[Section 8]

HUMAN GENETIC RESEARCH

Human genetic research involves the study of genetic factors responsible for human traits and the interaction of those factors with each other and, in some instances, with the environment. Research in this area includes identification of the genes that make up the human genome, the functions of the genes, and the characterization of normal and disease conditions in individuals, biological relatives, families and groups. Observation of different forms of the gene may be important among biological relatives and within and among different groups.

Accordingly, human genetic research is concerned with the use of genetic material. Genes and their alleles are being identified as part of the Human Genome Project, but the function of each gene and its relationship to human health may not be clear. Although the research is both exciting and rapidly changing, the recently acquired knowledge regarding genes and their mutations is not yet matched with a full understanding of the implications for human subjects.

In single gene disorders, for example, a mutation altering a biochemical pathway is directly related to disease. However, the presence of other genes or environmental factors will modulate expression. In disorders that are influenced by multiple genes and environmental factors (i.e. multifactorial inheritance), there may not be a clear differentiation between the normal and the abnormal. In addition, identification of genetic factors may only indicate predisposition because other genetic and non-genetic factors may also influence the development of disease (e.g., an inherited predisposition to breast cancer). Such factors indicate that identifying a particular genetic predisposition (e.g., by predictive testing) in individuals, biological relatives or a population may not mean that the person will definitely suffer from the disease, but may be perceived as such; the benefits of predictive testing, however, can include intervention strategies (e.g., dietary management with an inherited hypercholesterolemia).

Because genetic material is by its very nature shared by biological relatives, identifying a genetic causative agent has implications beyond the individual. Thus, issues of privacy and confidentiality may affect the individual, the family and the group to which the individual belongs. For example, in population studies, a particular group can be identified by common descent, geographic location, ethnic origin, etc. The results, if revealed and publicized, may stigmatize the other individuals in that group.

New technologies to analyze genetic material are being developed at an unprecedented rate. Indeed, new discoveries may be quickly incorporated into health care practices without sufficient research into their effectiveness or means of delivery. Given the present inability to know the limits or effects of such research, or the context in which genetic information is interpreted and used, caution should be exercised. These rapid changes and the potential financial gain from marketing the technologies, drive the need to be sensitive to ethical issues in genetic research.

The potential ability to identify all human genes and their mutations has profound social implications. Misunderstanding or misuse of the results of genetic testing has the potential to interfere with an individual's self identity and sense of self-worth, and to stigmatize the entire group to which that individual belongs. A number of issues remain unresolved and require continuing deliberation by the research community and the public.

Accordingly, this section reviews some of the major unique ethical issues presented by genetic research involving human subjects. The section should be read particularly in the context of other sections of this Policy.

A. The Individual, Families and Biological Relatives

Article 8.1 **The genetics researcher shall seek free and informed consent from the individual and report results to that individual if the individual so desires.**

Article 8.1 extends the general requirement for free and informed consent of Section 2, to their particular application in genetic research. Because genetic research involves the family and/or the community—in terms of family history, linkage and other studies—a potential tension exists between the individuals in the study and the families who are thereby implicated. Therefore, free and informed consent shall also involve those social structures, as far as is practical and possible. Because genetic counselling and research studies begin with a family history provided by a family member, medical genetic charts will reflect the health and social history of the entire family, not just the individual. Because linkage and mutation analyses involve biological relatives, interpreting the results may not be possible without the cooperation of the family or the cultural group (see Section 6). The researcher should be aware that, in certain situations, members within a family may be coerced by other members to join the study. Further conflict within a family may exist if some members hold that the rights of the family to genetic information override the rights of the individual.

When the wishes of the family or a group are in conflict, enhancing communication is preferable to compelling either the group or the individual to overcome their reluctance. The researcher should recognize the potential for conflict within a family regarding participation in research endeavours but, above all, should honestly present to family members the goals, advantages and disadvantages of the research.

B. Privacy, Confidentiality, Loss of Benefits, and Other Harms

Article 8.2 **The researcher and the REB shall ensure that the results of genetic testing and genetic counselling records are protected from access by third parties, unless free and informed consent is given by the subject. Family information in databanks shall be coded so as to remove the possibility of identification of subjects within the bank itself.**

Because the potential for gathering genetic knowledge about biological relatives or groups by studying only a few individuals is unique to genetic studies, an individual may not be assured of privacy within the group, unless extra precautions are taken. The status of an individual may be known simply from data obtained on a parent or a child. Consequently, the knowledge by a third party (e.g., an employer or insurer) of a specific risk or diagnosis may lead to discrimination in employment, insurance, etc.

Article 8.2 should be read in conjunction with the general provisions on privacy and confidentiality of Section 3. The article recognizes the special privacy and confidentiality issues that may arise due to the unique nature of genetic information. Unless special precautions are taken, for example, databases containing genetic information may identify multiple biological relatives. Similarly, publication of pedigrees from families having rare conditions may identify not only the particular family, but also specific individuals within that family, because such families tend to be known within the genetics research community. The researcher is then faced with a dilemma: maintaining accuracy of the data, or publishing an altered pedigree that potentially contains either sensitive social information (e.g., non-paternity) or sensitive diagnostic information (e.g., where individuals have inherited a particular disease allele). However, an altered pedigree can wrongly target others, and alteration may impair replication in future research or lead to flawed conclusions by other researchers.

DNA banking allows family histories, clinical details and genetic material to be available for other researchers to make specific diagnoses of genetic alterations, to allow studies of genotype/phenotype correlations, or to answer basic questions regarding human development. If appropriate guidelines are not respected, confidentiality may be compromised by DNA banking (see Article 8.6).

Accordingly, the researcher should be aware of these potential risks to confidentiality, and be able to inform the REB as to how the publication of data or other handling of such information will be accomplished. In particular, the researcher should clarify how subjects will be made aware of limits to the protection of confidentiality.

Article 8.3 **Researchers and genetic counsellors involving families and groups in genetic research studies shall reveal potential harms to the REB and outline how such harms will be dealt with as part of the research project.**

Article 8.3 obliges researchers to address the potential harms of genetic research. With the exception of gene therapy, physical risks in genetic research are generally similar to those seen in other forms of research. However, the potential for social and psychological harm as a consequence of genetic research is a reality. Harm in genetic research includes moral, physical, psychological and social harms. Merely being involved in a study may lead to harm for a subject. For example, receiving information regarding susceptibility to genetic disease or even carrier status may provoke anxiety, disrupt relationships or undermine an individual's sense of life opportunities. The individual's position within the family may be challenged by the decision of whether to participate. Such issues may be exacerbated in cases involving single gene disorders where confirmation of high risk or carrier status cannot be followed by effective therapy or prevention. As well, even receiving information of low-risk status may be psychologically harmful if the individual is perceived as no longer sharing the family burden.

As in other areas of research ethics, genetic research involving children involves special ethical obligations and protection. Children may be at particular risk for stigmatization, both within and beyond the family, because of knowledge gained through genetic studies. Therefore, genetic research involving children should not be done unless an effective intervention is available and the information to be gained outweighs the risk of harm. It may be appropriate, for example, to offer testing to children in a family for an early-onset condition such as polyposis coli, for which the knowledge affects treatment options, but inappropriate to test children for an adult-onset condition such as Huntington's disease, for which no effective prevention yet exists.

C. Genetic Counselling

Article 8.4 **Genetics researchers and the REB shall ensure that the research protocol makes provision for access to genetic counselling for the subjects, where appropriate.**

Genetic counsellors who are formally trained to impart genetic information have two main roles in dealing with a family: the first is to educate regarding the condition in question, and the second is to counsel by presenting options or possible action scenarios in a non-directive manner. The complexity of genetic information and its social implications usually requires that free and informed consent be supplemented with genetic counselling.

Genetic research involves families and groups in different ways. Individuals questioned about intimate family details and groups approached for a study may be unaware of harms beyond those of a physical nature. Accordingly, counselling regarding the potential benefits, harms and limitations of each study is crucial both before the individual gives free and informed consent and after results are available. For example, in predictive testing for Huntington's disease, pre- and post-test counselling have been essential.

In studies examining allelic differences or predisposing alleles in a particular condition, the clinical implications may as yet be unknown. Accordingly, the researcher will need to advise research subjects and the REB about the potential meaning of the anticipated results to the subjects, and how counselling will be handled. Subjects may also need follow-up, and the question will remain as to when follow-up should occur and where the researcher's obligation ends. One option is for the researcher to identify a contact person within the family to be given information to be shared. Even though the onus should be on the researcher to outline suggestions for such ongoing education and counselling, new genetic knowledge and therapeutic interventions are being developed unpredictably. It is, therefore, sometimes only practical to explain to research subjects that they will need to contact their physician to keep informed, because researchers may not be able to maintain contact after the research is completed. The extent of continuing duties should be discussed with the REB.

In newer applications of predictive testing, such as inherited breast cancer, pre- and post-test counselling are integral to the research project. Therefore, the researcher must recognize that educating the subjects regarding the factors involved in predictive testing (e.g., interpreting the results and providing further counselling when results are available) is essential in this complex area. Consideration should also be given to combining clinical expertise with that of the research geneticist.

At present, the geneticist or genetic counsellor may have the most expertise regarding the counselling issues involved in research projects. However, as technology continues to outpace our understanding of the impact and consequences of genetic knowledge, even the most experienced genetic counsellors may be unable to predict future consequences. The prudent researcher cannot assume that he or she can anticipate all harms inherent in a particular project.

Families may define themselves in different ways in terms of biological, social and cultural relationships. There may be important cultural differences regarding notions of genetic inheritance. There is also a problem that the higher frequency of disease and/or genetic changes in a group or region that has historically confined reproduction to within its own members could reinforce discriminatory use of ethnicity, culture or racial labels. Researchers who propose to study ethnically related genetic changes should understand this issue and be able to provide the necessary counselling.

D. Gene Alteration

Article 8.5 **Gene alteration (including "gene therapy") that involves human germline cells or human embryos is not ethically acceptable. Gene alteration for therapeutic purposes and involving human somatic cells may be considered for approval.**

Gene alteration involves the transfer in various vectors (or carriers) of genes into cells to induce an altered capacity of the cell. Commonly used vectors are viruses that introduce the gene into the host genome or plasmids (where integration does not occur, e.g., a method used with DNA vaccines). Alteration of human genes may be used to treat disease in an individual, alter germ cells to prevent the disease or alter for cosmetic "improvement." Since gene alteration remains experimental and is not "therapy" in the accepted sense of the word, the use of animal models continues to be crucial in this area of incomplete knowledge. At present, the most common research in gene alteration concerns serious single gene disorders, such as adenosine-deaminase deficiency, a subtype of an immune disorder, or life-threatening malignancies.

The possible use of germline alteration in the embryo implies alteration of cells not yet committed to specific organs, and therefore would alter future reproductive cells. Accordingly, resulting changes could be transmitted to future generations. Two Canadian documents, the Medical Research Council's *Guidelines on Somatic Cell Gene Therapy in Humans* (1990) and the *Report of the Royal Commission on New Reproductive Technologies* (1993), report that germline therapy raises serious ethical concerns and should not be undertaken.

Gene alteration outside the context of well-defined serious single gene conditions or malignancies poses the following concerns: long-term follow-up of already treated individuals is not available; the numbers of such individuals is small; and the lack of information regarding long-term harms makes it inappropriate for such technology to be used for enhancement purposes or for non-life-threatening disorders.

Gene alteration is irreversible; the cell and its descendants are forever altered and cannot be removed from the patient. In addition, the need for lifetime follow-up is crucial to establish harms, benefits and unrecognized concerns. The special circumstances of gene alteration must be clarified to potential subjects, and sometimes their families, in advance of participation.

The following issues, which are articulated in the Medical Research Council's *Guidelines on Somatic Cell Gene Therapy in Humans* (1990), should be considered when evaluating the harms-benefits ratio in gene alteration projects:

- A dilemma exists in that the most likely diseases to be considered for gene alteration are severe, progressive and fatal in childhood (e.g., immune deficiencies). Early treatment for maximal effect means the subject is less able to give free and informed consent because of immaturity. Furthermore, long-term effects are unknown in this age group. However, if research is restricted to those who are able to give consent, many severely affected children would be excluded.

- The withdrawal of the subject from the research project makes early recognition of harms less likely and denies knowledge of such harms to future subjects and researchers involved in gene alteration.

- *In utero* uses of somatic cell gene alteration may not involve the embryo because the germ cells may be affected.

- The potential risks of gene alteration include re-infectivity and oncogenicity of the viral vector, interruption of a normal host gene with negative consequences, bacterial contamination, establishment of the inserted gene in germ cells with unanticipated consequences, and only partial correction of the genetic disease, thus converting a fatal condition to a chronic progressive one.

- In the case of rare genetic diseases, the survival and subsequent reproduction of treated subjects is unlikely to have a significant impact on the gene pool.

E. Eugenic Concerns

The aim of genetic research should be to advance knowledge or to alleviate disease, not to "improve" or "enhance" a population by cosmetic manipulation. Further, the aim should be to better understand genetic disease, the genetic contribution to health and disease, the human genome, and to help individuals and families with genetic conditions. Accordingly, care should be taken to avoid isolating specific populations so that the group feels either stigmatized by the genetic disorder or targeted for "improvement."

The rights and freedoms attached to personal relationships, reproduction, and the support of those with handicapping conditions should also be maintained. The freedom of couples who are at risk to plan and carry potentially affected pregnancies, and the support of children and adults with handicapping conditions, should not be compromised.

F. Banking of Genetic Material

Article 8.6 **Though the banking of genetic material is expected to yield benefits, it may also pose potential harms to individuals, their families and the groups to which they may belong. Accordingly, researchers who propose research involving the banking of genetic material have a duty to satisfy the REB and prospective research subjects that they have addressed the associated ethical issues, including confidentiality, privacy, storage, use of the data and results, withdrawal by the subject, and future contact of subjects, families and groups.**

Consistent with the data confidentiality provisions of Section 3, above, Article 8.6 outlines the duty of researchers to address ethical issues raised by the banking of genetic material. In this context, although consensus has not been reached, a number of issues need to be considered by the researcher and clarified for the REB, particularly concerning privacy, confidentiality of records, and information derived from stored genetic material. A special concern arises when it is difficult to separate genetic information on an individual from information on his or her biological relatives or community. Access to genetic material and to the results of the research should be limited to the researcher, and if such limitation will not be the case, then the issue should be discussed with the research subject. Similarly, unauthorized access to stored genetic material or results by third parties should be prevented. Specifying whether banked genetic material will be anonymized, i.e., without identifiers, may help alleviate the concerns that other biological relatives may inadvertently be identified by linked data.

Though no international consensus currently exists regarding long-term banking of genetic material for the purposes of genetic research, the storage of samples should be for a defined term; some researchers state five years, while others prefer 25 years to allow another generation to potentially benefit from the information. In the case of immortalized cell lines, researchers have a duty to explain that the sample may be stored indefinitely. The researcher should outline, in the protocol, future uses of genetic material or research data. In some cases, the genetic material will be used to investigate only the specific genetic condition affecting the biological relatives. In other cases, a variety of genetic mutations may be evaluated using this material. In yet other cases, future uses may simply be unknown.

Suggested methods to handle secondary use of genetic material or research data include a comprehensive consent form, which allows the research subject to choose from a number of options (e.g., use of the material only in the present study, use restricted to the condition, or other clearly specified use) or a more limited consent form, which specifies arrangements to maintain contact with the subject regarding future uses. Either method must be clearly explained during the process of free and informed consent.

As stated previously, the biological aspects of genetic variability or disease-causing mutations imply that information gained from banked genetic material pertains not only to the individual, but also to biological relatives. If possible, researchers should clarify with the subject whether results are to be used for the individual and/or for biological relatives. In addition, clarifying whether results will be available from any analysis, and whether the subject wishes to receive results, assists the subject in the process of free and informed consent.

The right to withdraw from a research study is a necessary component of the process of free and informed consent. Where banking is concerned, withdrawal affects not only the individual but also the biological relatives. Therefore, withdrawal could involve actual destruction of genetic material or research data, or the removal of all identifiers. These options need to be discussed with the subject.

Differentiating between already-stored genetic material (e.g., materials previously obtained perhaps without consideration of the factors referred to throughout this section) and a proposed banking project is important. In the latter situation, the REB should expect that the researcher has considered all of the factors referred to herein in the description of the study and in the process of free and informed consent. In projects involving already-stored genetic material, an REB should consider the importance of the factors on a project-by-project basis since the research subjects may no longer be living, or the material to be used was obtained from samples previously collected or left over after routine care. Until consensus has been reached in the area of genetic banking, full disclosure to the research subject of the factors referred to herein would seem to be the prudent course.

G. Commercial Use of Genetic Data

Article 8.7 **At the outset of a research project, the researcher shall discuss with the REB and the research subject the possibility and/or probability that the genetic material and the information derived from its use may have potential commercial uses.**

Article 8.7 adds a specific obligation to the disclosure requirements for obtaining free and informed consent from those being subjected to genetic research: the potential for commercial use of genetic data. There is significant legal and moral controversy regarding ownership of genetic material or research data, and concepts of ownership may vary from one cultural group to another and between legal systems. It is unethical for a researcher to claim ownership of genetic material by claiming that the concept of private ownership did not exist in the community involved. Consistent with the free and informed consent provisions of Section 2, the researcher may have to seek further permission from the group. The fact of commercial sponsorship of genetic research should be revealed to the subject at the beginning of the project. Similarly, possible commercialization occurring after involvement in research should also be revealed at the outset if possible.