yang serius, maka Jawatankuasa Fatwa memberi saranan agar setiap individu Muslim

mendapatkan nasihat pakar agama bagi mengelakkan sebarang keputusan yang melanggar Aqidah, Syariat dan etika Islam yang bakal dibuat oleh individu tersebut.

**Rekomendasi 17 :**

Daripada rekomendasi ini, timbul pertanyaan hukum menjalankan Ujian Ramalan (*Predictive Testing*). Jawatankuasa Fatwa dalam perkara ini berpendapat bahawa secara dasar tiada halangan bagi setiap individu menjalankan *Predictive Testing*. Sekiranya keputusan atau natijah *Predictive Testing* menjelaskan terdapat penyakit yang tiada ubatnya di masa akan datang, maka Jawatankuasa Fatwa memberi saranan agar setiap individu Muslim mendapatkan nasihat pakar agama bagi mengelakkan sebarang tindakan yang melanggar Aqidah, Syariat dan etika Islam dan bagaimana menghadapi situasi ini menurut pendirian agama.

Nota disiapkan oleh,  
Kamaruzaman Afandi

Diedit oleh,  
Ustaz Mohd Murat Md Aris

10 Jun 2005

## **TRANSLATION**

### **THE FATWA COMMITTEE'S RESPONSE TO THE PROPOSAL BY THE BIO-ETHICS ADVISORY COMMITTEE ON GENETICS TESTING**

#### **INTRODUCTION**

The Fatwa Committee welcomes all advancements in knowledge, in particular, in the field of life sciences. The Committee adopts this view as Islam is a religion premised on knowledge. The knowledge is deemed acceptable so long as it does not violate two fundamental conditions stated below, namely :

- i. It (the knowledge) is not expressly prohibited by Islamic law through the injunctions in the Holy Qur'an or the Prophetic Tradition (As-Sunnah)
- ii. It does not cause harm to mankind

The Syariah of Allah resides in any knowledge and research that promotes welfare of the human society or eradicates harm from it. Imam Ibn Al-Qayyim said :

(Arabic Text)

“ The Syariah (Islamic Jurisprudence) is established on the basis of laws and in the promotion of the well-being of mankind in this world and the hereafter. The Syariah, in its entirety, is about the promotion of justice, blessing, benefit to mankind and wisdom. Therefore, solutions to problems that inhibit justice from being served, and that do not promote justice, the spirit of blessing, the needs and welfare of mankind and wisdom, do not constitute Syariah “<sup>1</sup>

Dr Ali Qurra Daghi in his article on genetic medicine also said :

(Arabic Text)

“ Islamic Syariah is established on the principle of ensuring the preservation of the well being of mankind and alleviation of evil. Therefore, wherever well being resides, that is where the Syariah resides. Syariah, in its entirety, is about justice, and brings forth blessing and goodness. Therefore anything within which lies

danger, compulsion, cruelty, deviation, evil and harm does not constitute the Syariah.”<sup>2</sup>

### **The Views of The Fatwa Committee In Respect of The Recommendations of the Bioethics Advisory Committee on the Issue of The Ethics of Genetics Testing**

The Fatwa Committee has deliberated and examined the contents of the recommendations regarding the “Ethical, Legal and Social Issues in Genetic Testing and Research prepared by the Bioethics Advisory Committee. As an outcome to their deliberation, the Fatwa Committee is of the view that, in principle, all the 24 recommendations contained in the medical ethics recommendations on genetic testing set out in the paper are deemed acceptable as they do not violate any of the principles of Syara’ (Islamic Laws) and al-Urf (customs). They constitute technical issues that do not infringe upon the rights of individuals and with no element of coercion present. Accordingly the Fatwa Committee opines that, in principle, genetic testing is permissible.

However, the Fatwa Committee wishes to emphasize a number of recommendations that it felt needed further explanation and elaboration as they may have religious implications. These are as follow:

#### **Recommendation 3 :**

The Fatwa Committee welcomes this recommendation which, among others, emphasizes that genetic testing must be conducted on a selective/ voluntary and not by coercion.

#### **Recommendation 5 :**

The Fatwa Committee also truly welcome the content of this recommendation which states that both the parents are not recommended to perform genetic testing for their children. The choice for genetic testing is left to the children themselves when they have reached a mature age/age of discretion.

#### **Recommendation 7 :**

The suggestion made in this recommendation that the result or outcome of a person’s genetic testing should not be disclosed to a third party is also concurred by the Fatwa Committee

#### **Recommendation 12 :**

The Fatwa Committee is of the opinion that tissue typing in order to produce remedy/treatment for the future is a permissible act. Accordingly, the example cited of a couple wishing to have a second child made possible through tissue

typing for the purpose of treating the disease of their first child is deemed acceptable as it falls into the category of efforts taken in finding a treatment. However, it must be noted that the procedure must not endanger the lives of parties involved.

**Recommendations 14 & 15**

These recommendations raise the question of the ruling governing Prenatal Genetic Diagnosis to ascertain defects during pregnancy as well as identifying serious diseases. The Fatwa Committee in this instance is of the opinion that, in principle, there is no objection to an individual to undergo Prenatal Genetic Diagnosis. If the result or outcome of the Prenatal Genetic Diagnosis clearly demonstrates that there are defects or serious disease to the pregnancy, the Fatwa Committee proposes that every individual Muslim should obtain expert religious counseling/advice to avoid making any decision which violates the Islamic Faith, Laws and Ethics that may be committed by the individual concerned.

**Recommendation 17 :**

**This recommendation raises the issue of the ruling governing Predictive Testing. On this subject, the Fatwa Committee is of the opinion that, in principle, there is no objection for every individual to undergo Predictive Testing. If the outcome or results of the Predictive Testing clearly show the presence of untreatable/ incurable diseases in the future, the Fatwa Committee proposes that every individual Muslim should obtain expert religious counseling/advice to avoid making any decision which would violate the Islamic Faith, Laws and Ethics and to be informed how to manage this situation from the religious perspective.**

**Notes prepared by:**

Ustaz Kamaruzaman Afandi

**Edited and approved by**

Ustaz Mohd Murat Md Aris

16 June 2005



12<sup>th</sup> May 2005

By Fax & Mail

Judge Richard Magnus  
Deputy Chairman  
**Bioethics Advisory Committee**  
20 Biopolis Way, #08-01 Centros  
Singapore 138668

Dear Richard

**A CONSULTATION PAPER  
ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND  
GENETICS RESEARCH.**

Thank you for your letter of 27<sup>th</sup> April 2005.

I am attaching herewith our comments on the above paper.

Please note that the following two members from NCCS will be attending the dialogue session on 17<sup>th</sup> May 2005 at 3.30 pm.

1. Dr Roland Chia (TTC)
2. Prof Soong Tuck Wah (Neuroscience Centre)

We apologise for the delay in submitting this information.

Yours sincerely

Rt Rev Dr John Chew  
President, NCCS

Encl.

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## **Feedback on the BAC Consultation Paper entitled, 'Ethical, Legal and Social Issues in Genetic Testing and Genetic Research'**

### **INTRODUCTION**

Genetic testing for diagnosis or research is an important advancement in science and medicine whose promises and perils we are unable to fully appreciate at this point in time. As such the National Council of Churches (NCCS) welcomes the efforts of the Bioethics Advisory Committee (BAC) to provide appropriate ethical guidelines to prevent abuse of the available technologies and misuse of the genetic information that is obtained by them. The NCCS therefore applauds that the BAC sees the need to ensure that 'genetic testing is conducted with due consideration and protection of the individual's interests and rights'.

Below are some brief comments on the Consultation paper entitled, 'Ethical, Legal and Social Issues in Genetic Testing and Genetic Research' prepared by the BAC. While the NCCS supports most of the stipulations delineated in the paper and broadly endorses most of the recommendations, we wish to highlight several major concerns and raise other issues that are not directly addressed.

### **SOME MAJOR CONCERNS**

#### *Preimplantation Genetic Diagnosis*

The main issue surrounding preimplantation genetic diagnosis (PGD) from the standpoint of the NCCS has to do with the nature of the early embryo or zygote. Here we reiterate our position that the zygote from the moment of conception is a human being bearing the image of God and must therefore be accorded the same respect due to all human beings. The zygote of human parentage is a human being because of its source, and because it cannot articulate itself into another animal. Furthermore, the zygote is growing, and therefore alive. These two observations lead to the conclusion that the one-celled zygote is a human type of life. Furthermore its particular combination of genetic instruction is unique, making it an individual.

The NCCS does not support the creation of embryos through *in vitro fertilization* (IVF) because the practise requires numerous fertilisations and the destruction of human embryos. The practice presupposes hyperovulation in which a number of ova are withdrawn from the woman, fertilised and cultivated *in vitro* for a number of days. Not all the fertilised ova are transferred into the uterus of the woman. Some embryos, which

are called ‘spare’, are either destroyed or frozen. These frozen embryos may be used for research and later destroyed. Furthermore, the question of ownership pertaining to the embryos that are left frozen in laboratories becomes problematic, especially in cases where the couple does not wish any further *in vitro* attempts or when there is a divorce or when one of the parents dies. For these reasons, the NCCS cannot support *homologous* IVF, even though it poses less ethical problems than *heterologous* procedures, which uses third party reproductive materials.

### *Preimplantation Tissue Typing*

Without a doubt, the benefits and potentials of Preimplantation Tissue Typing (PTT) are staggering, given its ability to save lives. These benefits notwithstanding, the NCCS has serious reservations and therefore does not support this procedure. The NCCS maintains that the objection to PTT that is briefly discussed and answered in 6.22 must be given more careful and serious consideration. No human being should be seen as a commodity serving utilitarian ends. The language of the HFEA definition suggests commodification when it describes PTT as the procedure which ‘allows the selection of embryos in order to bring about the birth of a child who can provide a matched tissue donation to an existing sibling ...’ The underlying philosophy of the commodification of human beings is a utilitarianism which regards humans as objects that are not valued for who they are but for their usefulness. Such approaches should never be countenanced no matter how ‘great’ or ‘noble’ the ends may be. The theological vision of our humanity espoused by the Christian Tradition demands that each and every human being is treated as inherently valuable. This vision promotes an egalitarianism that treats persons as ends and never merely as means to an end.

The paper mentions lack of evidence to support concerns over commodification in PTT. But this begs the question regarding the way in which that evidence is gathered and analysed since PTT was only approved in 2001 in the UK, the number of PTT approved may be limited and the children born after PTT must be young. How can the assertion in 6.22 be justified based on limited data and not supported by more robust research?

It is in a sense true to say that ‘parents who conceive a child to save a life may be on higher moral ground than those who procreate as an unanticipated consequence of sexual pleasure or for some selfish purpose’ (6.22). But from the standpoint of moral argument, this logic is flawed. An act that is morally unacceptable is wrong even if it may not be as repugnant as other morally unacceptable acts. The more fundamental question therefore is whether an act, although in some ways more superior to others, is *in itself* morally unacceptable. We maintain that to bring about the birth of a child with the appropriate genotype in order that he may provide a matched tissue donation to a sick child is morally unacceptable.

The UK HFEA 2001 recommendation seeks to limit the use of the PTT child for cord blood only and not for other tissues and organs. This constraint, however, can be breached, especially if the affected sibling later develops organ failure. The PTT child would then be under tremendous pressure to be an organ donor because matched organ



transplantation is life-saving. But even if this constraint is not breached, and the PTT child is used only to provide cord blood, the fundamental objection remains: a child must be received as a gift; providing matched tissue donation must never be the basis of its existence.

The paper deals with the purported love of the parent for the child, but fails to consider the possible impact on the PTT child when he discovers that part of the reason for his existence was for deriving matched tissues, although for an altruistic and noble cause.

The Christian Tradition maintains that children are gifts from God who must be accepted with thanksgiving and gratitude. They are not the products of the parent or the scientist, and they do not exist to fulfil their parents' projects. There is therefore a sense in which parents should see their child not simply as 'their' child; that is, the child does not simply exist for their happiness or sense of fulfilment. The child exists for itself because it has its own integrity and dignity as a person. To exert control over the genotype of the embryo so that it may donate a matched tissue to an existing sibling is already to treat it as a product, as a means to an end. This subtle shift in society's attitude towards children should never be taken lightly, for the serious consequences that will result in time would change the very moral fabric of our society.

#### *Prenatal Genetic Diagnosis*

While the NCCS broadly supports prenatal genetic screening and diagnosis, it does not do so unreservedly. Prenatal genetic screening is morally appropriate as long as the benefit of obtaining the information is greater than the risks involved in the test. While many have argued that PND has the benefit of preparing the couple for their child, it also creates a certain distance between them and the unborn child. This is because before the results of the tests are out, the couple does not yet know whether they are going to sustain their bond with the unborn child or whether they will walk away. Under the abortion assumption, PND makes the commitment between the parent and the child conditional. We must never under-estimate what this conditional commitment symbolised by PND entails, and its implications to society. PND cannot avoid the charge of providing impetus to the 'quality control' mindset, where the unborn child is already seen as a product that must satisfy the expectations of his parents. For this reason, PND far from helping the couple prepare for their child, is in fact poor preparation for parenthood.

What parents do with the outcome of the test and the information gleaned from it is very important. Needless to say, the NCCS cannot countenance the termination of the pregnancy as a morally acceptable option for dealing with a foetus with genetic disorders (Recommendation 14). Unfavourable results should not compel the couple to resort to abortion. The abortion assumption, however, looms large in the literature concerning PND. The term 'aminocentesis', for instance, which is often employed in such literature not only refers to testing but also assumes that the couple will authorise abortion if the foetus is found to have some genetic defect. The general argument frequently made by health officials that PND reduces the incidence of genetic diseases is also underpinned by the abortion assumption. The abortion assumption, to be sure, is understandable. To learn

that their unborn child has a genetic defect is a crushing disappointment that many couples would like to put behind them. Furthermore, most couples wish to avoid the emotional, physical and financial strain of raising a handicapped child. To them, abortion may appear to be the best solution and even a reasonable course of action.

The ethical justification for ending the child's life because of the discovery that the child is not healthy *in utero*, however, requires serious reconsideration for the following reasons:

1. The couple must realise that there is a margin of error in PND. The AFP test, for instance, is notorious for its false positives and false negatives. Amniocentesis likewise is not 100% accurate.
2. Even if the tests are accurate, it is difficult to predict the degree of disability in the child. For example there are various degrees of abnormality in children with Down Syndrome, some quite severe while others very mild.
3. The abortion assumption is based on the quality of life argument. But it is presumptuous to conclude that genetically or otherwise disabled persons are not able to enjoy a certain quality of life and therefore do not deserve to live.
4. Finally, and most importantly, abortion should never be an option because a genetically deformed foetus is still a human person.

As stated above, according to the Christian understanding, the human embryo at the moment of conception is already a human being created in the image of God. On this premise, we conclude that abortion is tantamount to the killing of an innocent human being. But the Christian rejection of abortion does not have to do exclusively with the question of the personhood of the embryo or foetus, although this consideration is very significant. It is also based on the profound view that the whole of life must be seen in light of God's creative and redemptive act. The unborn child in his mother's womb must be seen as God's creation, a gift from the hands of the Creator. In this sense, the unborn child in the womb cannot be subjected to our – i.e., his mother's, his father's, the doctor's and society's – evaluation, and his future cannot be based on whether or not we 'want' the child. Our estimate of the child and his worth must be brought into alignment with God's will for the child and his estimate for him.

According to the Christian understanding, the diseases and genetic deficiencies that affect our children and us are the result of human rebellion and sin which disrupts the harmony and balance in our world. Christians are not oblivious or insensitive to the sufferings of a couple whose unborn child is carrying a gene that predisposes him to Huntington disease, for instance. Neither are Christians immune from similar suffering themselves. But Christians would readily agree with Socrates who said that it is better to suffer evil than to do it. It is easy to rid ourselves of the child who is unwanted and so save ourselves (and the child, so the argument goes) from pain and misery. But by so doing we ironically surrender ourselves unwittingly to the very destructive powers in the world that we detest and resist.

## OTHER ISSUES

### *Genetic Information*

The NCCS concurs that genetic information derived from clinical genetic testing should be confined to a health care context, and that such information should be regarded as medical information and that ‘the highest ethical standard should be applied in its derivation, management and use’ (Recommendation 1). We agree with the point made in 2.11 that when used by a third parties ‘for non-medical purposes’ (i.e., for research) genetic information should be ‘accorded greater ethical and legal safeguards’. The problem that may arise here is that sometimes ‘diagnostic investigations’ and ‘research’ may overlap. For example, a project to retrospectively screen blood and archived tissues of sudden death victims for genes usually implicated for various forms of fatal cardiac arrhythmias<sup>1</sup> may be described as part of the ‘diagnostic investigation’ when it is actually research by a third party (parties). Clearer definitions of ‘diagnosis’ and ‘research’ must be forwarded in order to prevent abuses.

### *Informed Consent*

The BAC rightly recognises the fact that obtaining informed consent before genetic testing has to do with the ‘broader societal value of respect for persons’ (3.5). It presents two exhaustive lists of information that must be made available to individuals before genetic testing is done, either for therapy (3.7) or for research (3.9). In Recommendation 3 of the paper, a distinction is made between consent for diagnosis and research. This distinction is important in order to prevent the use of excess blood or tissue samples obtained for diagnostic purposes for future research.

It is important that we go beyond the formal procedures of informal consent and begin to study the quality of informed consent in our community. Obtaining informed consent, is not a straightforward matter. In the first place, this exercise requires that the participant is competent enough to understand the relevant information and can choose according to his life plan. To be competent to make the necessary decision means that the individual must at least understand the information regarding the tests and the freedom to refuse them without penalty. Ethicists as well as researchers have found it difficult to assess the competence of participants when dealing with scientific procedures about which they know very little. This problem becomes more acute when the particular decision and its implications are varied and complex. Beauchamp and Childress maintain that it is important that there must be sufficient assurance that participants are indeed able to comprehend the information.<sup>2</sup> These authors are not requiring greater participant *ability*, but a clearer *verification* of that ability. Furthermore certain terms used by the counsellor or researcher can also influence the decision of the participants. For instance, terms like ‘therapy’ and ‘treatment’ may imply greater effectiveness than has yet been shown. It is

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<sup>1</sup> The alleged genes are KCNQ1, HERG, KCNE1, KCNE2, SCN5A, ryanodine receptor 2 (RYR2) and caldesquestrin 2 (CASQ2).

<sup>2</sup> See Tom L. Beauchamp and James J. Childress, *Principles of Biomedical Ethics*, 4<sup>th</sup> ed. (New York: Oxford University Press, 1994), 142-169.

them in blocks of wax for periods of ten years or more. Genetic material can be obtained indiscriminately and irresponsibly from these samples if no proper ethical and legal safeguards are in place.

#### *Supply of Genetic Testing*

The BAC recognises the availability of certain types of genetic testing overseas as well as the prospect of ‘do-it-yourself’ devices that enable such testing to be done. In following the 2003 UK HGC report, the BAC wisely recommends that genetic testing ‘should be conducted through the intermediation of a qualified healthcare professional’ while strongly discouraging ‘the advertising of genetic tests by manufacturers or suppliers to the public’ (Recommendation 8). The paper also announces that a regulatory framework for the registration of genetic testing devices and services is being put together by the Medical Device Regulation (CMDR) of the Health Sciences Authority (HSA).

Even with a sound regulatory framework in place individuals cannot be prevented from gaining access to genetic testing. Perhaps the BAC should also recommend guidelines for post-testing counselling, especially probabilities counselling for those who have taken these tests from providers that are not registered with MOH or HSA. Such persons may be advised to undergo similar tests again with authorised centres or hospitals. Counselling should also help individuals to deal with unexpected information, that is, when tests done for a particular condition reveals other conditions. It should help individuals to make decisions regarding his future and that of his family, since it is often said that genetic tests offer less fate and more responsibility.



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16 May 2005

Associate Professor Terry Kaan  
 Chairman  
 Human Genetics Subcommittee  
 Bioethics Advisory Committee  
 20 Biopolis Way, #08-01 Centros  
 Singapore 138668

**BY FAX & POST**

Fax: 6478 9581

Dear Prof Kaan

**REQUEST FOR FEEDBACK ON CONSULTATION PAPER:  
 ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETICS  
 RESEARCH**

1. I refer to your letter of 4 April 2005 to Dr Yuen Kwong Wing, Chairman, Clinical Board, National Dental Centre, requesting for feedback on the above consultation paper. I have been asked to provide my comments.
2. The paper is comprehensive and well-written, though I propose some modifications. They are as follows:
  - A) Pg 9 – Section on “Free and Informed Consent: Freedom of Consent and the Right to Information”  
 Under 3.7: We propose that information to be provided to individuals before any Genetic Testing should include:
    - (e) implications (including social, *economic and legal* risks) of the test result (negative and positive) for the individual and his or her family. *The possible need for disclosure to third parties such as insurers and employers must be highlighted. Patients must be informed that failure to disclose a genetic information disorder/condition at the time of application for insurance cover may render the insurance legally ineffective.*
    - (i) that the confidentiality of the test result would be maintained *except in special circumstances e.g.*
      - i. when there is a high probability both that harm will occur to identifiable individuals or the society at large if the information is*

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*withheld and that the disclosed information may actually be used to avert harm.*

- ii. *when the harm that identifiable individuals (if any) would suffer would be serious.*

I am well aware that these points have been addressed under the section of “Genetic Counselling: Pre-test Genetic Counselling” on Pg 34, 6.58. But as the paper has rightly stated that the physician taking consent for the genetic test may not be the same offering genetic counselling, it is thus imperative that these points be reiterated in the section on “Free and Informed Consent”. It is also better that these points be stated in the Patient Information and Consent Form as these carry the most important and pertinent implications to the patient apart from the psychological/emotional burden to the patient and his genetic relatives. If I am a patient, I will certainly want to know these and weigh these against the benefits of genetic testing. When the test is undertaken will also become a consideration.

- B) Pg 18 – Section on “Direct Supply of Genetic Testing to the Public”: -  
Under 4.11 Last Line: For a similar reason, the advertising of direct genetic tests to the public should be strongly discouraged.

I am of the opinion that this is open to interpretation, and is not legally binding. Since your committee has recommended that Clinical Genetic Testing should be confined to a healthcare context (Recommendation 1) and discourages free public access to Genetic Testing, would it not be more appropriate to “prohibit advertising of direct genetic tests to the public”, particularly by medical laboratories. This should be differentiated from Patient Information Pamphlets/ Notices versus advertising to “sell a product/service”.

3. Except for a typo error on Pg 23, 6.14, Line 1 – “*practiced*” should be replaced by “*practised*” - I congratulate you and your committee on a job well done.

Yours sincerely



DR TEH LUAN YOOK  
CHAIRMAN  
NDC INSTITUTIONAL BOARD REVIEW

Cc Dr Kwa Chong Teck, Executive Director, NDC  
Dr Yuen Kwong Wing, Clinical Advisor, NDC



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**Reg No 199801148C**

10 May 2005

A/Prof Terry Kaan  
Chairman, Human Genetics Subcommittee  
Bioethics Advisory Committee  
20 Biopolis Way #08-01  
Centros  
Singapore 138668

Dear A/Prof Kaan

**REQUEST FOR FEEDBACK ON CONSULTATION PAPER**

Thank you for your letter of 4 April 2005.

As requested, please find enclosed feedback from Dr Hwang Nian Chih, Acting Head, Cardiac Anaesthesia, National Heart Centre.

Thank you.

Yours sincerely

A handwritten signature in black ink, appearing to be the initials "h" or "Koh".

A/Prof Koh Tian Hai  
Medical Director, National Heart Centre

A:bac - feedback 100505

A member of  SingHealth

- 3.21 In cases of dependent relationships, it is important to ensure that consent is both informed and freely given. The Nuffield Council on Bioethics stated that special care is necessary when seeking consent from prisoners, student volunteers and individuals who do not speak English.<sup>15</sup> Similarly, it would be unacceptable for those in positions of power to engage in actions that either coerce individuals into taking genetic tests or inhibit individuals from taking the same for fear of social or economic disadvantage as stated by the Human Genetics Society of Australasia.<sup>16</sup> We agree with these statements. Where there are reasons to believe that a person agrees to Genetic Testing for fear of losing healthcare benefits, this misconception should be corrected. One way to do this is to expressly indicate when obtaining consent that however a person decides, any healthcare, employment, welfare, or other benefits that are currently provided or in prospect, will not be jeopardised.

**Recommendation 6: Genetic Testing involving vulnerable persons should be conducted only if appropriate free and informed consent has been obtained. In the case of persons in special relationships, extra care should be taken to ensure that the consent is freely given. Clinical Genetic Testing should only be conducted if it is medically beneficial. Genetic Testing for research should only be conducted if the research is considered of sufficient importance and there is no appropriate alternative test population.**

#### *Confidentiality and Privacy*

- 3.22 Healthcare professionals and researchers involved in Genetic Testing have an obligation to protect the confidentiality of Genetic Information. We note Article 7 of the 1997 *Universal Declaration on the Human Genome and Human Rights* of the United Nations Educational, Scientific and Cultural Organisation (UNESCO), which states: "Genetic data associated with an identifiable person and stored or processed for the purposes of research or any other purpose must be held confidential in the conditions set by law." The WHO has similarly stated: "Genetic data should only be used to advantage and empower an individual or family, and for better treatment or prevention of disease. Data relevant to health care should be collected and kept by medical geneticists in secure confidential files."<sup>17</sup> We agree with these statements and we are of the view that genetic test results should not be disclosed to third parties, including insurers and employers, without the free and informed consent of the individual.
- 3.23 Individuals should be provided information on how their privacy will be protected, before they consent to Genetic Testing. We agree with the HGC's position that Genetic Information should generally not be obtained, held or communicated without the free and informed consent of the individual.<sup>18</sup> Certain individuals may be unwilling to share or divulge their Genetic Information to their family members, other healthcare professionals or researchers. Hence, healthcare professionals and researchers should exercise special care in protecting the individual's privacy and the confidentiality of such information. However, we reiterate our view that the ethical principle of privacy and confidentiality is not an absolute right in itself. There may be

<sup>15</sup> Nuffield Council on Bioethics, *Genetic Screening: Ethical Issues* (1993), paragraph 4.27.

<sup>16</sup> Human Genetics Society of Australasia, *Predictive Genetic Testing and Insurance* (1999).

<sup>17</sup> WHO, *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetics Services* (1998), Executive Summary.

<sup>18</sup> HGC, *Inside Information: Balancing Interests in the Use of Personal Genetic Data* (2002), at page 42.





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16 May 2005

The Secretariat  
Bioethics Advisory Committee  
20 Biopolis Way  
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Singapore 138668

**PATRON**  
Mrs Goh Chok Tong

**PATRON**  
**GOLDEN HEARTS FUND**  
**FOR THE ELDERLY**  
Mr Jacky Cheung

Dear Sir,

Consultation paper feedback on "Ethical, Legal and Social Issues in Genetic Testing and Genetics Research"

**EXECUTIVE COMMITTEE**  
**IMMEDIATE PAST CHAIRMAN**  
Prof Khoo Oon Teik

Thank you for allowing the National Kidney Foundation Singapore an opportunity to provide feedback on the consultation paper: "Ethical, Legal and Social Issues in Genetic Testing and Genetics Research".

**CHAIRMAN**  
Mr Richard Yong

We feel that this consultation paper represents an extremely important move in the right direction, given the context of an increasing amount of biomedical research being carried out in Singapore.

**VICE-CHAIRPERSONS**  
Ms Lee Seok Tin  
Mr Alwyn Lim  
Assoc Prof Lawrence Ch

After thorough reading and examination of this paper, we have the following comments to offer:

**HON SECRETARY**  
Mr T T Durai

1) In **Recommendation 3**, 'consent should also be obtained for future clinical and/ or research use of tissue specimens' - This has implications for many of the current research practices being carried out in our healthcare institutions. Currently, blood and tissue samples being collected for routine investigational purposes are not subject to the consent process. It is assumed that if the data is de-identified and retrospective in nature, it may be suitable for usage. Our view is that de-identified data should fall under this category also and that consent should thus be sought. It would be useful if the council could provide a template for consent for future, hitherto unknown research purposes to be used at the point of tissue collection.

**HON TREASURER**  
Mr Loo Say San

2) In **Recommendation 15**, reference is made to 'serious genetic diseases'. We submit that the definition of serious genetic diseases should be made clear and a list of such diseases provided as an annex to the recommendations.

**ASST HON TREASURER**  
Mr Kweh Soon Han

3) In **Recommendation 21** on the qualifications of personnel who can interpret genetic tests - 'Healthcare professionals who are appropriately qualified or have sufficient experience'. We feel that this statement is insufficient and too vague as a safeguard to ensure that only a select group of healthcare professionals have ready access to genetic tests. Perhaps a register of such professionals should be established at least initially and the guidelines gradually relaxed. This should prevent unnecessary abuse of confidential data. Previous similar exemplary safeguards can be drawn from the pharmaceutical industry - when Viagra was first introduced, only endocrinologists and urologists were allowed to prescribe and once the safety was well established, this was expanded to all practitioners.

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4) Lastly, may we also recommend the inclusion of a broad clause allowing non-consented use of tissue/ blood samples in times of national emergencies i.e. for identification of subjects during mass casualty events.

We hope that our comments were constructive and of use to the committee. Once again, please accept our appreciation for the opportunity to provide feedback on an issue that is of prime importance in our drive to be a premier biomedical research hub.

Thank you

Yours sincerely,

A handwritten signature in black ink, appearing to read "Benjamin Chua".

Dr Benjamin Chua  
MBBS, MHSc(Duke), MRCS(Ed)  
Associate Director  
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A handwritten signature in black ink, appearing to read "Jeremy Lim".

Dr Jeremy Lim  
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Head, Medical Affairs and Planning  
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**NMEC’s input to BAC’s Consultation Paper on  
“Ethical, Legal and Social Issues  
in Genetic Testing and Genetics Research”**

**1 General Ethical Considerations**

- 1.1 With regards to Para 3.3 stating that “If there is a possibility for sample taken for clinical purposes which may be used for research in future, this must be made known to the patient....”, NMEC proposes that this be made known to the patient in writing.
- 1.2 With regards to Para 3.9(e) stating that “participants in genetic testing for research should be provided with information regarding the confidentiality of records identifying the tested individuals. NMEC suggests that the clause “subject to the regulation of discovery of medical information in Singapore” be added.

**2 Recommendation 1 (Genetic Information Derived from Clinical Genetic Testing should be confined to a healthcare context, owing to its complex nature and the need for professional input. Accordingly, it should be regarded as medical information and the highest ethical standard should be applied in its derivation, management and use)**

- 2.1 NMEC proposes to add that the approval for genetic testing/ trial should be sought from the Institutional Review Board (IRB)/Institutional Ethics Committee (which reviews and monitors all research work with special attention to the requirements for free and informed consent and medical confidentiality).
- 2.2 NMEC proposes that BAC defines what the “highest ethical standards” for medical and genetic information’s management and use will be, as medical records are actually discoverable.

**3 Recommendation 3 (Genetic Testing should be voluntary and conducted only after free and informed consent has been obtained. Consent must be based on sufficient information, which includes the nature, purpose, risks and implications of the test. Consent should also be obtained for future clinical and/or research use of tissue specimens)**

- 3.1 NMEC suggests that re-consent (signed) is necessary for a change in purpose for the use of the genetic information. If this is not possible, re-approval from the IRB should be sought.
- 3.2 In Para 3.9(g), in the context of research involving genetic testing, while it is agreed that subjects should be told they can withdraw from the research at any

time, it is generally felt that subjects should also be told what the withdrawal means. Most subjects being laypersons, would imagine that their withdrawal would mean not only their sample is destroyed but also the genetic information already derived from the sample would be destroyed. But this may not always be the case. On the contrary, the information is often de-identified and retained. If the researcher is willing to remove all patient identifiers and make the information subsequently untraceable, can the researcher keep the information even after the subject withdraws his consent? The implications of a withdrawal from the research should be properly explained to the subjects.

- 3.3 NMEC suggests that the report clarifies whether tissue typing performed to detect the HLA typing of an individual is considered as genetic testing.

**4 Recommendation 4 (An individual should be informed of the test result without undue delay unless he or she has indicated the wish not to know. However, the test result of newborn babies and children for treatable conditions should be disclosed. In research involving genetic testing, researchers should inform the individual prior to participation in the research whether the genetic information so derived will be disclosed from him or her)**

- 4.1 NMEC proposes that the researchers should also inform the subject the following information:

- For how long the specimen will be kept, and when it will be destroyed;
- That he may request for the specimen to be withdrawn from storage and destroyed at any time;
- That confidentiality will be maximized by double-coding; one code for the sample and another for the DNA; and
- That genetic information if released could potentially be misused and affect his employability and insurability.

- 4.2 In Para 3.10, there should not be an issue as to the individual refusing to disclose a test result that may be medically beneficial to a third party. Individual rights take precedence and free and informed consent from the individual should still be obtained.

- 4.3 With regards to Para 3.11 stating that "...a healthcare professional may decide to postpone disclosure of the test result if the individual is not in a suitable condition to receive such information. This may arise when the test result reveals a condition that cannot be medically treated or alleviated", it is generally understood that sometimes the disclosure should be deferred if the patient is too ill to receive the information at the time, However, it is not clear why this should be the case when the test results reveals a condition that cannot be medically treated or alleviated, or whether it should also apply if the patient is well, but just that the information relates to a condition that cannot be medically treated or alleviated.

- 4.4 Hence, it is proposed that so long as the genetic counseling prior to the test is performed correctly, the possibility of the information revealing such a untreatable condition should already be told to the patient and if he has agreed he wants to know, it is not for the doctor to exercise therapeutic privilege to withhold the information anyway. Therefore, the report should clarify if it means to refer only to a deferment of the disclosure or whether it is suggesting that doctors should have a right not to disclose the information at all so long as the test result reveals a condition that cannot be medically treated or alleviated, if they feel that the person would be unwilling to accept the information. There are problems if the patient is not informed even if the concern is based on a therapeutic privilege - this is because conditions that cannot be medically treated or alleviated at the present time may not always be so in the future, and if doctors wishes to withhold the information, are they going to be responsible to keep track of the information so that the information can be disclosed at a subsequent time when treatments for the condition become available? That would be a terrible burden for doctors to bear. It would be best to do a proper job of **pre-genetic testing counselling** to ensure the person is ready to receive the information, then disclose it when available
- 5 **Recommendation 5** (We do not recommend the broad use of Genetic Testing on children and adolescents. Confirmatory Testing and Predictive Testing for genetic conditions where preventive intervention or treatment is available and beneficial in childhood are recommended. Carrier Testing should generally be deferred till the child is mature or when required to make reproductive decisions. Predictive Testing should generally be deferred where there is no preventive intervention or treatment, or where intervention or treatment is only available and beneficial during adulthood. However, in exceptional circumstances, parents and the physician should have the discretion to decide regarding Carrier and Predictive Testing, and genetic counselling should be an intrinsic part of the testing process)
- 5.1 NMEC proposes to insert the definition of “Predictive Testing” for genetic condition as its scope changes with technology. It can be defined as testing that:
- Improves life based on results.
  - Provides information helpful for prescribing drugs.
  - Suggests ways to avoid disease that one may be predisposed to.
  - Predicts drug reactions.
- 5.2 In Para 3.14, it is stated that “when considering whether the child or adolescent’s best interest is met by genetic testing, it should be considered in the context of the family”. NMEC recommends deleting this statement and substituting that the context should in the interest of the minors only and the minor should not be tested in the family’s interest.

- 5.3 In Para 3.16, it is recommended to include psychological assessment to determine the capacity of the child or adolescent to participate in consent-taking process.
- 6 Recommendation 6 (Genetic Testing involving vulnerable persons should be conducted only if appropriate free and informed consent has been obtained. In the case of persons in special relationships, extra care should be taken to ensure that the consent is freely given. Clinical Genetic Testing should only be conducted if it is medically beneficial. Genetic Testing for research should only be conducted if the research is considered of sufficient importance and there is no appropriate alternative test population)**
- 6.1 NMEC recommends that the report clarifies “vulnerable” persons who do not have the capacity to give consent like the mentally ill or impaired. It should also be useful to elaborate what the term “medically beneficial” to whom / the person having the test done.
- 6.2 In Para 3.19, the report recommends that “genetic testing for the mentally impaired should only be allowed with the consent of a person legally authorised to decide on his or her behalf”. It is not clear if this is meant to apply only to Genetic Testing for research, or to Genetic Testing in general. Para 3.18 seems to differentiate between the two but in the final statement in 3.19, it just refers to "Genetic Testing". Therefore, whether the need for a court order appointing a Committee of the Estate or Person and consent from that person should be a strict requirement also for Clinical Genetic Testing when it is in the best interests of the mentally impaired person? Or when will it be imperative to diagnose the existence of genetic disease in family members? Right now, doctors can decide to carry out treatment in the best interests of a patient who is unable to give consent and when there is no one authorised to consent on his behalf. Is the requirement of consent from a court ordered legal guardian going to impose new requirements to be fulfilled if genetic testing is to be allowed?
- 6.3 In Para 3.20, it is proposed that the NS men and those serving in the military should also be considered to be persons in relationships of dependence. This is particularly so since their employer is the government whose access to information may be far greater than your typical employer. What if the military wants the genetic information of a soldier to be put into a dossier on the individual? Would they be allowed to call for the information?
- 7 Recommendation 7 (Genetic test results should not be disclosed to third parties, including employers and insurers, without the free and informed consent of the individual)**
- 7.1 NMEC agrees with the recommendation in Para 3.22 that “genetic test results should not be disclosed to 3<sup>rd</sup> parties, including insurers and employers, without the free and informed consent of the individuals”. However, this is in conflict

- with statements in Para 3.10 and Para 3.23 that the ethical principle of privacy and confidentiality is not an absolute right in itself. This statement also contradicts our current legislation on discovery of medical information in Singapore.
- 7.2 In Para 3.24, while the report provides some guidance in this area of when a doctor can disclose in breach of the duty of confidentiality, it is strongly recommended that this area be covered by legislation much like we see for HIV/AIDS disclosure in the Infectious Diseases Act, so that doctors are properly protected and there is greater clarity of when the exceptions apply.
- 8 Recommendation 8 (Genetic Testing should be conducted through the intermediation of a qualified healthcare professional. Accordingly, the advertising of genetic tests by manufacturers or suppliers to the public is strongly discouraged. A comprehensive regulatory framework should be established for access to Genetic Testing services. Genetic tests that provide predictive health information should not be directly offered to the public)**
- 8.1 NMEC proposes to add that advertising is strongly discouraged and should be regulated by the Ministry of Health or designated bodies. A regulatory framework is needed as soon as possible.
- 8.2 In Para 4.10, it was suggested that a comprehensive regulatory framework be established – however, such regulatory bodies will not have jurisdiction over internet or alternative suppliers. Eventually, there may be propositions to suggest that our tight regulatory framework may impede our progress for genetic testing, falling behind our neighbours for such services. Therefore, it is proposed that cooperation with other countries would be needed – probably within ASEAN.
- 9 Section V on “Special Ethical Considerations for Human Genetics Research”**
- 9.1 NMEC proposes that in Para 5.6(e), there is a need to elaborate the 14 day rules for the embryos – i.e. notochord development etc.
- 10 Recommendation 10 (Pre-implantation genetic diagnosis is permissible provided that it is subject to control by a relevant authority and limited to serious medical conditions. The relevant authority should license, monitor and assess preimplantation genetic diagnosis to ensure that it is employed within legal and ethical limits)**
- 10.1 NMEC recommends that approval by the IRB is required for the clinical use of PGD as it is still regarded as experimental. A Registry of non-infertile couples undergoing the procedure should be established to review the short- and long-term outcomes of the parents and children.

- 10.2 In Para 6.15, NMEC proposes that it should be explicitly highlighted what “serious medical conditions” mean and constitute.
- 11 Recommendation 11 (Use of preimplantation genetic diagnosis for sex selection and the selection of certain desired traits for non-medical reasons should be prohibited)**
- 11.1 It should be added that PGD may be viewed as a technology by which cloning may be performed. Therefore, the report should clearly differentiate between these 2 terms.
- 12 Recommendation 12 (Preimplantation tissue typing, whether as the sole objective or in conjunction with preimplantation genetic diagnosis to avoid a serious genetic disorder, is permissible but should be licensed and evaluated on a case-by-case basis)**
- 12.1 NMEC proposes that an appropriate body or agency (e.g. licensing authority or hospital ethics committee) should be named in the report to issue licenses and evaluate the cases for PTT and PGD. Lay participation should be included within these agencies. There should also be an appeal mechanism included in cases of disagreements or disputes with this agency’s views. In addition, if PTT for non-medical reasons are not allowed, BAC should address whether Singaporeans could go overseas for PTT and will this child then be registered as a Singaporean.
- 12.2 In the UK, there is a specific authority licensing any unit that proposes to carry out PGD. It looks at various points, including the reliability of the centre (it is quite difficult technically), the risk to benefits ratio of the specific disease tested for - compared to other methods (and will look at specificity and sensitivity issues), the availability of genetic counselling before and after the testing, etc. The license is site and disease specific.
- 13 Recommendation 14 (Prenatal genetic diagnosis should be voluntary, conducted with informed consent and with appropriate pre- and post-test counselling. The prospective parents’ choice of whether a genetic disorder warrants a prenatal genetic diagnosis or termination of the pregnancy should be respected)**
- 13.1 NMEC wishes to clarify whether this recommendation would mean that prospective parents have full autonomy to decide on PGD and PTT or only on termination of pregnancy.
- 13.2 With reference to Para 6.27(c), NMEC proposes to substitute “at 12 and 22 weeks” to “between...”.



- 13.3 In Para 6.31, it is right to state that it is unacceptable to use PND for the selection of any physical, social or psychological characteristics or normal physical variations. However when it pertains to a late-onset diseases in a foetus, this may be a slippery slope. BAC is recommending that PND be limited to serious genetic diseases. But what if it is albeit a serious disease, and the genetic testing can only show a slightly higher susceptibility to developing this late onset disease? Or what if it is serious, but a treatable condition? Can parents still decide to insist on PND because if the foetus can be potentially affected, they would want to have an abortion as they would rather try to conceive a "healthier" child the next time round? The guidelines on PND may have to be more specific if we do not want a slippery slope towards a form of prenatal selection using abortion.
- 14 Recommendation 16 (The appropriate professional bodies should prescribe detailed ethical guidelines on the practice of prenatal genetic diagnosis for their members)**
- 14.1 If the professionals are the “guardians” of the Ethical guidelines, the report should also propose a separate central licensing authority that is able to overrule the Professional body if need be.
- 15 Recommendation 17 (Presymptomatic testing should be available for adults at risk who request it, even in the absence of treatment, after proper counselling and informed consent)**
- 15.1 NMEC proposes to state that presymptomatic testing should be restricted to be performed by medical professionals only.
- 16 Recommendation 21 (Interpretation of genetic test results should only be performed by healthcare professionals who are appropriately qualified or have sufficient experience. Genetic counselling should immediately follow the disclosure of the test result, particularly if the test result is not favourable)**
- 16.1 NMEC recommends that all healthcare professionals providing self-directed genetic testing should employ the services of trained/approved geneticists.
- 17 Additional Comment**
- 17.1 It seems extraordinarily restrictive for paediatricians managing patients with potential genetic problems. For example, a child with beta major could have the diagnosis clearly made on blood films, FBC and Hb electrophoresis. Management of future pregnancies for the parents is vital. Genetic tests should not be restrictive in such circumstances.



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4 May 2005

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Dear Prof Kaan

**REQUEST FOR FEEDBACK ON CONSULTATION PAPER**

Thank you and your committee for producing this very well written consultation paper.

I have read the paper and also sought comments from relevant colleagues in the NSC. We generally agree with the recommendations contained in the paper.

Other comments are:

- 1) How feasible is it to monitor and police laboratories offering genetic testing from overseas or via the Internet?
- 2) In view of the fact that there are numerous genetic tests and a long list of genetic illnesses, is it better to concentrate on conditions that are severe or have significant ethical, legal and social impacts?
- 3) What would be the advice for doctors who advise genetic testing in children whose parents adamantly refuse such testing, and such testing will be of benefit?
- 4) What would the advice be for matured children wanting to be tested but parents refusing such testing?
- 5) Would the archiving of specimens obtained for genetic testing be allowed and under what conditions?

Yours sincerely

A/Prof Roy Chan  
Director

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20 May 2005

Associate Professor Terry Kaan  
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Dear Terry

### REQUEST FOR FEEDBACK ON CONSULTATION PAPER

I refer to your Request for Feedback on Consultation Paper entitled "Ethical, Legal and Social Issues in Genetic Testing and Genetic Research". I am pleased to inform you that the feedback from our clinicians have been very favourable and agree with the 24 recommendations.


For your perusal.

Dr Tay Eng Hseon  
President

Office of Life Sciences



May 30, 2005

 Associate Professor Terry Kaan  
Chairman  
Human Genetics Subcommittee  
Bioethics Advisory Committee  
20 Biopolis Way,  
#08-01 Centros  
Singapore 138668

Dear *Terry*,

**REQUEST FOR FEEDBACK ON CONSULATATION PAPER**

Thank you for the opportunity to comment on the consultation paper entitled "Ethical, Legal and Social issues in Genetic Testing and Genetic Research".

The Office of Life Sciences thinks that the paper is well thought out and very comprehensive. However we would like to suggest that for Predictive Testing (point 2.3e), perhaps genotypes should be included in the definition with regards to individual therapy. Similarly for Susceptibility (or predisposition, point 6.34b) tests, perhaps individual susceptibility to drug effects or even adverse drug effects and toxicity should be included.

We hope that you would find the above feedback useful.

Yours sincerely

A handwritten signature in black ink, appearing to be 'JW', is located below the 'Yours sincerely' text.

Professor John Wong  
Director  
Office of Life Sciences  
National University of Singapore



## SINGAPORE NURSING BOARD

11 May 2005

Associate Professor Terry Kaan  
Chairman  
Human Genetics Subcommittee  
Bioethics Advisory Committee

Dear Prof Kaan

**REQUEST FOR FEEDBACK ON CONSULTATION PAPER  
ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND  
GENETIC RESEARCH**

Thank you for inviting the Singapore Nursing Board to give its views on the paper.

We would like to congratulate the Human Genetics Subcommittee for producing such a comprehensive paper. The paper has covered all the important aspects of genetic testing and genetic research.

A Board member has one comment on recommendation 7 (page 15). Normally in application forms (for jobs/insurance), the applicant has to make a declaration that he/she has submitted all the information (especially with regard to health or potential health risks e.g. diabetic parent) to the best of his/her knowledge. The paper could consider the legal implications should the applicant not disclose genetic test results which he/she knows.

Best wishes

Yours sincerely

A handwritten signature in black ink, appearing to read 'Ang Beng Choo'.

Ms Ang Beng Choo  
Registrar  
Singapore Nursing Board



**Society of  
Bioscience & Technology**

**In Response to the Call for Feedback  
on Genetic Testing and Research (GTR) in  
Singapore**

**Executive Committee  
May 2005**

### 1.0.0 Introduction

We, the Society of Bioscience & Technology provide this feedback with the aim of contributing our views towards the call for feedback pertaining to Genetic Testing and Research (GTR). It is our wish that all policies henceforth formed with regards to the aforementioned are to benefit and protect the citizens of the Republic of Singapore via the safe, effective and ethical application of new genetic knowledge and technologies associated with its use. We hereby strongly advocate the use of human genetics with the highest order of Government regulation to uphold the value and integrity of human life and in addition, to prevent any potential abuse associated with its application that will infringe on human rights or culminate in any discrimination arising from the recourse of eugenics in socio-developments.

### 2.0.0 Background

Ongoing advances in human genetics and technologies will certainly impact Singapore at large. Unequivocally, new sophisticated discoveries arising from the pervasive and specialised use of human genetics in bioscience research will continue to emerge indefinitely throughout this millennium. Some of these will redefine, alter and enhance the limits of medicine in present health-care systems.

As with current advancements in genetics knowledge, it is already impossible to ignore its potential impact and prolific use in bioscience applications that will invariably influence many aspects of daily living; typically in mainstream health-care, drug development in biopharmaceuticals (to provide novel and efficacious pharmacogenetic therapies) and in forensics associated with identity testing in law enforcement. With such an imminent course of revolutionary change, it is therefore, crucial to assemble a clear, relevant and comprehensive legislative framework to identify and assign legally acceptable limits in the use of genetics knowledge and associated technologies. In addition, due to its immense potential benefits it offers to the medical fraternity and the public, it is important that there is a clear understanding in its application and implications by members of the public such that an educated and consentaneous decision can be made pertaining to *de novo* options provided by developments in biotechnology.

At present, genetic testing in clinical laboratories is employed for the following circumstances:

- Diagnosis of individuals with symptomatic conditions of rare inherited disorders.
- Identify individuals with an inherited genetic change that may render them highly susceptible to certain cancers (e.g. breast and bowel cancer).
- Identify the presence of a genetic change in healthy individuals (e.g. Fragile X) that may have specific implications for their offspring and relatives.
- Prenatal screening of foetuses for genetic disorders (e.g. Down's syndrome).
- Neonatal screening of newborn babies for genetic diseases (e.g. Phenylketonuria, PKU).
- To determine if an individual is a carrier of recessive disorder (e.g. Cystic fibrosis, sickle-cell anemia or Tay-Sachs disease) in carrier testing.
- To predict an individual's predisposition to the late-onset of acute diseases (e.g. Huntington's disease) based on family history.
- To resolve ambiguity in legal claims of biological parentage.

- Characterisation of abnormalities such as leukaemias and tumours by analysing acquired genetic changes.

### 3.0.0 Positive implications in the use of Human Genetics.

After fifty years since the discovery of DNA structure as the “molecule and blueprint of life” by Watson and Crick and the landmark success of the Human Genome Project (HGP) in 2000, a revolutionary breakthrough in human genetics propels the world in a number of ways; health-care, biopharmaceutics and economy. Since genetics is associated with various sub-disciplines in the biosciences, similar breakthroughs have been accorded respectively and may eventually leave an indelible impact on humanity, direct or indirectly. Advances in human genetics offer much promise in:

#### Health-care:

Human life expectancy in the modern era has to a large extent, increased due to better nutrition, hygiene and health-care. It is expected that many are able to survive up to the sixth decade of their lives but will however, be encumbered with debilitating illnesses/diseases; hence the compromise on their quality of life. Through the profound knowledge and research in advanced human genetics today, there is strong evidence that in the following few decades, human suffering and distress can be ameliorated while quality of life is enhanced.

Genes in general, form the significant basis of physiological function and disease development. Detection of genes associated with disease by genetic testing is now becoming readily available and can advance understanding of a medical condition. Such tests are not limited to the clinical diagnosis of a symptomatic medical condition or syndrome but are also used to predict in patients and their offspring, the likely development of a specific medical condition. Predictive detection of disease predisposition is advantageous in that, it offers an opportunity for clinical geneticists to provide early monitoring, lifestyle counseling and pre-emptive medical treatment to be employed to avert its onset.

Genetic testing is considered a direct test that is normally performed before and after a medical condition is symptomatic. Such tests often provide diagnostic (e.g. distinguishing different types of leukemia) and prognostic (e.g. identifying the product of a mutated p53 tumor-suppressor gene that flags the likely aggressive growth of cancers) information based on the analysis of DNA structure (cytogenetic testing) or aberrant changes in the DNA sequence itself (molecular testing). However, in recent times, genetic testing is also employed to study acquired changes in cancer tumours. In essence, genetic tests examine genes or human chromosomes for genetic markers that may indicate the presence or susceptibility of diseases or conditions (e.g. breast cancer or Alzheimers); hence the ability to predict the probability of acquiring the disease in the future. In certain instances as in Huntington's disease, a neurologic disorder with late onset, such diagnosis can inform future lifestyle and reproductive decisions.

Present focus in diagnostics for disease prevention of sequenced human genomes has progressed from single-gene disorders to those of major diseases (e.g. cancer and cardiac disease) whereby their etiologies are multifactorial and often include lifestyle and the environment. It is necessary however, to emphasise that a genetic test merely indicates an individual's susceptibility to the disease



personal genomic data also extends to issues pertaining to employment, schools and adoption agencies.

Additionally, other prevailing issues include the likely impact on national security and law enforcement. Since genomic data form the basic molecular blueprint of an individual, such information, when illegally acquired could lead to the demise of innocent individuals who may be wrongfully implicated for crimes committed by another. Similarly, if genomic data is authorised for use as a means of personal identification, doctoring of such identification through the use of illicit genomic data is a possible concern for national security in that "genomic forgery" will replace passport forgery.

Where jurisdictions intend to use such genomic data as criminal evidence in law enforcement, it is imperative that they wait for more advanced methods to provide error-free matches since current methods used to interpret genomic data is still prone to a relatively high percentage of error (DNA profile error rate of 4%) [3, 4] arising from the incidence of human error despite the inclusive use of quality assurance. Furthermore, research into the improvement and agreement in the standardisation of genetic testing methods is also necessary since different test agencies employ different considerations of loci-matching. In addition, there is also a certain discrepancy between results obtained when performing genetic tests using PCR and RFLP techniques. Hence, the subject of GTR remains highly controversial in the abovementioned situations.

#### 5.0.0 Conclusion

In conclusion, we believe that:

- i) **The use of GTR of an individual should be voluntary and not be mandatory; this should apply to Singaporeans, foreigners and foreign workers alike. The latter two being already entitled to their human rights according to their own home countries.**

We disagree with mandatory GTR as we believe that individuals in Singapore should be able to make an elective choice concerning the use of their genetic information for GTR. Due to the sensitive nature of such information, being private and confidential, the need for GTR should only be limited to medical treatment, diagnosis and disease detection/prediction. The individual should be consulted and be able to provide his/her consent after being informed about the intended use of his/her confidential genetic profile.

As in the United Kingdom, GTR in Singapore should similarly be subject to a legal code and remain elective except where a search warrant or court order prevails. At present, the United Kingdom holds the most extensive DNA database in the world (>2 million records) [1] but the endeavours by Biobank, U.K involved in genetic data acquisition and storage have demonstrated the initiative to be resource intensive. In addition, it is found that the cumulative size of the genetic databases comprising sequenced genetic data exceeds its initially projected use that promises useful clinical applications since more developments are yet needed to process and accurately translate the voluminous stored raw data into clinically useful information and therapies [2]. Other issues also need to be addressed; the safe handling (to prevent incidence of test error during analysis) and disposal of DNA after testing.

- ii) **GTR should be employed and limited only to medical genetics research to benefit, improve health-care and for life-saving circumstances via the use of screening and diagnostics in disease predisposition concerning genetic, recessive and inherited disorders (e.g. Cystic Fibrosis and Huntington's disease).**

It is evident that current genetics knowledge can provide a useful basis in disease screening and diagnostics; hence GTR should be used in existing health-care systems to predict in advance, the predisposition of an individual to a disease so that clinical geneticists are able to monitor and counsel the individual to prevent its onset and to allow possible early pharmacologic treatment. There are however, some concerns with regards to the possible psychological impact of employing GTR for such predictive intent as it is likely that the results can psychologically affect the individual. It is therefore, important to implement adequate counseling for pre- and post-testing.

- iii) **Since genetic databases are stored in computer-based systems, they are therefore not tamper-proof as seen in recent cases of security breach involving the remote hacking of highly-secured government agencies. Hence the reliability of such means of genetic data storage is inferior. Additionally, the high expense in terms of resources (mainly time and manpower investment) to acquire such invaluable genetic databases may be easily destroyed by malicious computer viral attacks given the current capabilities.**

- iv) **There should be an independent Non-Governmental Organisation (NGO) to monitor and manage the appropriate use of such sensitive information even if the genetic databases comprise those of volunteers.**

Due to the need to provide sufficient mechanisms to monitor, manage and control the accessibility of such sensitive genetic information, it is necessary to engage the involvement of an NGO. The latter should perform an independent and essential role in ensuring transparency; to provide stringent accounting to the public domain on developments concerning the use of genetic databases and the security safeguards of genetic databases. Additionally, its role also includes the evaluation and monitoring of research developments and provide feedback and education to the public.

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16 May 2005

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Dear Professor Kaan

**Feedback on Consultation Paper**

I refer to your letter dated 4 April 2005 soliciting our comments on a consultation paper 'Ethical, Legal and Social Issues in Genetic Testing and Genetics Research'.

We have studied the consultation paper with great interest and have the following comments:

1. In the section on 'Defining Genetic Testing' (page 4), it is proposed that only testing carried out on DNA, RNA and chromosomes and linkage studies are defined as genetic testing. We feel human leucocyte antigen (HLA) testing using Terasaki microcytotoxicity should be considered a form of genetic testing because it provides information that may be used to infer genetic inheritance. Loosely speaking, this may come under the category of 'linkage studies' in the definition. Regardless, the results of HLA testing using this technique should be kept confidential because they have a bearing on disease predilection and paternity issues.
2. We agree that the results of genetic testing should be accorded the same level of confidentiality as medical information, and special care should be place on sensitive genetic information. We wish to point out that while information that can be draw from a person's entire genetic make-up is vast, doctors usually ask for very specific tests that has limited impact. It is the capacity to perform tests that are not medically indicated on the DNA obtained for legitimate reasons that is has the greatest potential for misuse.
3. In the section 'Specific Ethical Considerations for Human Genetics Research', there are no recommendations on the disposal of genetic material after a research study has been completed. It is possible that researchers may store genetic material. A statement regarding this issue will be very useful.

Best Regards,

A/Prof Philip Choo  
Chairman, Medical Board

My doc/Julie/Bioethics Adv Cttee

Affiliated Teaching Hospital  
of the National University  
of Singapore



A member of National Healthcare Group  
Adding years of healthy life

Dr Amar Bhat Director, Office of Asia and the Pacific U.S. Department of Health and Humans Services
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May 16, 2005

Dr. Sylvia Lim  
Assistant Head, Secretariat  
Bioethics Advisory Committee  
20 Biopolis Way  
#08-01 Centros  
Singapore 138668

Dear Dr. Lim

We at the U.S. Department of Health and Human Services (HHS) have taken the opportunity provided by the Singapore Bioethics Advisory Committee (BAC) to comment on your consultation paper entitled “Ethical, Legal, and Social Issues in Genetic Testing and Genetics Research.” These comments were prepared by staff of the HHS Secretary’s Advisory Committee on Health, Genetics and Society (SAGHS), with input from representatives of our National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, and the Health Resources and Services Administration.

We commend the efforts of the Human Genetics Subcommittee (HGS) on drafting a thoughtful, comprehensive, and balanced treatment of many of the issues currently surrounding genetic testing and genetic information. The concepts are conveyed with clarity, sensitivity, and an appreciation of the complexities of genetic testing and the clinical, ethical, legal, and social issues related to genetic information. We were also pleased to see clear rationales provided for the recommendations, with numerous references to the work of other advisory bodies and the approaches taken by other countries, suggesting that the HGS considered and built upon the thinking of other nations.

You may already know that the recommendations are mostly consistent with current U.S. policies and standard practices. In some cases the consultation paper goes beyond current U.S. positions. One example is that the HGS has suggested specific policy statements relating to the disclosure of confidential genetic information to an affected family member, and the appropriateness of pre-implantation genetic diagnosis and pre-implantation tissue typing. General matters that HHS has identified in the consultation paper are outlined below. Specific questions and comments about various

sections of the consultation paper are included in the attachment, and offer HHS perspectives and/or note the usefulness of additional clarification about specific issues.

We observed that the document combines the discussion of ethical issues in the research setting and in the clinical care setting into one section, even though there are a number of important ethical concerns that affect these two settings differently. Differences include the range of acceptable informed consent processes, the amount of counseling and other information provided to patients, and the uses of the information gathered from the genetic tests. In some kinds of screening programs or clinical care situations, the emphasis on voluntary participation may be less relevant than it would be in a research setting. Examples include newborn screening programs and urgent care settings, where a rapid diagnostic test is needed in order to ascertain the best treatment for the patient. In a research project, a premium is placed on voluntary participation and consent, and some genetic tests may be used that are not clinically validated and where the specific health implications for the individual are unknown. The use of these tests in a clinical care setting would be entirely inappropriate, but in the research context, there may be scientifically and ethically valid reasons to include these tests. The document would benefit from additional clarity in the treatment of clinical versus research uses of genetic information and testing, and the potential interaction between the two purposes under some circumstances such as when only a research-caliber test is available for a particular disorder. The recommendations would be better served if each recommendation were divided into two sections; alternatively, the research-related recommendations could be incorporated into the section dealing specifically with research. Separate criteria should be laid out for the conditions of use for genetic tests in clinical versus research programs.

Although we recognize that the consultation paper is deliberately limited in scope to genetic testing for certain specified purposes and genetic tests for heritable disorders, the paper should acknowledge that the scope of genetic testing is evolving rapidly. Historically, genetic tests involving DNA, RNA, or proteins have been used to identify single gene disorders caused by germline or heritable variations. However, nowadays the term “genetic test” is often used more broadly to refer to any test performed using molecular biology methods to test DNA or RNA, including heritable and acquired somatic variations. As genomic medicine advances and evolves, with acquired somatic variations evaluated in the context of an individual’s entire genomic variations, the definition of a genetic test may become even broader. We note that there is no reference to pharmacogenomics and its ethical and policy implications. There is also no discussion of genomic research more generally, which differs from single gene testing in its search of the entire genome for variations that have implications for basic genetic processes or human health. The committee should clarify if it intends to address these areas in future work, or if they have been omitted for specific reasons pertaining to the committee’s purview or mandate.

The United States has been considering many of the issues raised in this consultation paper over the past several years. The SACGHS was first established in 2002 to support broad-based public policy development to address the benefits and challenges

of genetic knowledge and genetic testing. Information about SACGHS and current U.S. policy positions can be found at the following website:

<http://www4.od.nih.gov/oba/SACGHS.HTM>

HHS would like to thank you once again for providing the opportunity to comment on this consultation paper. We look forward to working with you as Singapore develops its bioethics policy.

Sincerely,

Amar Bhat, PhD  
Director, Office of Asia and the Pacific

Attachment: Specific HHS Comments and Questions

**Attachment 1**  
*Specific Comments and Questions*  
*Provided by the U.S. Department of Health and Human Services*

**Section I. Introduction**

1.8 The statement that “the conduct of genetic testing should be limited to medical or related purposes” could be read to mean that the BAC believes that genetic testing should not be used for forensic and identification purposes. Assuming this is not the intent, it might be helpful to clarify the meaning of the statement.

**Section II. Genetic Testing and Genetic Information**

2.3 (a) Consider replacing “the definitive genetic cause” with “the genetic basis”

2.3 (c) Consider replacing “genetic disorder” with “genetic mutation”

2.4 Last paragraph, consider replacing part of the sentence beginning “Genetic Testing does not include these methods when they are not...” with “Genetic Testing only includes these methods when they are primarily designed to detect specific genetic defects, rather than to screen for overall biochemical.....”

2.10 Last sentence, consider replacing “accordingly bear ultimate responsibility towards them” with “bear ultimate responsibility with regard to the use of the test and its interpretation.”

**Section III. General Ethical Considerations**

3.2 Note that in the U.S., the term "voluntary" is used rather than "free" when referring to consent.

3.7 In (e), consider including a reference to financial risks of the test result.

3.8 If extra tissue (not just surplus tissue) will be collected for future research, the consent should make this clear.

3.9 Consider adding the following between (c) and (d), “whether or not the test itself is experimental and gives information on what is known about the clinical implications of the test itself, if any; inform as to how the test results relate to the overall purpose of the research.”

3.16 It would be helpful to discuss how a child's understanding will be evaluated and the role of consent monitors in this regard.

3.19 With regard to provisions for genetic testing on persons with impaired mental capacity, it is important to consider medical care situations where information is needed to diagnose and treat a disorder. At times, it may be impossible to obtain the consent of a parent or guardian, and the health of the individual may be at risk. In these settings, the clinical care needs should be distinguished from those of research.

3.24 Since it would be beneficial to further emphasize that full information should be provided to the patient about the urgency of informing others of the test result, prior to overriding this person's wishes, consider adding the following as the first item: "Efforts have already been undertaken to fully educate and explain to the individual the implications of the test results for a third person" and "The genetic information should not be disclosed to others beyond the individuals or entities that need to know in order to avert harm."

#### **Section IV. Public Access to Genetic Testing**

Currently, there is no nationwide consensus in the United States that direct access to genetic tests should be banned or strictly controlled. The American College of Medical Genetics (ACMG), a U.S.-based professional organization representing medical geneticists, issued a policy statement in 2003 discouraging direct access to genetic testing without the involvement of an appropriately qualified health care professional to ensure appropriate use, interpretation, counseling and follow-up. ACMG cautions against self-ordering of genetic tests and use of genetic "home testing" kits due to the complexities of genetic testing and the potential for harm. Yet, many U.S. consumers view direct access to tests and information about tests as empowering, enabling the exercise of greater control over their health and well-being.

In the U.S., States are responsible for controlling who may order laboratory tests, including genetic tests, and who may receive test results. As of 2003, 21 states had no limits on access, 12 allowed limited access and 17 prohibited direct consumer access to laboratory testing. The Food and Drug Administration (FDA) within the Department of Health and Human Services (HHS) and Federal Trade Commission (FTC) both have roles in protecting consumers from false and misleading advertisements in the health care arena, and FTC has a general responsibility for truth-in-advertising in all areas.

SACGHS is addressing direct-to-consumer marketing of genetic tests. In December 2004, the Committee sent a letter to the Secretary expressing concern about the potential harms of direct-to-consumer marketing of genetic tests and recommending that relevant HHS agencies: 1) collaborate with the Federal Trade Commission and provide information about advertisements that could potentially mislead consumers as to the efficacy and safety of genetic tests marketed directly to them; 2) clarify their own roles and responsibilities in monitoring the advertising of genetic tests offered as laboratory services, especially with respect to so called "homebrew" tests; and 3) collect the necessary data and conduct an analysis of the public health impact of direct-to-consumer advertising and direct access to genetic tests. The Committee will be briefed at its upcoming meeting (June 15-16, 2005) about the agencies' efforts.



- 4.2 Consider adding an additional harm: “Misguided reproductive decisions based on misunderstanding or misinformation from a test.”

### **Section V. Specific Ethical Considerations for Human Genetics Research**

- 5.2 Consider replacing “genetic basis of common diseases” with “role of genetic variation in contributing to common diseases.”

### **Section VI. Specific Ethical Considerations for Clinical Genetic Testing**

6.24 U.S. policy also opposes germline genetic modification. However, since the subject of germline genetic modification is, as explicitly noted in 6.25, outside the scope of this report, it is not clear why the topic is included in the document.

6.34 In (b), consider replacing “Such disorders are generally due to the interaction of genes and...” with “Such disorders are often the result of the interaction of multiple genes and environmental factors.”

6.45 Consider adding that laboratories recognize that results may not always be returned to health care providers familiar with genetic principles, and that pertinent information and follow up recommendations (i.e., for genetic counseling) should be made in a useful and comprehensible way. Ideally, adequacy of the reports should be evaluated with both laboratory and health care provider input.

6.47 This paragraph discusses the importance of assuring test accuracy in the testing process and raises a specific concern about direct access “as there is no assurance of the quality of the test result.” However, with regard to direct access, a major concern is that information purported to be health-related will be provided to persons in the absence of the necessary medical expertise important for its appropriate understanding and use (or that the test should have even been taken in the first place).

6.49 CLIA is now referred to as the Clinical Laboratory Improvement Amendments. The reference to the data can be dropped since there have been significant changes since. The second sentence should be clarified because American Board of Medical Genetics and American College of Medical Genetics have different purposes.

Also, in the United States, the Clinical Laboratory Improvement Amendments establishes quality standards for all clinical testing laboratories to ensure the accuracy, reliability, and timeliness of the test result. At this time, there are no specific requirements under CLIA that address genetic testing although there are efforts underway to augment the current regulations. In the United States, professionals directing genetic testing laboratories are qualified under a number of mechanisms. These mechanisms range, based on federal and depending upon State laws, from holding licensure as a doctor of medicine or osteopathy together with laboratory training or experience to achieving board certification (of which the

American Board of Medical Genetics and the Molecular Genetic Pathology subspecialty of the American Board of Pathology and ABMG are examples) to demonstrated previous specific experience as director of a clinical laboratory. Many laboratory directors are members of the American College of Medical Genetics or other relevant professional organizations. See [www.acmg.net](http://www.acmg.net) for more information.

### **Section C**

The discussion in this section recognizes that the use of genetic information will continue to increase in medical practice and urges that this information be considered as part of general medical information. U.S. practice does not require that genetic counseling be provided in all cases but rather that the degree of counselling be based on the risks associated with a particular test. This allows support resources to be directed to those who may need additional services due to the potential implications of the test results. With the increased use of genetic tests that are less predictive, the delivery of information to the patient will be less in the realm of traditional genetic counseling and more in the area of guidance from primary care providers. The document mandates non-directive genetic counseling for genetic tests. While this is appropriate for traditional genetics based on single gene disorders, such services will be impossible (and likely not appropriate) for wide-spread genomic applications in health care that are based on variation in one or multiple genes. In addition, counseling in these circumstances may be directive (e.g., avoidance of environmental exposures). Educational efforts for primary care providers who will be applying these tests in their practice are essential.

6.63 Some countries have established certification standards for genetic counseling. In the United States, the American Board of Genetic Counseling accredits training centers and certifies genetic counselors. See [www.abgc.net](http://www.abgc.net) for more information.

Dr Alvin Wong Seng Cheong M.B.B.S., M.R.C.P. (U.K.)
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26 May 2005

Members of the Bioethics Advisory Committee:

I thank you for the opportunity to have spoken at the meeting at the Sheraton Towers on Tuesday 17 May 2005. I was asked by the Catholic Medical Guild (CMG) to be part of their panel, and I had earlier submitted a short paper to them. In the course of the meeting and while listening to the other distinguished speakers, I realised that having come from a background of both clinical medicine and laboratory research I could contribute more specifically from a philosophical and bio-scientific viewpoint. It is important for those of us in positions of government to be conversant with both the *science of reasoning* as well as the *science of technology*.

As I had received many positive and kind comments after my presentation (from members of the panel as well as the different groups present, even from the secretary), I thought it would be opportune to collate those points on paper, with some additions.

A. When is the beginning of human life?

1. I started out by addressing a point raised by Chairman that the some religious groups had used differing time points: e.g. 4 months of pregnancy, 40 days of pregnancy etc, to guide what could or could not be done to the embryo or foetus. The 14-day rule itself, supposedly based on the beginnings of the nervous system in the embryo, is one such other definition of the beginning of life.
2. I questioned those present (without meaning to offend any party), whether it was possible to determine accurately those time points. Do we judge the decision on the licit-ness to terminate a pregnancy based on the woman's memory of her last menstrual period? Do we go by the ultrasound technique dependent on the operator's personal experience and skill? How arbitrary can it seem for us to say that it is licit to destroy the embryo today but not tomorrow, if the defined time point (40 days or 4 months) is supposedly at midnight tonight? How many days is one month supposed to have?
3. I had a letter published in the Straits Times a few years ago on the arbitrariness of the 14-day rule. We had surely come to know of the 'beginnings of the nervous system at 14 days' after some technological advancements gave us the ability to do so; before such a time in the history of medicine we did *not* have the means to know. So as science advances further might we not find the evidence that the beginnings of the nervous system are even earlier? That the incipient stages of the embryo's 'sensation' are already in motion? *Are we again going to change the*

*definition of life then?* Is it our technological abilities that determine when life begins? Will the avid proponents of the 14-day rule say something avidly against the definition for a ‘legal abortion’ at 24 weeks?

4. I underlined the fact that from human reasoning alone, from *philosophy*, one can form certain principles on the beginning of human life. I urge the BAC to understand the premise that we *do not even need to argue from the standpoint of faith*. The robustness of our ethical decision-making can be judged on *how scientific our reasoning process has been*.
5. In medical school I remember using the recommended textbook on embryology by Keith Moore. Medical students are told, right at the beginning of their arduous course: “Human development begins at fertilization when a male gamete or sperm (spermatozoon) unites with a female gamete or oocyte (ovum) to form a single cell—a zygote. *This highly specialized, totipotent cell marked the beginning of each of us as a unique individual*”<sup>1</sup> (emphasis added). It is without a doubt that human life, including yours and mine, begins at this point. *This is what the science of embryology tells us*.

#### B. But the culture of death has arrived!

1. March this year saw the publication of the Groningen protocol in the New England Journal of Medicine, which was about the euthanasia of severely ill newborns. As euthanasia was already part of the culture of the Netherlands, the article was even about a systematic way “to provide all the information needed for assessment and to prevent interrogations by police officers ... for cases in which a decision is made to actively end the life of a newborn”.<sup>2</sup>
2. *There is no real difference between the infanticide of the Dutch seen here, and what we do in PGD, PTT, or PND with a view to abortion*. It is the active termination of human life. It is also called murder. The culture of death desensitizes us to this fact. Murder is disguised as compassion, as reproductive choice, as medical advancement. The culture of death has arrived in a most insidious way.

#### C. What is good medicine?

1. In my training years in medical oncology, I remember being told one day by my consultant of a pregnant woman who was diagnosed with breast cancer. The first ‘therapy’ that he seemed to recommend was that of an abortion, which I of course disagreed with. Some years later, the University of Texas M.D. Anderson Cancer

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<sup>1</sup> Keith L. Moore and T.N.V. Persaud, *The Developing Human: Clinically Oriented Embryology*, 5<sup>th</sup> edition.

<sup>2</sup> *Eduard Verhagen, M.D., J.D., and Pieter J.J. Sauer, M.D., Ph.D.* The Groningen Protocol — Euthanasia in Severely Ill Newborns. *N Engl J Med*, March 10 2005, Volume 352:959-962.

Centre in Houston published a prospective clinical trial of chemotherapy administered to pregnant women with breast cancer from the 2<sup>nd</sup> trimester onwards, showing its feasibility and efficacy. I recently treated a 38-year old lady with high-risk (lymph node positive) breast cancer diagnosed while she was carrying her 3<sup>rd</sup> child. She had her mastectomy done in the 1<sup>st</sup> trimester, and adjuvant chemotherapy (consisting of cyclophosphamide, adriamycin and 5-fluorouracil) was commenced in the 2<sup>nd</sup> trimester. She completed 6 cycles of chemotherapy and has delivered a healthy baby 3 weeks ago. She is now preparing to undergo adjuvant radiotherapy.

2. If termination of pregnancy was seen as the answer to all medical problems that the expectant mother develops, we would have very little 'medical obstetrics' per se. Medicine is about finding solutions to medical problems, either for cure or control of disease, or for palliation. To extinguish the very lives we are supposed to be responsible for is *not* medicine at all.
3. I know that there are *probably* cases of abortion done every year for thalassemia. When I was in medical school I saw children with  $\beta$ -thalassemia major who were blood transfusion-dependant and had 'chipmunk-like facies'. Last week my paediatrician colleague told me that he had a *25-year old* patient with thalassemia major: "she has *no facies* ... she looks beautiful ... she has a boyfriend ...". I repeated to those of you present: "she has *no facies*...".
4. I quoted from a 1999 publication in the New England Journal:

The marked increase in survival, to the fifth decade of life, of patients with well-managed  $\beta$ -thalassemia in developed countries represents one of the most dramatic alterations in morbidity and mortality associated with a genetic disease in this century.<sup>3</sup>

And from a more recent one:

In the last decades, treatment of patients with beta-thalassemia has changed considerably, with advances in red cell transfusion and the introduction of iron chelation therapy. This progress has greatly increased the probability for a thalassaemic child to reach adult age with a good quality of life. At present, the prognosis for thalassemia major patients is "open-ended". Compliance with the conventional treatment and psychological support are critical to obtain good results. The expectancy of a long survival of good quality encourages the patients to plan their future life, having a job, a family and often children. Optimal treatment of thalassemia major is expensive and for this reason, unfortunately, available only for a minority of patients in the world. Despite the significant advances, other progresses are expected to further improve survival and quality of life. The major aim is the cure of the disease, increasing the possibility of bone marrow transplantation using HLA-matched unrelated donors, and hopefully, in the future, gene therapy. However, even the conventional treatment and in particular iron chelation is expected to improve. Efforts should be made by the Western countries, and by the international health and economic organizations to provide continuous and concrete support for achieving a high standard of management for thalassemia in all places of the world.<sup>4</sup>

<sup>3</sup> Olivieri NF. The beta-thalassemyias. N Engl J Med. 1999 Jul 8. Vol 341(2):99-109.

<sup>4</sup> Galanello R. A thalassaemic child becomes adult. Rev Clin Exp Hematol. 2003 Mar;7(1):4-21.

5. Members of the BAC, *this* is medicine: when we develop over time, with biotechnological advancements, notwithstanding the arduous demanded, true and ethical solutions for the diseases that we face. Transfusion therapy and iron chelation techniques have been key factors in improved thalassemia treatment. Bone marrow transplantation is known to be even curative. I came across foreign<sup>5</sup> and local<sup>6</sup> authors trying to open up greater possibilities for the sources of hematopoietic stem cells using matched unrelated cord blood, perhaps a fortuitous resource provided by nature, just waiting to be tapped. The potential in this resource highlighted by these authors could thus be *the ethical alternative to PTT*.
6. I looked at the survival curves in thalassemia major and found this<sup>7</sup>:

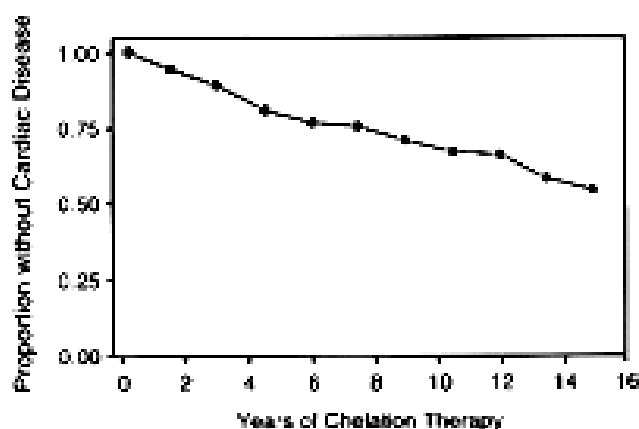


Figure 1. Survival without Cardiac Disease during Chelation Therapy in 97 Patients with Thalassemia Major.

This curve was obtained more than 10 years ago! What could it be like now?

7. In advanced cancer treatment, which I am more familiar with, history can be made by an average improvement in the median survival of 2 or 3 months. Both the pharmaceutical industry and the scientific community get excited over this magnitude of gain as long as it can be proved to be statistically significant. The

<sup>5</sup> Jaing TH, Hung IJ, Yang CP et al. Rapid and Complete Donor Chimerism after Unrelated Mismatched Cord Blood Transplantation in 5 Children with beta-Thalassemia Major. *Biol Blood Marrow Transplant*. 2005 May;11(5):349-53.

<sup>6</sup> Tan PL, Shek PC, Lim LC, et al. Umbilical cord blood stem cell from unrelated donors is a feasible alternate stem cell source for transplant in patients with genetic diseases. *Ann Acad Med Singapore*. 2004 Sep;33(5 Suppl):S82-3.

<sup>7</sup> Nancy F. Olivieri, David G. Nathan, James H. MacMillan, et al. Survival in Medically Treated Patients with Homozygous  $\beta$ -Thalassemia. *N Engl J Med*, 1994 Sep 1. Volume 331:574-578.

economic repercussions are tremendous. In thalassemia major we are talking in terms of *years and years of life*, which most advanced cancer patients are presently far from achieving ... Can we say we are practising *medicine* by doing PGD, PTT, or PND with a view to abortion for thalassemia? These techniques look more like *bad medicine*, or may I say, *not medicine* at all.

8. In another recent publication, it seemed that the threshold of cure for the terrible severe combined immunodeficiency had been broached<sup>8</sup>, although many safety<sup>9</sup> and ethical issues remain to be resolved. We live in exciting times where *good science* can achieve what was once thought impossible. The philosophy of PGD, PTT and PND with a view to abortion, run counter to this.
9. Mr Chairman, I remember urging you at the meeting, as an endocrinologist, to consider the success behind the screening and treatment of congenital hypothyroidism. What great medicine we have! Could we have seen this day if we chose instead to exterminate all cretins?
10. In no way do I mean to ridicule the aims of medical oncology in *advanced* cancer patients – far from it in fact. My colleagues in the department have recently returned from the American Society of Clinical Oncology (ASCO) annual meeting in the U.S. (together with thousands of others), where many important advances would have been presented.
11. We are in the age of *targeted therapy*. You may call these ‘smart bombs’ or ‘guided missiles’, which only destroy the target cancer cells but not others. I recently had a patient with advanced lung cancer on the verge of death. A few days after starting him on a drug called Gefitinib (Iressa®), he took off his oxygen tubes and went home without breathlessness. I reviewed him recently in the clinic and he was well. Interestingly, Asians could be more responsive to this drug, based on the incidence of certain mutations of the Epidermal Growth Factor Receptor, especially in lung cancers developing in non-smokers<sup>10,11</sup>. The manner and degree of clinical improvement and prolongation in survival of these patients is unprecedented. Imatinib (Glivec®) is another such drug used to great effect in not just one but several cancers: chronic myeloid leukaemia, gastro-intestinal stromal tumour (GIST) etc. Almost instantaneous ‘functional’ response has been documented on

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<sup>8</sup> Hacein-Bey-Abina S, Le Deist F, Carlier F, et al. Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. *N Engl J Med*. 2002 Apr 18;346(16):1185-93.

<sup>9</sup> Hacein-Bey-Abina S, von Kalle C, Schmidt M, et al. A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. *N Engl J Med*. 2003 Jan 16;348(3):255-6.

<sup>10</sup> Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol*. 2005 Apr 10;23(11):2513-20.

<sup>11</sup> Han SW, Kim TY, Hwang PG, et al. Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol*. 2005 Apr 10;23(11):2493-501.

- positron emission tomography (PET) in GIST patients treated with Imatinib, supporting the ingenious molecular design of the drug targeting a specific receptor on the cancer cell, producing impressive clinical results in a tumour for which no treatment for inoperable cases was previously known<sup>12</sup>.
12. I say again, we are in the age of *targeted therapy*. *Designer medicine* if you will. Medicine designed to heal and not to kill. Let us not miss out on it.
  13. I could go on since I am aware of the landmark advancements in the field of oncology and haematology: the use of platinum based chemotherapy in curing ovarian cancer, the use of all-trans retinoic acid (ATRA) in acute myeloid leukaemia (M3 subtype), the use of bone marrow transplantation in various haematological conditions, of which thalassemia has already mentioned, etc. Who is this man called Lance Armstrong, winner of 6 Tour de France championships, who was cured of testicular cancer, which had spread even to his brain?
  14. Are we not excited about the possibilities of in-utero surgery to correct life-threatening congenital conditions? Our efforts to practise good medicine, great medicine, previously thought to be *impossible medicine*, are undermined by the very aims of PGD, PTT and PND with a view to abortion.
  15. I have another colleague in the field of palliative medicine who trained in Australia. He is an expert in interventional palliative techniques such as intrathecal analgesia, where a catheter is inserted into the thecal space of the spinal canal and pain-relieving medicine infused directly into the central nervous system. He is looking to expand the use of this technique to many clinical situations. When we cannot cure or control a disease, the emphasis shifts to palliation. While we can only *sometimes* cure a disease and *often* are reduced to controlling it, "*to comfort always*" we must ... so I was taught by my teachers in medicine who, needless to say, are men of greater stature. The Groningen protocol is not a solution in the realm of medicine, neither is PGD, PTT, nor PND with a view to abortion. My colleagues in the field of palliative medicine tell me that this important branch of clinical medicine has not achieved formal accreditation status as a specialty yet. Why are we slow to recognize the efforts of those who have trained in the science (and art) of alleviating human suffering?
  16. You may argue that all these latest medical treatments are expensive. Treating a thalassaemic child may seem to be a burden on resources. You probably know that the procedures being debated, especially PGD and PTT, are not simple nor cheap either. I mentioned the drug Imatinib (Glivec®) earlier for treatment of unresectable GIST. I have patients with this previously untreatable disease who are in remission thanks to the generosity of the Max Foundation, started by Pedro Rivarola in honour of his late son Maximiliano. This foundation funds Glivec®, which costs

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<sup>12</sup> Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002 Aug 15;347(7):472-80.



thousand of dollars each month, for needy patients worldwide<sup>13</sup>. The founder, whose “vision, leadership and compassion have enabled The Max Foundation to assist countless sick persons across the globe”<sup>13</sup>, has since gone on to pursue other international opportunities related to cord blood research<sup>14</sup>. I recently had another patient with lymphoma who had her treatment (including Rituximab, a state-of-the-art monoclonal antibody) funded by the Leukemia and Lymphoma Foundation. The National Kidney Foundation, which has been supporting the life prolonging dialysis treatments of so many kidney failure patients in Singapore, has even announced its plan to fund cancer therapy<sup>15</sup>. It is obvious that the resources are out there waiting to be garnered. There will always be generous people who will endorse *good medicine* with their money, time and effort.

#### D. Motherhood versus manufacture

1. I recounted this incident for the benefit of the BAC. My female colleague who was pregnant with her 3<sup>rd</sup> child had severe nausea one day. She had come to work that day but looked as though she could not continue with her duties. When I offered to give her an anti-emetic to relieve her symptoms, she politely declined, saying: “nothing artificial ...”. I was impressed, and will remember what she said for a long time.
2. For this is motherhood. When a mother forgoes her own, even legitimate, comforts for the sake of the child she has conceived. The anti-emetic I had offered would be something that had been time-tried and proven safe in pregnancy. Yet this mother reacted with a maternal instinct so powerful that I had no answer. There are very few things more powerful than a mother’s love for her baby.
3. Members of the BAC, which mother never experienced *any* pain? Those of you with spouses and children, have you not experienced for yourselves that *sorrow is the touchstone of love*? And which child never experienced pain too? Another friend of mine has 4 children. I got to know that the 4<sup>th</sup> child has Down’s Syndrome. One day I heard the father speak about the joys that the other normal siblings would have when they played with their little brother. I know of another couple, whose own children had already grown up and married, who bravely adopted a Down’s child. After a stormy infancy, he is now “uncle” to his nephews and nieces, and so much a part of the family. I urge you not to underestimate the capacity of the human heart to love a sick child or any other sick family member. If we did not have this capacity we would not be human.
4. True parenthood is about sacrifice. Are we about to endorse a new era of *manufacture* instead of motherhood? PGD, PTT, and PND with a view to abortion

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<sup>13</sup> [www.themaxfoundation.org](http://www.themaxfoundation.org)

<sup>14</sup> <http://www.themaxfoundation.org/News/News.aspx?trgt=newsfullstory&storyid=68&lang=engl>

<sup>15</sup> <http://www.nkfs.org/events.htm>

are totally contradictory to the essence of parenthood, which is about self-giving, not selfishness.

E. The right to object is an objective right

1. It goes without saying, that conscientious objectors to abortion should be protected by law. I have witnessed a fellow houseman (and have heard of others), who did not ask to work in obstetrics and gynaecology, stand firm in his refusal to *cooperate* in the evil of abortion and the like. This houseman was told by his superiors of the possibility of having his posting disqualified. Could the law have protected him?
2. As health administrators and healthcare workers, our rights in conscientious objection should be protected. This should apply *in any act that may result in the evil of abortion*, including something like the notification of thalassemia carriers to the National Thalassemia Registry. I encouraged Professor Kaan to take up the issue of making legal requirements for such notification forms to include clauses that protect the consciences of the physicians concerned, since notification may also be done for ethical reasons. I have also advised the CMG to specifically mention this in their submission, and included an example as to how this clause might be phrased.
3. Let us not assume that everyone agrees with everything permitted by civil law. When I attended the recent launch of former Member of Parliament Joseph Conceicao's memoirs, the guest-of-honour, DPM Jayakumar talked about how Mr Conceicao had previously raised objection to the Abortion Bill in parliament<sup>16</sup>. I took this as a commendation of someone who dared to stand up for his principles.

F. In conclusion

1. At our meeting, in response to what Chairman had alluded to regarding arguments based on faith, I reminded the BAC of what Hippocrates, in the *pre-Christian* era, swore in his famous oath:

I will neither give a deadly drug to anybody who asked for it, nor will I make a suggestion to this effect. Similarly I will not give to a woman an abortive remedy. In purity and holiness I will guard my life and my art...

2. I encourage members of the BAC to re-live a little the times of the ancient Greek thinkers such as Aristotle, whose conclusions and methods, though perhaps not perfect, give us an insight into what must unite humanity when judging its behaviour – a common *natural law*. I am talking about *a moral law inscribed in the hearts of men*, inherent in and based on his very human nature, which is above that of a purely animal nature. This human nature has to be the same for all of us, or else

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<sup>16</sup> “As an MP he spoke his mind on the issues, and when the Whip was lifted, he voted against the Abortion Bill.” Remarks by DPM Jayakumar on the occasion of the launch of Mr Joe Conceicao's book. Press releases: 24/09/2004. <http://www.mfa.gov.sg/internet/>

we are admitting that humanity is a race composed of different species. In this common natural law the need to be *absolute* in matters essential to the human nature (issues of life and death, sexuality) becomes obvious. *Moral relativism, by definition, cannot sustain itself, since it is a self-defeating principle.*

3. I hope I have inspired the BAC to take on the challenge to find the ethical solutions. The future is in our hands! The ethical solution to every problem can only be within the reach of our ingenuity and creativity. My colleagues at the National University Hospital were studying how bone marrow stem cells taken from the chest bone at a cardiac bypass operation can improve cardiac function after being injected into the damaged heart. When the surgeon splits open the chest bone en route to accessing the heart, the bone marrow containing stem cells are already there, staring at him in the face<sup>17</sup>. Often times the providential solution could be right “under our noses”<sup>18</sup>. Exciting and unprecedented developments take place as we speak<sup>19</sup>.
4. Lastly, I did encourage the BAC to peruse parts of “Beyond Therapy: Biotechnology and the Pursuit of Perfection” from the U.S. President’s Council on Bioethics (October 2003)<sup>20</sup>. Chapter 2 of this document “Better Children” for example, gives some insights into the dangerous ramifications of implementing PGD, PTT and PND with a view to abortion, ramifications of which I’m sure the Committee is already aware to some degree. As a known phenomenon, the pendulum of nature could well strike back with emphatic reproach for our mistakes.

Dr Alvin Wong Seng Cheong  
M.B.B.S., M.R.C.P. (U.K.)  
Consultant  
Dept of Haematology Oncology  
National University Hospital

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<sup>17</sup> <http://wired-vig.wired.com/news/print/0,1294,44671,00.html>

<sup>18</sup> Murrell W, Feron F, Wetzig A, et al. Multipotent stem cells from adult olfactory mucosa. *Dev Dyn*. 2005 Jun;233(2):496-515.

<sup>19</sup> Escolar ML, Poe MD, Provenzale JM, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. *N Engl J Med*. 2005 May 19;352(20):2069-81.

<sup>20</sup> <http://www.bioethics.gov/reports/beyondtherapy/index.html>

From: Dr Peter Ang  
Consultant  
Department of Medical Oncology  
National Cancer Centre

Received by email: 10 May 2005

“This is my feedback to the BAC.

I would like to add my views to the recommendation of the BAC on:  
“Ethical, Legal and Social Issues in Genetic Testing and Genetics Research”

Specifically, with respect to the following: “Recommendation 18: Susceptibility testing should not be applied clinically unless there is unequivocal empirical evidence of validity and utility.”

The field of susceptibility testing is evolving rapidly since the sequencing of the genome. As we understand more of the genes involved in cancer, more information regarding risk reduction or prevention is becoming available. Most of these highly penetrant cancer genes are not common and it is difficult for clinical trials or studies to truly provide “unequivocal empirical evidence” for it to be useful. Nonetheless, there is emerging data albeit slowly emerging through studies done in such families and some may be less than perfect data. I do agree that frivolous genetic testing without adequate information and counselling is not useful or even be harmful.

Please reconsider the wording of the recommendation.”

From: Aviva Ltd
Received by email: 17 May 2005

“Thank you for inviting comments on the consultation paper on the Ethical, Legal and Social Issues in Genetic Testing and Genetics Research. The paper was circulated via the Life Insurance Association of Singapore, and Aviva Ltd, being one of its members, is happy to be able to express our views.

As mentioned by Mr John Lockyer in his letter to you and his attached paper, a contract of utmost good faith with an obligation on each party to disclose relevant information. We feel very strongly about this. An insurance applicant’s knowledge of his or her mortality or morbidity would undoubtedly be classified as material information, because the non-disclosure of such information goes against this core principle of insurance, and would greatly prejudice an insurer. Consequently, such inequality of information would lead to the risk of anti-selection to the detriment of insurers and the insurance industry. This moral hazard is further accentuated by the fact that clinical genetic testing has a far greater predictive value than any current medical examination or investigation to determine to a significantly higher degree of probability a person's mortality and morbidity.

Therefore, though we appreciate the ethical and social issues surrounding the disclosure of genetic testing information, we strongly feel that the law must not bar any insurer from obtaining such information if a free and informed consent is given by the applicant. The treatment of disclosure of information must accordingly be regarded as any other medical information currently available and all provisions of confidentiality and privacy equally applied.

One other view that we would like to present with regards to non-disclosure of genetic testing information is that at the present moment, genetic testing is a very deliberate and expensive procedure. It can therefore be inferred that such testing would have been done with the full knowledge and conscious consent of the subject. Except under conditions of research where the subject can opt not to know the results of the testing, the proposed framework stipulates that the results must be communicated without undue delay to the subject. This strongly suggests that any non-disclosure of knowledge of results can only be fraudulent and the insurer would therefore be entitled to handle the matter as it would any instance of fraudulent non-disclosure.

In conclusion, we support the efforts of BAC to establish clear policies and framework on genetic testing. We urge that any policies will not impede the conduct of life insurance business in Singapore, and feel that with the existing infrastructure of handling private and confidential medical information, with some refinements, could sufficiently address concerns raised in the consultation paper.”

From:	Chief Actuary's Office Great Eastern Life Assurance Co Ltd
Received by email:	12 May 2005

“Our only comment is as follows:-

*‘Recommendation 7: Genetic test results should not be disclosed to third parties, including employers and insurers, without the free and informed consent of the individual.’*

Agree. If an applicant's attending doctor indicates that a genetic test has been done, insurance companies should be able to see the results. Insurers need to have access to all information applicants have, in order to avoid anti-selection since applicants might use their own genetic information to obtain the highest and most comprehensive insurance coverage.

However, insurers should be prohibited from requiring that new tests to be performed to secure coverage.

Insurers should also educate the public that disclosing results of genetic tests done does not necessary mean that their coverage will be declined. Insurers should also ensure that their underwriters have the adequate knowledge on genetic conditions so that they will not decline coverage because it is a rare condition.”

From: Mr Seah Seng Choon  
Executive Director  
Consumers Association of Singapore

Received by email: 31 May 2005

“General comments

We agree that all precautions should be taken to ensure that parties involved in such testing are clear of their roles and obligations. We are concerned that there is no explicit mention of measures that will be put in place to deter breaches of the rules suggested in your recommendations although you have alluded to some possible action such as ensuring the parties work "within legal and ethical limits". We feel that it may be better to be explicit about the matter in order to ensure compliance.

On Recommendation 7, two operative words are noted:-

- a) "should not be disclosed" - as opposed to 'shall not' which is stronger. This opens up the possibility that there may be circumstances that the testing agency can disclose without the consent of the individual.
- b) "without the free and informed consent of the individual" - This is easily circumvented as follows. The testing agency itself may not disclose the information to the insurer or third party, however, the individual himself may be obliged render full co-operation to the insurer or third party have the data disclosed. Under insurance law, the insured has a duty to disclose all material facts, in this case, the test results known or obtained, at the time the proposal for insurance is being made to the insurance company. If the insurer has knowledge that the insured had participated in such a test, it is quite likely that if the insured refuses to give his consent for the data to be released that (1) the insurer may refuse to pay for the insured failure to disclose material facts and/or (2) if the insured sues the insurer, for the insurer to obtain a court order for the data to be disclosed. Of course, it may be possible for the insured's solicitors to argue that the insurer is trying to 'fish' for info and does not have any basis for saying that the data is relevant but we think it is unlikely that such an argument in this instance would be successful.”

**From:** "Dean-Biological Sciences" <D-SBS@ntu.edu.sg>  
**To:** <contactus@bioethics-singapore.org>  
**Sent:** Tuesday, May 17, 2005 5:36 PM  
**Subject:** Feedback on Consultation Paper

**School of Biological Sciences**

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Tel: +65 6316 2800 Fax: +65 6791 3856  
URL: <http://www.ntu.edu.sg/sbs>

**Nanyang**  
Technological University

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17 May 2005

Associate Professor Terry Kaan  
Chairman, Human Genetics Subcommittee  
Bioethics Advisory Committee  
20 Biopolis Way  
#08-01 Centros  
Singapore (65) 64789581

Dear A/Prof Kaan

**FEEDBACK ON CONSULTATION PAPER**

We refer to the 'ethical, legal and social issues in genetic testing and genetics research' consultation paper, and our comments are as follows:

- 1) Should probably encourage to implement part 4.12 "Involuntary Genetic Testing" according to UK legislation ASAP.
- 2) With regards to recommendation 24, genetic counselling should be conducted by certified genetic counsellors. To implement this regulation, the Singapore Board of Genetic Counselling has to be established to prepare and administer examinations to certify individuals who provide services in the genetic counselling. Please see [<http://www.abgc.net/genetics/abgc/abgcmenu.shtml>].

Thank you.

Yours sincerely,

James Tam  
Professor and Dean



**DIALOGUE SESSION WITH RELIGIOUS GROUPS**  
**4.00 PM, 17 MAY 2005**  
**SHERATON TOWERS HOTEL**

**Present:** Bioethics Advisory Committee (BAC)  
Professor Lim Pin  
Chairman

Senior District Judge Richard Magnus  
Deputy Chairman

Associate Professor Terry Kaan  
Chairman, Human Genetics Subcommittee

Associate Professor John Elliott  
Member

Mr Charles Lim  
Member

Participants

Fourteen representatives from the following religious groups:

1. Graduate Christian Fellowship
2. Inter-Religious Organisation, Singapore
3. Majlis Ugama Islam Singapura (Islamic Religious Council of Singapore)
4. National Council of Churches of Singapore
5. Singapore Buddhist Federation
6. The Catholic Medical Guild of Singapore
7. The Jewish Welfare Board
8. The Spiritual Assembly of the Baha'is of Singapore

**Report:**

The dialogue session was chaired by the BAC Chairman, Professor Lim Pin. Representatives from the religious organisations were invited to share their views and concerns on the issues discussed and the recommendations proposed in the Consultation Paper, *Ethical, Legal and Social Issues in Genetic Testing and Genetics Research*. The views of the participants centred on the following issues:

- Respect for the embryo and the concept of personhood;
- Preimplantation genetic testing;
- Prenatal genetic diagnosis;

- The importance of free and informed consent;
- Safeguards for privacy and confidentiality; and
- A conscientious objection provision for healthcare professionals.

Most of the views expressed had earlier been submitted in writing to the BAC. Additional comments are provided below.

- The Singapore Buddhist Federation's representative shared a guiding moral principle in Buddhism that as long as a deed, for example research, was beneficial to mankind or the world, it would generally be acceptable. In Buddhism, the morality of any deed is determined more by the intention of the one who performs the deed than the deed itself.
- The representative from the Jewish Welfare Board was concerned with voluntariness of 'consent'. In donating tissues for research, pressure should not be imposed on anyone to consent without being fully informed. The BAC's recommendation on the requirement for free and informed consent was welcomed.
- As the Inter-Religious Organisation comprised of members from various religions, there was a diversity of views on the issues considered by the BAC. The preference would be for the BAC to find a common ground in the ethical, legal and social issues that would help unite the communities in Singapore, and promote Singapore as a progressive nation with high ethical standards and moral values.
- Representatives from the Graduate Christian Fellowship, the National Council of Churches of Singapore and the Catholic Medical Guild reiterated at some length their continued difficulty in accepting research or medical procedures that entailed the sacrifice of embryos, for reasons set out in all their submissions to the BAC. The BAC Chairman and members felt that this intractable issue should not be reopened as different faiths took different views. Nevertheless the position of these organisations and their emphasis on the importance of effective conscientious objection provision were noted.

The BAC Chairman and members present agreed that the final recommendations on genetic testing and genetic research should include a provision to allow healthcare professionals to opt out of activities to which they have a conscientious objection.

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**DIALOGUE SESSION WITH MEDICAL PROFESSIONALS**  
**4.00 PM, 1 JUNE 2005**  
**BIOPOLIS**

**Present:** Bioethics Advisory Committee (BAC)  
Professor Lim Pin  
Chairman

Dr Denise Goh  
Member, Human Genetics Subcommittee (HGS)

Participants:

Nineteen representatives from the following healthcare institutions and *in vitro* fertilisation (IVF) service providers:

1. Centre for Assisted Reproduction Pte Ltd
2. Embryonics International
3. Christopher Chen Centre for Reproductive Medicine Pte Ltd
4. Institute of Mental Health
5. KK Women's and Children's Hospital
6. National Cancer Centre
7. National Neuroscience Institute
8. National University Hospital
9. O & G Partners Clinic for Women & Fertility Centre
10. Singapore General Hospital
11. Singapore National Eye Centre
12. Tan Tock Seng Hospital
13. The Heart Institute
14. Thomson Medical Centre

**Report:**

The dialogue session was chaired by Professor Lim Pin. Participants were invited to share their views and concerns on the issues discussed and the recommendations proposed in the Consultation Paper, *Ethical, Legal and Social Issues in Genetic Testing and Genetics Research*. The views of the participants centred on the following issues:

- Implementation and impact of the recommendations;
- The need for regular review of the guidelines;
- The stringency of guidelines for susceptibility testing and the use of preimplantation genetic diagnosis for sex selection;
- Treating genetic information as medical information;
- The practice of genetic counselling;
- More detailed guidance for researchers in genetic research; and
- Genetic testing of children.

### ***Implementation and Impact of the Recommendations***

One participant pointed out that earlier reports had been published on the same issues as the BAC's Consultation Paper, for example, the *Ethical Guidelines for Gene Technology* produced by the National Medical Ethics Committee. He asked how the proposed measures in this Paper would affect current government policy or medical practice if they were to be implemented.

Another participant was in favour of broad guidelines for the protection of consumers while allowing flexibility in medical practice and for circumstances peculiar to individual patients. She enquired about the entity that would be responsible for monitoring compliance with the proposed regulations and details of the enforcement mechanisms.

Professor Lim explained that recommendations from the BAC would be translated into government policies when approved and hence would supercede previous guidelines. The present recommendations were prepared for the Life Sciences Ministerial Committee. If these recommendations were accepted, the measures to be taken would be the responsibility of the relevant authority, possibly the Ministry of Health (MOH). Therefore, BAC's recommendations would remain as guidelines unless superceded by legislation or regulations. The appropriate authority would eventually decide which recommendations ought to be made into law and which ones adopted as professional guidelines, practice directions or policies not requiring legislation.

### ***Future Review of the Recommendations***

There was concern that with the rapid and continuous evolution of science and medicine, the standards of benefit and harm might change accordingly and it was suggested that the BAC included a statement of intent to review its recommendations at a later time.

Another related concern was the possible inadequacy of policy if it lags too far behind science. The IVF guidelines were reviewed in 1993 and last in 1999. Since then, tremendous developments have taken place. Hence, it would be timely to review these guidelines.

Professor Lim felt that these were good points to note. He added that societal values and expectations would also change with time. For this reason, BAC's guidelines should never be cast in iron. Public feedback should be continually solicited and reviewed.

### ***Susceptibility Testing***

One participant felt that the requirement for “unequivocal empirical” evidence before a new susceptibility test could be introduced (Recommendation 18)<sup>1</sup> was not practical. Such a requirement was unrealistic as many genetic diseases were rare and it would take time for susceptibility tests to be developed. Moreover, as many people were unwilling to undergo susceptibility tests, the collection of data to support such tests posed a problem.

Dr Denise Goh agreed that data collection to validate susceptibility tests was not easy. But the intention of Recommendation 18 was to protect people from being subject to susceptibility testing when the basis for the test was very weak. Evidence-gathering testing should belong to the realm of research testing instead of clinical testing, until the evidence was sufficiently strong.

### ***Status of Genetic Information with Respect to Other Medical Information***

One participant suggested that genetic test results be clearly separated from other medical information and only be disclosed to insurers with specific consent and not the general consent which some patients might be asked to sign on the application forms without fully comprehending the implications. Treating genetic information separately from other medical information would help restrict the handling of genetic information to only qualified healthcare professionals.

Professor Lim clarified that genetic information should be treated like medical information as a matter of general practice. The BAC planned to provide recommendations for the access to genetic information in special situations, such as insurance and employment, in the next report which would deal with linked medical registries and genetic databases.

Dr Goh felt that attributing a higher level of confidentiality to genetic test result as opposed to other medical information might lead to impractical restrictions on common genetic tests and screenings. Furthermore, certain health conditions could not be exclusively classified into the genetic category. She felt that the better option would be to educate healthcare professionals, not so much on how to interpret genetic test results, but rather on the serious implications and the necessity to refer the patient to specialists, when indicated.

### ***Preimplantation Genetic Diagnosis (PGD)***

Two participants felt that certain circumstances, such as families yearning for a boy after having daughters in succession, might present a strong case for sex selection by

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<sup>1</sup> This recommendation stated that: “Susceptibility testing should not be applied clinically unless there is unequivocal empirical evidence of validity and utility.”

PGD. One of the participants enquired about the possibility of including an option for families to appeal to the regulator on a case-by-case basis for permission to select sex by PGD, instead of completely disallowing the procedure for non-medical reasons. People might wonder why they were denied their right to balance their family despite the availability of the technology.

Another participant added that foreigners had questioned why abortion was legal in Singapore while sex selection of the foetus was not. A fourth participant asked about the possibility of using alternative methods to PGD for selecting the sex of the embryo.

Professor Lim replied that at the ethical and moral level, sex selection for reasons other than medical ones were generally unacceptable. No major jurisdictions had approved the use of PGD for sex selection for non-medical reasons. He felt that the public would generally not accept such use of the technology. He explained that legalisation of abortion was brought about many years ago and the historical context of that time was very different from the present. Dr Goh added that if sex selection was allowed, there would be greater adverse public reactions. She clarified that in formulating policies, the principles underlying sex selection for medical reasons should be the focus and they should not be dependent on the means. The HGS felt that sex selection should only be allowed for medical reasons.

Another participant expressed preference for an overall guideline to disallow social uses of PGD. She asked if the limitation of PGD to “serious medical conditions” would be specified by individual institutions, clinicians or by the MOH as guidelines. Another participant indicated that he would like to see clearer definitions for “serious medical conditions” and counselling requirements for mothers.

Dr Goh said that the MOH had recently approved a research trial for PGD to be used to diagnose beta-thalassaemia major. She believed that the MOH would specify the conditions for which PGD could be done, should PGD be accepted for clinical practice.

### ***Genetic Counselling and General Comments***

Referring to the second line in Recommendation 21,<sup>2</sup> one participant recommended that the word “immediately” should be replaced with “as far as is practicable”, because there is usually a lot of preparation to be done by the genetic counsellor before counselling a patient. It might not be practicable for counselling to be provided immediately after the disclosure of the test result. He also added that genetic counselling was better described as a ‘sustained’ process, rather than a “time consuming” one, since genetic counselling might not necessarily be a one-off procedure, but may even last a lifetime.

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<sup>2</sup> This recommendation stated that: “...Genetic counselling should immediately follow the disclosure of the test result, particularly if the test result is not favourable.”

### ***Research Genetic Testing***

A participant cited a moral dilemma often encountered in research. He said that despite informing research participants that the outcome of the research programme could not be ascertained until more knowledge accrued and therefore the research findings would not be made known to them, many participants would still write to enquire about the research findings even after several years. He asked whether researchers were obligated to re-contact and inform the participants if the research were to yield findings of medical relevance to them, assuming it was possible to trace them. If such an obligation were to rest on the researcher, the researcher would be required to keep track of new information following new discoveries that may be of medical benefit to his research participants.

Dr Goh suggested that the IRB decides at the outset whether the researcher should or should not inform research participants of the research findings. An alternative solution proposed by the American Board of Medical Geneticists (ABMG) was for the researcher to inform research participants that they would not be provided with individual results, but might be provided with research findings based on the whole research group. However, the options would be different if the research involved testing a gene of established medical relevance (e.g. BRCA1 for breast cancer). The ABMG suggested that in such cases, a research participant screened positive for a well accepted disease gene be advised to seek a genetic consult and take a clinical test. The duty to re-contact research participants would place a great burden on researchers. Furthermore, researchers might not remain in the same field of research indefinitely and some research participants might not welcome the information.

### ***Genetic Testing in Children***

One participant stated that the basic guiding principle in the testing of children was the benefit to the child's health. She thought that the assessment should be based on whether there was a need to know the child's genetic status.

Another participant asked for further guidance for situations in which a child assessed to be mature had conflicting desire with his or her parents regarding genetic testing. He felt that BAC's recommendations were broad enough to allow the child's decision to take precedence if the child's decision was in line with the doctor's professional opinion. Otherwise, the child could not overrule the parents' decision.

The BAC Chairman noted all the views expressed and assured those present that their views would be considered in further discussions and preparation of the final report.

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## FOCUS GROUP DISCUSSIONS 14 May to 9 July 2005

As part of its public consultation process, the BAC organised a series of focus group discussions to understand public views and concerns regarding genetic testing and emerging reproductive technologies. The recommendations of the BAC in the Consultation Paper entitled *Ethical, Legal and Social Issues in Genetic Testing and Genetics Research*, address some of the concerns voiced at the focus group discussions.

The public was invited to participate in the discussions through the Feedback Unit of the Ministry of Community Development, Youth and Sports, the BAC website and announcements in local newspapers. Fourteen focus group discussions were conducted. Two groups comprised students from junior colleges and polytechnics. The discussions involving the public took place at the Tanjong Pagar Community Club on Saturday mornings, while the student groups were held at Biopolis during the school vacation in June. There were a total of 93 participants (55 Chinese, 13 Malays and 25 Indians) ranging from 17 years of age to those in their 60s. Forty-four participants were males, and 49 were females.

Each discussion group, divided according to age, gender and ethnicity, consisted of 4 to 11 participants and was led by one or two facilitators. Associate Professor Wong Mee Lian from the Department of Community, Occupational and Family Medicine, National University of Singapore, provided guidance to facilitators on conducting the discussions. The BAC is grateful to Associate Professor Wong and all the facilitators – Dr Hussaini bin Hafiz, Mr Calvin Ho, Dr Predeebha Kannan, Dr Patrick Kee, Mr Ahmad Khalis bin Abdul Ghani, Dr Lee Soo Chin, Dr Rathi Mahendran, Ms Airani Ramli, Ms Linda Tan, Dr T Thirumoorthy and Ms Sharon Wee – for their generous contributions.

The discussions were focused on the following issues:

1. Genetic testing in general;
2. Predictive genetic testing in children;
3. Direct supply of genetic tests to the public;
4. Privacy and confidentiality of genetic information;
5. Access to and use of genetic information;
6. Preimplantation genetic diagnosis (PGD); and
7. Preimplantation tissue typing (PTT).

Participants were presented with two written scenarios and encouraged, through a series of open-ended questions, to share their personal views with the group:

- Scenario 1: a mother of two, with a strong family history of colon cancer considering genetic testing.
- Scenario 2: a couple who has a 5-year-old son with Duchenne Muscular Dystrophy considering PGD with the hope of conceiving a healthy child.



The discussions were lively and interesting as many participants freely shared their views and experiences. Most participants enjoyed the discussion and many expressed that they had greatly benefited from it. Generally, the BAC's views and recommendations correctly represented public views and concerns as expressed by these participants.

## **Opinions on Genetic Testing and Emerging Reproductive Genetic Technologies**

### ***Genetic testing***

We find the following to be the main factors that are likely to influence a person's decision to undergo genetic testing:

- (a) knowing that a genetic test is available;
- (b) the certainty or predictive value of the test result;
- (c) the nature of the disease concerned;
- (d) what can be done if the test result is positive;
- (e) the cost implications and follow-up options for a positive test result; and
- (f) privacy and confidentiality of the test result.

Most participants were aware of the risks and benefits in genetic testing and recognised the need to weigh individual interests against the interests of society when faced with conflict. It was generally agreed that the availability of or access to controversial technologies should not be completely barred, nor can such technologies be freely open to all. Clear rules and effective controls are needed to maintain public confidence.

Generally, participants valued the freedom of making decisions, although a certain level of regulatory control was desired to protect the welfare of individuals. The freedom of choice should be limited if its exercise would pose harm to wider societal interests.

### ***Predictive genetic testing in children***

Many participants felt that parents have the responsibility and right to decide for their children regarding genetic testing for a late-onset disease. Others felt that children not mature enough to make medical decisions should not be subjected to such tests.

### ***Direct supply of genetic tests to the public***

With increasing public availability of genetic testing services and at lower cost, several participants seemed prepared to try out such services procured overseas, via the Internet or over the counter, and without the mediation of a medical professional. Some of them thought that this would be the best way to ensure that their genetic test results were kept private. The majority, however, would consult a medical professional to confirm the diagnosis, especially for serious disease such as colon cancer, as they considered professional counselling to be beneficial.

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### ***Privacy and confidentiality of genetic information and access to and use of genetic information***

While no participants were willing to volunteer their genetic information to third parties like employers or insurers about a condition which they have not developed or might not even develop within their lifetime, the majority was willing to share the information with family members. The reasons were namely “social responsibility” on the part of the tested individual to inform genetic relatives of a hereditary condition and the sharing of financial, emotional and psychological burdens among family members.

### ***Preimplantation Genetic Testing***

The factors identified as important in preimplantation genetic testing were:

- (a) religious and personal values;
- (b) the probability of success balanced against the cost of the procedure;
- (c) the well-being of the existing sick child after the birth of a healthy sibling through PGD;
- (d) the well-being of the sibling who would be conceived through PGD or PTT; and
- (e) the physical and emotional stress on the woman undergoing the clinical procedure.

Participants weighed these factors differently because of differences in their beliefs and values, experiences and outlook in life, social and economic background and, to some extent, gender.

Most of the Christian participants would not consider PGD because of the destruction of surplus embryos or the belief that it is “God’s will” if their children were born with any genetic disorder. A few Muslim participants shared similar reservations towards PGD but the majority thought that PGD did not conflict with Islamic principles. Several Muslim participants suggested that Muslim patients be assisted by a Muslim counsellor or religious teacher before and/or after testing to ensure that their decisions and actions would not contravene Islamic law.

A great majority of the participants thought PGD and PTT appropriate if used to avoid a life-threatening disease. These participants differed in their opinions on what severity of disease should be allowed for the use of PGD and PTT, but they did not think that such technologies should be allowed for minor conditions such as myopia. None of the participants agreed to the use of PGD for selection of desirable traits. A majority of participants objected to applying PGD in selecting gender for social reasons. However, a few participants thought that use of PGD to balance the gender ratio in families might be permissible in extreme cases.

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