Ethical Guidelines for Gene Technology

The National Medical Ethics Committee
Foreword

The state of the art in gene technology is now reaching a stage hitherto found only in science fiction. The mapping of the human genome has the potential to reveal each person’s life story as an open book. Unlike a novel, the knowledge of the contents inside each person’s genetic manual cannot be liberally disseminated. Such information can be used both to benefit (in the case of early detection of a disease to allow early intervention) or disadvantage that person (creating bias against the person). Beyond genetic testing, there is the issue of genetic manipulation with the risk of passing on unintended alterations to the genetic code.

The ethical issues are many and wide-ranging. These guidelines produced by the National Medical Ethics Committee focus on gene technology in the context of medical practice and the doctor-patient relationship. The guidelines are meant to assist clinicians and doctor-researchers in making ethical decisions involving gene technology. Nevertheless, the fast-changing landscape of gene research means that doctors will have to read widely and keep themselves informed of developments, if they are to provide the best care for their patients in this area.

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Summary of recommendations

Recommendations on performing clinical genetic testing

1. Patients or test subjects, and/or their families must have access to adequate genetic counselling prior to and after genetic testing.

Items that should be included in counselling where appropriate are listed in section 2.1. of the main guidelines.

2. Informed consent should be obtained before genetic testing can proceed.

Specific situations and exceptions are described in section 2.2. of the main guidelines.

3. The physician should determine if the patient/subject has any objection to the test material being used for research purposes, and if the patient/subject would like to be informed if clinically relevant information is obtained from such research.

4. Informed consent for genetic testing should be obtained from:
   - subjects 21 years or older and who are deemed to be mentally capable of making the decision.
   - parents or guardian of subjects under 21 years old.
   - parents or guardian of subjects 21 years or older but not mentally capable of making the decision.

5. In regard of pedigree analysis, if a key relative refuses to allow genetic tests to be performed, even in the face of a life-threatening disease, his/her wishes should be respected.

6. In general, test results should only be released to individuals for whom the test subject has given his/her consent. However, a physician’s ethical duty of confidentiality to an immediate patient or client can be overridden if several conditions are satisfied concurrently; these conditions are listed in section 2.4.1. of the main guidelines.

7. Aggregate test results, devoid of identifiers, may be reported to government agencies for statistical and planning purposes.

8. On the issue of discovery of non-paternity, clinicians would need to make a judgement as to the best course of action based on his/her knowledge of the patient and the patient’s family unit.

9. Guidelines for doctors on disclosure of genetic test results are listed in section 2.5. of the main guidelines.

Recommendations on introduction of genetic tests into clinical practice

10. 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.

Specific guidelines on genetic test development are in section 3.1. of the main guidelines.

11. Direct genetic testing by manufacturers and suppliers of genetic testing kits, without the intervention of a doctor, should be strongly discouraged.
12 The advertising and marketing of predictive gene tests to the public is strongly discouraged.

**Recommendations on evaluation of research protocols involving the application of gene technology in human research**

13 Rigorous peer review of research protocols on application of gene technology is mandatory to ensure that proposed studies are scientifically sound and are well-designed to address specific hypotheses, with well-defined and valid molecular, biochemical and/or quantitative clinical endpoints.

14 Criteria to recruit human subjects for research into applications of gene technology are in section 4.2. of the main guidelines.

**Recommendations on Gene Therapy in general**

15 Gene therapy must be evaluated through rigorous clinical studies before clinical adoption.

16 Germ-line gene therapy to transmit genetic changes to offspring should not be done.

**Recommendations on Somatic Gene Marking and Therapy**

17 Gene marking studies in humans must be supported by a clear data base demonstrating that the specific procedure has a very high safety margin and is very likely to yield valuable knowledge.

18 Informed consent must be obtained for the performance of clinical gene therapy. Careful explanation of the complexities involved is necessary.

19 Gene therapy is permissible in subjects who do not have end-stage illness. Risks, benefits and alternative (i.e. non-gene) therapy options must be fully considered first.

20 Ethical committees that have to review gene therapy protocols need not make an ethical distinction between gene therapy for monogenic disease and polygenic disease.

21 Gene therapy in humans should be confined to alleviating disease in individual patients. Gene therapy to change or enhance normal traits is strictly prohibited.

22 Somatic gene therapy should be deferred till the last trimester of pregnancy or postpartum unless the perceived benefits to the mother clearly outweigh the risks to the foetus.

23 Gene therapy protocols should follow up subjects indefinitely.

24 Human gene therapy should receive the same scrutiny and peer review as other applications for experimental therapies.

25 Those involved in gene therapy should exercise restraint in public discussions of gene therapy. Accurate information should be provided not only on the promise of gene therapy, but also on its current limitations and experimental nature.
Ethical Guidelines for Gene Technology
1 Definition of Gene Technology

1.1 Gene technology is defined as the use of techniques for the analysis and/or manipulation of DNA (deoxyribonucleic acid), RNA (ribonucleic acid) and/or chromosomes.

1.2 A genetic test is one that involves 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. These include, but are not limited to, predicting risk of disease, identifying carriers, establishing antenatal and clinical diagnosis or prognosis, monitoring and antenatal screening. This definition excludes tests conducted purely for research, tests for somatic (as opposed to inherited) mutations, and testing for forensic purposes; it also excludes eliciting genetic information from a family history.

2 General ethical principles and guidelines for performing clinical genetic testing

2.1 Genetic counselling

Patients or subjects, and/or their families must have access to adequate genetic counselling prior to and after genetic testing. Counselling should include, where appropriate,

(a) nature of the condition to be tested for
(b) potential consequences of not being tested
(c) foreseeable consequences as a result of testing e.g.
   i non-paternity/undisclosed adoption
   ii results could compromise access to health and life insurance coverage
   iii psychological burden of knowing that one is at risk of a potentially serious condition or of transmitting a heritable trait to offspring
   iv change in family dynamics
   v false sense of security (patient or client should be aware that negative results are fully informative only if mutation has been identified in the family)
(d) test reliability and clinical validity, emphasising that not all mutations are detectable, that some mutations are of uncertain significance, that results indicate probability, not certainty, of developing the disease, and that the efficacy of interventions following genetic testing has not been proven in most diseases.

(e) treatment options
(f) alternative to genetic testing
2.2 Informed Consent

2.2.1. Informed consent should be obtained before genetic testing can proceed, although in some cases, informed consent for newborn can be waived as discussed below. Consent should be obtained after the individual has been given appropriate genetic counselling and informed about the nature of the test and significant risks posed by the test. Specific situations include:

(a) Development of clinical genetic tests:
   Informed consent must be obtained for any validation study whenever the specimen can be linked to the subject from whom it came.

(b) Testing for clinical indications:
   Testing must be voluntary and patients and/or families must not be coerced into undergoing predictive genetic testing. Regardless of the decision made, the care of the patient should not be compromised.

(c) Screening of newborn:
   For newborn screening tests which have well-established scientific and clinical validity, informed consent can be waived although parents must be provided with sufficient information to understand the reasons for screening. However, if the parents object to the tests, then testing should not proceed.

(d) Antenatal and carrier testing
   Informed consent must be obtained for antenatal and carrier testing, taking into account the subject’s or couple’s beliefs which would influence their decisions on abortion should the tests show the likelihood of a severe inherited disease in the fetus.

2.2.2. The physician should also determine if the patient has any objection to the material being used for research purposes and if the patient would like to be informed if clinically relevant information is obtained from such research.

2.2.3. Person(s) from whom informed consent should be obtained:

(a) Informed consent is obtained from the individual to be tested if he/she is 21 years or older and deemed by the physician to be mentally capable of making the decision.

(b) Informed consent is taken from the parents or guardian for children under 21 years old, particularly if the result would bring direct medical benefit to the child which would be lost by waiting for the child to reach adulthood and becomes able to independently decide on testing. It is generally held that parents are acting in the interests of their children and hence their consent is valid. However, if the physician firmly believes that genetic testing is more likely to harm the child, then he has the right to dissuade them and even refuse to perform the tests. For example, in the United States, Huntington Disease testing programs will not test persons under 18 years old.
2.3 **Decision against genetic testing**

Linkage study is still an inherent part of risk ascertainment. In certain instances, a relative may be a key figure in the pedigree analysis. If this key relative refuses to allow genetic tests to be performed, even in the face of a life-threatening disease, his/her wishes should be respected.

2.4 **Confidentiality : Access to genetic information**

2.4.1. The principle of patient-doctor confidentiality should be exercised. In general, results should only be released to those individuals for whom the test recipient has given his consent. However, a physician’s ethical duty of confidentiality to an immediate patient or client can be overridden if several 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 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 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

2.4.2. Aggregate results, devoid of identifiers, may be reported to government agencies for statistical and planning purposes.

2.4.3. The discovery of non-paternity is a difficult issue. The clinician involved would need to make a judgement as to the best course of action based on his/her knowledge of the patient and the family unit.

2.4.4. Disclosure of genetic testing results to insurance-providers and employers:

Health and life insurers should be denied access to genetic test results or information without the explicit consent of the person being tested.

2.5 **Disclosure of genetic test results** [as recommended by the ASCO Task Force on Cancer Genetics Education 1998]

The physician/investigator ordering the genetic test should

(a) Establish with the patient or client how the results will be disclosed *before* the tests are ordered.

(b) Maintain confidentiality and patient privacy when the results are disclosed.
3 General ethical guidelines and safeguards for the introduction of genetic tests into clinical practice

3.1 Genetic Test Development: Principles and criteria

3.1.1. 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.

3.1.2. Establishing associations between a disease, genes and inherited mutations:
The following criteria must be satisfied before either linked markers or putative disease-related mutations are used as the basis of a genetic test:

(a) The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of a disease or risk allele.

(b) The observations must be independently replicated and subject to peer review.

3.1.3. Analytical validity
For direct DNA-based tests of mutations, analytical validity is the probability that a test will be positive when the analyte it measures is present (analytical sensitivity) and the independent probability that the test will be negative when the analyte is absent. DNA-based tests, therefore, measure discontinuous variables (a mutation is present or absent). In contrast, enzyme and metabolite assays measure continuous variables.
(enzyme activity or metabolite concentration). Consequently, analytic validity is the probability that the measured value will be within a predefined range of the true activity or concentration.

After validation of the test analytically, the clinical test made available to patients should be as similar as possible to that used in the validation process. Analytical sensitivity and specificity must be determined before tests are made available in clinical practice.

3.1.4. Clinical validity

(a) Data to establish the clinical validity of genetic tests must be collected under investigative protocols.

(b) In clinical validation, the study sample must be drawn from a group of subjects that is representative of the population for whom the test is intended. All ethnic groups that could benefit from the test should be offered participation in such studies.

(c) Each intended use of a genetic test must be formally validated.

4 General ethical principles and guidelines for the evaluation of Research protocols involving the application of gene technology in human research

4.1 Rigorous peer review

Rigorous peer review of research protocols is mandatory to ensure that proposed studies are scientifically sound and are well-designed to address specific hypotheses, with well-defined and valid molecular, biochemical and/or quantitative clinical endpoints.

4.2 Recruitment of human subjects for research purposes

The following criteria should be satisfied:

(a) All criteria of section 2 of these guidelines should be fulfilled.

(b) If the participants enter and then withdraw from a study, the researcher is not required to destroy existing data, cell lines, DNA and other material. This should be made clear to the patient at the point of original consent to participate in the study.

(c) Public sources of information may be used to gather information. Non-public sources, e.g. adoption information, may not be obtained without consent.

3.2 Advertisement and marketing

3.2.1. Direct genetic testing by manufacturers and suppliers of genetic testing kits, without the intervention of a doctor, should be strongly discouraged.

3.2.2. The advertising or marketing of predictive genetic tests to the public should be strongly discouraged.
5  Definition of gene transfer and gene technology

5.1  **Gene transfer** refers to the transfer of DNA into recipient cells either outside the body (ex vivo) or by direct administration (in vivo).

5.2  **Gene therapy** is defined as: “the administration of nucleic acids to living systems with the intention to use the expression products of these nucleic acids for therapeutic purposes”. Expression of transferred genes is essential for successful gene therapy.

5.3  There is a difference between ‘gene therapy’ and ‘gene transfer’: there are important applications of gene transfer in clinical research which are not truly therapeutic. The most obvious examples are gene marking experiments which have increased understanding of how tumours relapse following autologous stem cell transplantation. It is important from the ethical standpoint to appreciate that subjects in such gene transfer experiments do not directly benefit from these procedures.

6  Current status of human gene therapy world-wide

6.1  Of all the clinical gene transfer trials that have been initiated, approximately three-quarters are gene therapy studies, while the remaining one-quarter concerns gene marking experiments. More than half of the clinical gene transfer trials target against cancers, using strategies such as immunotherapy, prodrug activation, replacement of tumour suppressor genes, antisense inactivation of oncogenes, and induction of chemoresistance to bone marrow stem cells. Non-malignant applications include adenosine deaminase deficiency (severe combined immune deficiency), familial hypercholesterolaemia, cystic fibrosis, Gaucher’s disease, Hunter’s syndrome, HIV infection, alpha-1-antitrypsin deficiency, rheumatoid arthritis, Fanconi’s anaemia, peripheral and coronary artery disease. Most of these studies are phase I studies whose main objectives are to assess the feasibility and safety of the gene therapy approaches in these conditions.
7 Justifications for experimental human gene therapy

7.1 Somatic gene therapy is a logical and natural progression in the application of fundamental biomedical science to medicine and offers extraordinary potential, in the long-term, for the management and correction of human diseases. More than 100 human gene therapy trials have been approved world-wide over the past decade. Several hundred patients have been subjected to clinical gene therapy. Despite this, the clinical benefit of gene therapy has not been conclusively demonstrated. This does not invalidate the concept of gene therapy, but rather it reflects the inadequacy of current gene transfer technology. Significant problems remain in many basic aspects of gene therapy.

7.2 However, we consider that human studies are warranted for several important reasons:
   (a) It is not always possible to extrapolate data from animal experiments to human studies.
   (b) For many human diseases, no satisfactory animal models are currently available.
   (c) Unanticipated questions or problems may become apparent in human studies which can help refocus research e.g. the immunogenicity of adenovirus vectors in man.

8 Categories of gene therapy

8.1 A major distinction must first be made between somatic and germ-line gene therapy. **Somatic gene therapy** is the correction of genetic defects in postnatal somatic cells in the body. This approach is fundamentally not different from any form of organ transplantation or even blood cells transfusion. Genetic changes thus introduced are confined to the subject whose cells are modified.

8.2.1 In contrast, **germ-line gene therapy**, which involves the insertion of foreign genes into fertilised eggs or very early embryos, can result in the transmission of the genetic changes to the offspring in the subsequent generations.

8.2.2 We strongly advocate that germ-line gene therapy with the result of passing on the genetic changes to the offspring should not be contemplated presently for the following reasons:

   (a) The ethical issue of whether and when a foetus becomes a patient remains highly controversial. Does the pre-viable foetus have as much an independent right as a patient (subject) as a viable foetus?
   (b) The potential risks to the mother during *in-utero* gene transfer have not been hitherto studied.
   (c) Given our limited knowledge on the long-term safety and risks of gene therapy, germ-line gene therapy is fraught with the risk of unanticipated, deleterious alterations in the genetic code that may be passed on from generation to generation.
As we are unaware of all the activities of a particular gene, one may select against and gradually eliminate alleles from the human gene pool that benefit humans in potentially unknown ways when they appear in the heterozygous state.

The line between germ-line gene therapy and eugenics is a tenuous one.

The rest of these guidelines discuss the ethics of only somatic gene marking or therapy.

9 Ethical Guidelines for somatic gene marking and therapy

9.1 Gene marking studies.

9.1.1. In the case of gene marking studies in humans, such procedures are not done primarily to benefit the subjects, and may in fact be of absolutely no benefit to the individuals involved.

9.1.2. We therefore recommend that proposals to carry out these human experiments must be supported by a clear data base demonstrating that the specific procedure planned is very safe and is highly likely to yield knowledge of value. In addition, the investigators should also provide evidence that such knowledge could not be obtained by non-gene transfer approaches or animal gene transfer experiments.

9.2 Somatic gene therapy:
Somatic gene therapy for disease is fundamentally not different from other forms of experimental treatment: essentially, the procedures are carried out with a clear therapeutic intent, and the effects (therapeutic or otherwise) are confined to the treated subjects only – i.e. the genetic modifications are not passed on to non-subjects and the population gene pool is not disturbed. However, the legal, moral and spiritual prerogatives of the subjects would be protected, and the principles of fairness, privacy, confidentiality and non-discrimination observed, as is practised in other forms of experimental therapy.
9.3 Informed consent.
Clinical research is generally safeguarded by the process of informed consent. This requires that the risks must be honestly described to the patient and all other therapeutic options fully explored. Obtaining consent for human gene therapy should follow the same principle. However, given the complexity of the science behind gene therapy, greater efforts on the part of the investigators may be required to ensure that sufficient and clear information is imparted to the patients to permit informed consent.

9.4 Patient selection.
Although there is no ethical reason to restrict clinical gene therapy research to patients with end-stage disease, it is customary and sensible that new methods of treatment such as gene therapy should first be tested in these patients. However, there could be selected clinical situations in which gene therapy is expected to be efficacious in only those patients who do not have advanced-stage diseases. As such, we see no ethical reason to prohibit gene therapy in subjects who do not have end-stage illness, as long as the same process of risk-benefit consideration is applied and all other non-gene therapy based treatment options have been discussed with the patient.

9.5 Disease selection.
From the ethical standpoint, there is no reason to discriminate between gene therapy for monogenic versus polygenic disorders, although it is intuitive that the former is more amenable to gene therapy.

9.6 Treatment versus enhancement.
A clear distinction must be made between treating a disease versus enhancing a normal human characteristic. The latter approach risks opening a Pandora’s box for many potential forms of human engineering that our society is not yet ready to cope with. We strongly recommend that gene therapy be confined to alleviating disease in individual patients, and should not be used to change or enhance normal traits.

9.7 Somatic gene therapy in pregnancy
The introduction of foreign therapeutic gene to the pregnant woman carries a theoretical risk of its inadvertent incorporation into the growing foetus. Such an event, although unlikely with the vector systems used today, is expected to have greater effects on the foetus in the earlier stages of pregnancy, when embryonic organogenesis is actively taking place. We recommend that somatic gene therapy should be deferred till the last trimester of pregnancy or postpartum unless the perceived benefits of gene therapy to the mother clearly outweigh the risks to the foetus.

9.8 Long-term follow-up.
There are medical, scientific and ethical imperatives to maintain long-term follow-up of patients who participate in clinical trials of somatic gene therapy. Medically, long-term follow-up allows new, unexpected adverse effects to be detected early so that treatment may be instituted promptly. In addition, this will provide invaluable data to modify other on-going or
future protocols that employ the same reagents or approach. Scientifically, long-term follow-up would provide information that may contribute to the improvement of the current gene transfer technology. Indeed, one of the critical issues in gene therapy is how to prolong the duration of gene expression, an issue that is pivotal in treating hereditary disorders. From an ethical imperative, the benefit-risk ratio of any clinical research can be greatly enhanced by the investigators’ commitment to identify and manage any resulting complications, even if they may occur years after the treatment.

We recommend that all gene therapy protocols follow up the subjects indefinitely.

9.9 Applications and review process
Rigorous scientific peer review is essential in the evaluation of gene therapy protocols, as it is with other forms of clinical research. When reviewing clinical gene therapy proposals, one must objectively compare them with currently available therapies as there is no reason to consider gene therapy in a different context to any other medical treatment. Gene therapy protocols need to meet the same high standards required for all forms of translational and clinical research, whatever the enthusiasm for this treatment approach might be.

9.10 Interaction with public.
It is important that investigators do not oversell the capabilities of clinical gene therapy, since overzealous representation of clinical gene therapy may obscure the exploratory nature of this form of treatment, colour the manner in which findings are portrayed to the scientific press and public, and lead to the mistaken perception that clinical gene therapy is already highly successful or has replaced standard therapy.

We recommend a concerted effort on the part of scientists, clinicians, science writers, research institutions, and the press to inform the public regarding not only the promise of gene therapy, but also current realities and limitations. It should be emphasised, in particular, that some time will be required to develop the science of the field and to translate these advances to clinical practice.
REFERENCES

**For Gene Technology:**


**For Gene Therapy:**

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The National Medical Ethics Committee (NMEC) was set up in January 1994 as the national authority to assist the medical profession in addressing ethical issues in medical practice and to ensure a high standard of ethical practice in Singapore. All members are appointed by the Minister for Health.

The ethical guidelines which have been drawn up are to facilitate medical professionals in making sound ethical decisions in clinical practice.

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