ETHICAL CONSIDERATIONS RELATING TO RESEARCH IN HUMAN GENETICS *

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- **In drafting these guidelines, the authors derived great benefit from referring to the Australia Guidelines of the NH & MRC**

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CONTENTS

Although there are well established moral and scientific principles to be followed in research on human subjects, it is thought that genetic research may present some unique problems to the researcher. An increasing number of situations are occurring where laboratory-based workers have the responsibility of considering the ethical applications of their work at early stages in the design of a protocol. As an introduction to this field, a set of guidelines has been summarised to assist in the preparation of protocols with sections that may be helpful to members of ethics committees in coping with novel aspects of research that emerge in the course of genetic research. A glossary is included for such general readers. These guidelines do not replace general guidelines for clinical research. These "points to consider" recognise that the interests in this type of research extent to researchers, participants recruited for this research and the providers of genetic services.

1. The Scope of Human Genetic Research

This aspect of medical research is becoming diverse and will continue to do so as technological advances are made. In addition to the general principles of ethics followed in clinical medicine, there are some approaches to genetics that may require special consideration. They could be categorised as follows:

- The identification of disease-associated genes -
  a) linkage analysis
  b) positional cloning

- Differential gene expression -
  ⇒ Comparison of gene expression by screening m-RNA in test and control

- Association genetics (large scale screening) -
  ⇒ Correlate polymorphisms with disease incidence

- Microbial genome programme -
  ⇒ Extrapolation of gene function from simple models to humans (covered by ERMA and possible animal ethics approval)

- Redefinition of disease by mechanism -
  ⇒ Leading to ability to match drug to mechanism
  ⇒ Genetic basis of variable response to drug effects

- Diagnosis by tracking mutations - followed by establishing biological relevance
  ⇒ Optimum time after preliminary research to begin testing programme
  ⇒ Need to institute counselling at correct time
  ⇒ Researchers and clinicians to work in synchrony

2. Genetic Research

In studying how genes and environmental factors interact to influence the health of individuals and populations, the knowledge generated has the potential to improve individual and community health. There are, however, ethical issues related to genetic research which are at the same time personal and shared with other family members and have uses which go beyond health care.

Genetic research can reveal information about the susceptibility of an individual to disease and hence about his/her future health. Such information may be of interest and benefit to research participants, especially if preventive strategies exist, but may also expose them to other risks or anxieties. Research of this nature often translates into clinical service and a number of negative factors, such as depression and feelings of guilt in survivors have been identified in family members receiving either "good" or "bad" news.

Participation of families rather than individuals is required for many genetic research studies. Research results and genetic material collected for research may be of significance to the health of blood relatives, including some who have not participated in the research. These family members may have a legitimate interest in the genetic material of their relative or in information which the research generates. Testing material or acquiring information about genetic status, could be used to improve their health. In addition, other family members, such as partners and spouses, may also have an interest because of concerns about the health of off-spring and the integrity of the family.

Researchers, in particular epidemiologists, may wish to study genes in populations to determine their contribution to disease incidence and prevalence in the community, so that best use can be made of the genetic material of the research participants and associated clinical information.

2(i) Misuse of genetic information

Genetic information may also be of interest to others such as insurance companies and employers.

There is potential for harm to participants arising from the use of genetic information, including stigmatisation or discrimination and researchers must take special care to protect the privacy and confidentiality of this information.

2(ii) Multiple use of genetic material

Consent procedures need to take account of the possibility that the material may be used for additional research, anticipated at the start of the research study. Consideration should also be given to de-identifying genetic material and any associated clinical information, or making it anonymous, in order to protect the privacy and confidentiality of research participants. (See below for definition.) This is particularly important if the planned or future research has the potential to reveal genetic susceptibility and participants have not had prior counselling with regard to this possibility. There are consequences for researchers of de-identified or anonymous information however, in that it may limit their ability to go back to participants for additional information or a repeat sample, or to communicate the results of the research to participants.

3. Informed Consent

With the diversity of research in genetics, a number of unique situations will emerge; many of which may not have been readily predictable. As with all clinical research however, the principle of informed consent also underlies **all** human genetics research.

The following additional points can be made:

Family Implications
Where the research requires confirmation of family information provided by research participants, all reasonable steps must be taken to obtain consent to access the information from those family members to which the information relates.

It is entirely appropriate to consider the implications for proband and family before embarking on tests which may have an impact on the family members. This is particularly so when the genetic component has not been recognised before.

Participants should be informed about the following aspects.

Anonymity
They should know whether their genetic material/information will be used for the proposed research in an identified, coded but identifiable (de-identified), or anonymous and not identifiable (anonymous) form.

Fate of material
It should be clear whether the genetic material is to be stored or destroyed on completion of the research. Consent to storage or destruction must be obtained before the start of the research. Genetic material must be destroyed in a way that takes into account any sensitivities which participants might have regarding their genetic material. Any such sensitivities should be established and recorded before the start of the research.

Storage
If the genetic material is to be stored, it may only be used for future research if,
either,

> The future research has the same, or closely related, research goals and the possibility of such future research has been discussed with the research participant and the participant has given consent and a new research proposal is submitted to an HSEC (and approved).

or,

> Genetic material and information is made anonymous and a new research proposal is submitted to an HSEC and approved.

Clinical Samples
Genetic material/information collected for routine clinical care can be used for research without consent if it is made anonymous and used according to a protocol that is submitted to an HSEC and approved.

Policy statements
Institutions wishing to conduct research on material collected for routine care or without consent for past research should develop and publicise a general policy to that effect, for future

HSEC-approved research. Patients and research participants should be informed that such a policy exists.

4. Counselling & anonymity

Where research may reveal information about an identified or identifiable participant's future health or risk of having children with a genetic disorder, the research protocol must provide for such consent procedures, counselling, support, test quality and test result confidentiality as are appropriate in clinical care. Otherwise such research may only be performed if the genetic material has been made anonymous.

5. Identification

Researchers must ensure the confidentiality and privacy of stored genetic information, genetic material or results of the research which relate to identified or identifiable participants. In particular, the research protocol must specify whether genetic information or genetic material and any information derived from studying the genetic material, will be stored in identified, de-identified or anonymous form. Researchers should consider carefully the consequences of storing information and material in anonymous form for the proposed research, future research and communication of research results to participants. Researchers should disclose where storage is to be and to whom their tissues will be accessible. TISSUE OR DNA SHOULD ONLY BE SENT ABROAD IF THIS IS ACCEPTABLE TO THE CONSENTING INDIVIDUAL

6. Relatives and recruitment

Researchers wishing to recruit relatives of participants to the research must consider any potential for harm which might result from an attempt to recruit, and in doing so, should take into consideration the privacy and any known sensitivities of the relatives, and accepted processes of communication with the family. In general, recruitment should be through a family member who is already a participant in the research.

7. Report back

Genetic research has the potential to generate information of relevance to the health of a research participant and members of the family of the participant.

- Research participants should be asked, at the time of giving consent, whether they wish to be notified of the outcome of the research and if so, it should be quite clear whether feedback should be in the form of general information of interest/relevance to:

  a) The entire group of research participants;

  or

  b) Specific information about any personal test result which may be generated by the research. Research investigation and clinical intervention remain separate. It is unusual for specific or individual tissue to be provided unless this has been previously agreed upon and consented to.

- Research on anonymous samples may have results which bear on the future health of research participants. As the samples are anonymous, it will not be possible to assign results to participants as individuals. It may be possible, however, to make the participants

as a group, aware of the research findings. This should be anticipated in the design of the protocol.

- Research participants should be informed that, if the research generates information of relevance to the health of other family members, their consent will be sought to disclosing the information to those members of their family. Researchers should define the mechanism for obtaining participants' consent to disclose their information to other family members.

- Participants should be asked if they wish their General Practitioner to be aware of their participation and any results generated by the research.

8. Post mortem

Researchers must specify the procedure to be followed if the participant, or a relative of the living participant, or a relative of the deceased participant, requests access to stored genetic material or information generated by the research. Consent to participation should cover post death requirements.

9. Funding implications

At the time of proposing and reporting the research, researchers must disclose the source of funding for the research, and any personal commercial affiliation or financial interest in the outcomes of the research. Research participants should also be made aware that research studies may produce findings with commercial potential.

10. Possible adverse effects on participants

Researchers must provide a particular justification for research on genes which might contribute to complex socially significant characteristics or research which studies such genes in groups of people. When assessing proposals of this type, HRECs should consider the extent to which the research might contribute to knowledge, and the extent to which there may be potential for harm to individuals or groups

11. Cultural considerations

Any research including Maori or focusing on Maori health must be done in the spirit of genuine partnership. The background to procedures and consultation can be found in "Guidelines for Researchers on Health Research including Maori". HRC 1998.

12. Privacy and consumer rights

Researchers should be advised to ensure their research design is compatible with the protections in the Health Information Privacy Code and the Health and Disability Services Consumers Code of Rights.

13. Specific rights of children

Researchers should be aware of the rights of children. The Ministry of Health guidelines outlines these issues in the document "Consent in Child and Youth Health".

Appendix A -

EXPECTATIONS AND COMMENTS

This list could be expanded but it may illustrate how conflicts may arise between the expectations of contributors and participants, particularly as there will not be a single "end user" of the research result.

(i) Expectations of the researcher -

a. New knowledge will emerge, publications, more financial support and possible patents or commercial benefits will be generated (not necessarily to participants)	Patents or inappropriate ownership may inhibit general use of future testing procedures. Patients may have shared interests.
b. Some degree of ownership will be retained.	Ideally, a draft contract or statement of policy is needed before commencement.
c. A relationship with Genetic Services will be set up with identifiable benefits. Research results will be incorporated according to acceptable good practice.	Merging research and clinical testing and full consideration of ethical issues require early communication between contributors.
d. Ownership rights to new knowledge.	Some degree of sharing might be expected (see (i)b).

(ii) Expectations of the recruited participants -

a. Health uncertainties may be removed.	Individual results should not emerge from research projects. Personal information presented through accepted clinical channels
b. Tests become available to detect carrier status, prenatal condition, predisposition or pre-implantation intervention.	Information regarding scope and limitations of test should be from the clinic and not the research arm of the co-operating team.
c. A cure will emerge. Information should include confidence levels probability, penetrance and predisposition v causal.	Unrealistic claims can be coercive or an unrealistic inducement with expectations beyond the individual to family or community.

(iii) Expectations of Regional Genetics Services -

a. Researchers consider the impact of the release of their results so that they do not adversely affect subsequent clinical treatment. b. Research will be able to be incorporated into good clinical practice. c. Projects have clinical significance in a New Zealand context, with priority given to important common genetic disorders found in New Zealand.

(iv) Expectations of society -

a. Results will be to the public good. No harm will be done. b. Knowledge may be found which is of no immediate use but may nevertheless be worth obtaining. (This may not always be appreciated.) c. Misinformation is corrected, general fears and myths about a condition will be expelled. d. The principles of confidentiality and informed consent will be maintained consistently throughout the research. e. Rigorous international guidelines for biomedical research are followed in a way that preserves a respect for the sensitivity of ethnic or social groups involved. f. Principles of risk estimation and management will be exercised.

Appendix B

CATEGORIES OF SUBJECTS RECRUITED

1. Randomly selected individuals.

   (i) Material/information donated for one reason
   (ii) Multiple use - indicated in protocol +/- informed consent

2. Individuals selected on basis of disease incidence or +/- susceptibility.

   (i) Counselling not required
   (ii) Counselling required -
   a) with informed consent
   b) later - as research results emerge
   - at end of study

3. Persons recruited as part of a group defined according to:

   (i) Ethnic origins
   a) special considerations required
   b) no special considerations (see section ii)

   (ii) Geographic origins
   a) appropriate controls available
   b) homogeneity of group appropriate

   (iii) Behavioural attributes - eg definition of condition adequate

   (iv) Chronological age - with possible complications
   a) special treatment - eg children
   b) informed consent may be difficult - eg limited comprehension of details

Appendix C

The following scenarios are described in order to draw attention to a range of issues which may be relevant in any given case:

Scenario :		**Issues:**
1.	A large family has lost 6 young people (<40) to a form of cancer in which the gene has not yet been identified. Analysis of data suggests that the more detailed analysis of a subgroup of the extended family are the key to research which is likely to lead to the identification of the gene or a linked genetic locus. This group are not keen to be involved. Many of the family members are less than 18 years of age.	• **Coercion & informed consent** • **Privacy & confidentiality** • **Family obligations - obligations to family and obligations of participating family members** • **Transition to clinical care (protocols)** • **Research on children**
2.	Research into a late onset neurological disorder seems accessible to your group. The results will be predictive of this severe progressive disorder by DNA analysis at a very early age/stage. You seek funding from a Neurological Society to fund this.	• **Transition to clinical care (protocols)** • **Predictive/prenatal/preimplantation** • **Interested third parties (insurance companies, employers)**
3.	A novel gene which affects susceptibility to an important disorder has been cloned by your group and has potential commercial application. The participants in your project are partially aware of this.	• **Full information disclosure** • **Patents** • **Intellectual property rights** • **Involvement of funding agency**
4.	You have found a gene which may be causal in a syndrome. You need normal controls to validate your research. You have DNA stored from a number of other unrelated projects. Should this be used?	• **Informed consent** • **Ownership of DNA** • **Patenting of DNA** • **Public good**
5.	Several members of a Maori family from a particular region of New Zealand have a unique late onset disorder. You believe you can identify the genetic basis of this disorder which may be clinically useful in the future.	• **Cultural issues (Section ii)** • **Individual/whanau/iwi** • **Consultation procedures** • **Transition to clinical practice** • **Defining personal beliefs** • **Counselling by experts and lay persons in partnership**

Appendix D

READING LIST

Scientific, Ethical and Regulatory Considerations in Pursuit of Cloning of Human Beings : *National Health and Medical Research Council - Australian Health Ethics Committee (1998)*

Guidelines for Researchers on Health Research involving Maori : *HRC 1998*

Priorities for Genetic Services in New Zealand : *National Advisory Committee on Core Health and Disability Support Services (1995)*

National Best Practice for Familial Cancer Clinics : *NHMRC National Breast Cancer Centre, Sydney (1998)*

Consent in Child and Youth Health: *Ministry of Health Guidelines*

Appendix E

Glossary of Terms

Allele One of two or more alternate forms of a gene.

Anonymous Not identifiable.

Carrier status An individual who is heterozygous for a mutant allele which causes a genetic disorder in the homozygous or hemizygous states.

Counselling In the genetic context, it is the use of a blend of information, advocacy and support to ensure appropriate advice has a sound, informed basis.

Deidentified Coded but identifiable.

Disease associated genes Genes which are responsible for specific or single gene disorders (bearing in mind that there are also multiple gene disorders).

Gene expression The manifestations of a functional gene.

Genetic susceptibility The existence of a predisposition to a health status that may be attributable to the genetic makeup (constitution).

Genome The complete DNA sequence of an organism containing its complete genetic information.

Incidence Rate or number of affected individuals within a population

Linkage analysis Genes may be linked if they are within a measurable distance of each other. The closer the positions (loci) of genes to each other, the more closely they are linked.

m-RNA A length of RNA, complementary to the DNA sequence of a gene which moves from the nucleus and acts as a template for a specific protein that is synthesised in the cytoplasm.

Mutation An alteration in the genetic material caused by a change, loss or gain of nucleotide bases within the gene.

Polymorphism The existence of alleles in more than one form.

Positional cloning Cloning of a gene on the basis of its chromosomal position rather than its functional properties. Also called 'reverse genetics'.

Predisposition intervention Predictive testing before signs or symptoms are detectable to assess the predisposition of an individual dependent on the presence or absence of specific gene mutations..

Preimplantation intervention The diagnosis of health status by the removal of two cells from an eight cell embryo prior to implantation.

Prenatal diagnosis Diagnosis of a disorder in a foetus, usually prior to the 20^{th} week of gestation.

Privacy The degree to which information is restricted to specific individuals, as defined by the Privacy Act.

Protocol The written design of any course of action in experimental service and/or medical intervention. The protocol will summarise the activities of the participants and considers the guidelines that should be followed and outlines the best practices that are generally recognised by professional persons who may be contributing to that course of action.

Risk estimation The likelihood of recurrence of a genetic disorder using standard statistical calculations.

Stored genetic information A situation in which the DNA of individuals are kept under stable conditions, usually stored frozen for an indefinite period.