ADVISORY COMMITTEE ON GENETIC TESTING

ADVICE TO RESEARCH ETHICS COMMITTEES

October 1998

ACGT ADVICE TO RESEARCH ETHICS COMMITTEES

Points to consider in ethical review of medical research involving genetic testing

BACKGROUND

In the United Kingdom, since 1967, there have been research ethics committees (RECs) whose function is to satisfy themselves of the ethics of all medical research proposals using human subjects. These committees have evolved gradually and have their origins in advice produced by the Royal College of Physicians and endorsed by the (then) Ministry of Health. As time has passed, more guidelines have been issued by the Health Departments and by medical and nursing professional bodies and international regulatory agencies.

Since 1991, each Health Authority has been required to resource and maintain at least one Local Research Ethics Committee (LREC) to advise NHS bodies in its area on research proposals. The Committees comprise medical, nursing and other health professionals and lay people. Researchers are asked to complete an application to the LREC covering information to justify the research, how it is to be conducted, what will be done to the research subjects and why, what information will be given and how the subjects' consent will be obtained.

In 1997, a system of multi-centre Research Ethics Committees (MRECs) was set up to streamline the handling of multi-centre research proposals. Each region has a MREC which reviews the science and general ethics of medical research protocols to be carried out within 5 or more LRECs geographical boundaries. If approved, the local researcher will submit the proposal to the LREC for review of any local aspects of the protocol. Although RECs are advisory bodies, they must come to a favourable view of each research project before it can commence.

GENETIC RESEARCH AND ETHICS

The ACGT Secretariat has received a number of enquiries from RECs seeking advice on research trials which include genetic testing. The Committee agreed at its meeting in January 1998 to provide RECs with guidance in the form of a "Points to Consider" document intended to help committees identify the questions that they might raise with researchers.

We set out below, in the form of questions to researchers, issues that RECs may wish to consider before giving ethical approval to research that includes genetic testing.

Definitions used in this paper

The Advisory Committee has used the following definitions in its most recent report*.

Genetic Testing

To detect the presence or absence of, or alteration in, a particular gene, chromosome or a gene product, in relation to a genetic disorder.

> **NOTE:** ACGT's definition of a genetic test is not restricted to a DNA or chromosome test. Many "biochemical" tests will indicate that a person is likely to have a genetic or familial disorder and these should be treated by RECs as "genetic tests".

(a) **Diagnostic Genetic Testing -** Use of genetic testing in a symptomatic individual to aid in their diagnosis, treatment and management.

(b) **Presymptomatic Genetic Testing -** primarily carried out in healthy or asymptomatic individuals to provide information about that individual's future health, with respect to specific inherited diseases. Such a test result may indicate that the individual has a high likelihood of developing the disorder or of excluding it. Presymptomatic testing is most frequently used in late onset autosomal dominant disorders such as Huntington's Disease.

(c) **Susceptibility Testing -** which provides information about the genetic component in a multifactorial disorder

(d) **Carrier Testing -** used to detect individuals who possess a single copy of a gene which follows an autosomal recessive pattern of inheritance (see below). Such an individual will not normally develop any disease or disorder but may pass on the gene to his or her offspring.

Multifactorial

Disorders whose genetic components are not the sole cause, but which work with other often environmental factors in determining a disease outcome. Multifactorial disorders include many cardiovascular diseases, most Alzheimer's Disease of old age and some forms of diabetes.

Autosomal Recessive Disorders

Disorders, where for a person to be affected, a mutation has to be inherited from both parents. Such parents are usually unaffected carriers because they only have a single copy of the mutant gene. Recessive disorders commonly have onset in childhood and include cystic fibrosis, sickle cell disease and thalassaemia.

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***** Advisory Committee on Genetic Testing:

Report on Genetic Testing for Late Onset Disorders. Department of Health

May 1998

DESIGN OF RESEARCH INVOLVING GENETIC TESTING

1. Research and Service Interface

1.1 Is there an adequate system for ensuring that the identity of those participating in research is kept confidential? Can the study be performed using fully anonymised samples?

There are some types of genetic research involving the general population or sub-sets of it, eg. epidemiological studies where fully anonymised samples will be appropriate. Such studies must be designed in such a way that there is no route by which participants and samples can be matched. This safeguard should be explained to the research subject.

More commonly it will be acceptable to carry out research, eg. in prospective studies, where some information on the subjects is held so securely that direct or simple matching of results and identity is not possible, and where links require decoding. In any study where it is possible to make such a match, it will be necessary to give careful consideration to the question of what circumstances, if any, might justify a research finding being passed on to the subject or added to their medical record. (see 2.1 below)

1.2 Is there to be a clear separation of the research specimen from service testing samples?

Good laboratory practice should ensure that whenever practical, a clear distinction is made between diagnostic testing, ie. testing a patient to aid in their diagnosis, treatment and management and genetic testing in the context of medical research.

If a research subject or their clinician later requests presymptomatic or diagnostic testing or other genetic services, then it should be normal practice that the request be considered on its merits and then if accepted a new specimen obtained. This aspect should be explained to the research subject.

If the concept of keeping research and `service' specimens entirely separate is not physically practical then there must be a proper control system in place that ensures that research samples can be easily identified as such. It will be especially important to be assured that there is a single high level of quality assurance and test control if the two aspects are not to be physically separated.

RECs and researchers should be aware that the Data Protection Act 1998, when it comes into force, and proposed subordinate legislation may have an impact on the use of genetic data.

2. Disclosure of research findings

2.1 *Is it intended that the test results be given to the research subject or added to the medical record in any circumstances?*

This is a fundamental issue which may affect a REC's actions on such research proposals. ACGT is of the view that if the result of a gene test undertaken as part of a research protocol may be passed on to the participant or added to the medical record, then that patient must have been fully informed about the test(s) and prior specific consent sought. Concern over disclosure is particularly acute where the research involves late onset disorders, but remains a significant issue in all genetic testing.

There is clearly a boundary between research and clinical practice which may only be crossed in the interests of the tested individual, and only with their prior knowledge and their prior consent (subject to the usual provisions for children etc). It is important that research protocols address this issue and that RECs are content that the implications of genetic testing for the subject and their families will be understood by the participants.

2.2 *Where results from research are intended to be, or may be, disclosed does the information to be provided make clear what use may be made of test results? Where test results may be disclosed, are the research subjects fully informed of potential adverse consequences, such as for insurance, employment, and effects on other family members?*

There is increasing awareness and concern over the possible use of genetic information by third parties such as the insurance industry. Such issues need properly to be considered. In addition, genetic testing may also directly or indirectly have effects on family members who have not themselves been tested or may not wish to be tested. In some genetic disorders an abnormal result in an individual may also mean that healthy siblings (or even a healthy parent) may be at risk. Such implications for other family members must be fully considered in the protocol. It is necessary to take account of the fact that these individuals may not wish to know that research involving another member of the family has revealed a genetic result with an implication for them. This `right not to know' is as important for some as the `right to know' is for others. The protocol must address these aspects if results are to be disclosed.

2.3 *Where relevant, will the individual be told of the appropriate voluntary organisations* *involved with genetic disorders who can also be a valuable source of information for those considering genetic testing*?

Many voluntary bodies have helped to provide valuable guidance for testing in their particular field, both in terms of written information and of support from their staff.

2.4 *Are research subjects to be given adequate time to absorb the information provided, before a decision is taken to be tested or a result is given?*

In genetics clinics, a two step approach has been found to be important in allowing time for reflection. Since a premium is often placed on avoiding delay in other laboratory testing situations, it is important that this time interval is protected.

3. Use of stored specimens for further research

3.1 *Has careful consideration been given as to whether it is practical to have a system in place for going back to research subjects to seek their consent for further uses of their stored samples for research?*

Except where the study is conducted in a truly anonymised fashion, ACGT believes that before any genetic test is carried out as part of medical research prior consent must have been obtained for each test. Genetic testing should not be added to an existing research study without consent being sought. Where an existing protocol has approval to test for a limited number of genes and the researchers have come back to the REC to add more gene tests, the Committee should consider whether a new `full ethical review' is appropriate or whether this can be handled as a protocol amendment.

3.2 *Are the gene tests in the revised protocol closely related to those for which approval has already been granted and consent obtained?*

It may be that the new tests can be considered as being covered in the original consent. However considerable caution is needed if further consent is not to be sought. If the new tests are associated with other diseases and disorders which were not discussed with participants, then the REC should conclude that both consent should be sought afresh and a new ethical review carried out.

Legally valid consent requires the opportunity to consider all the implications of the test(s). It is not ethically acceptable or participants to be asked to "consent" in a non-specific manner to the carrying out of any and all gene tests.

4. Multiple genetic testing

4.1 *Does the research protocol involve the use of technologies that permit multiple genetic tests to be performed?*

ACGT takes the view that research involving multiple gene tests is no different from that where the research protocol involves a single gene test.

Studies such as those labelled as "genotyping" or "genetic profiling" which are being used for drug development or in pharmacogenetics must be treated as genetic testing. The fundamental issues of information, consent, and confidentiality are unaltered. The challenge for researchers is to establish suitable, "user friendly" methods by which complex information about their research can be explained to participants.

5. Research involving "at risk" individuals and their families

5.1 Does the research place unacceptable burdens on individuals from a family with a known genetic disorder?

Where samples are to be taken from families with genetic disorders, it is important that healthy individuals are not sampled unless strictly necessary. There is often a tendency for researchers to view "healthy" members of a family as patients and this risks unnecessary "medicalisation" of these individuals. Where unaffected subjects are to be included in a study this must be carefully justified and there must be a clear plan as to what would done in the event of an abnormality being identified. Caution needs to be applied so that families with a known genetic disorder are not overwhelmed by approaches to participate in research projects.

6. Information requirements

6.1 *Is the information, including that on any disorder being tested for - full, accurate and appropriately presented, in a clear and simple manner that is readily understandable?*

While some individuals who may be invited to participate in research including genetic testing will have extensive experience of the condition, personally or in their family, others will not, or the information may be incomplete. Accurate information is essential if individuals are to make valid decisions regarding testing. Written information should be provided in an understandable form, and particular consideration should be given to providing information to those with hearing or visual disabilities, or whose first language is not English.

Where the test is to gain knowledge of the genetic determinants of a known disorder, the participants will need information on the purposes and implications for themselves and for their families if there is an intention to feed back results to participants.

Information should deal with both the benefits and potential disadvantages (see section 2.2) to the individual and/or the potential to increase wider knowledge about genetics.

6.2 *While written information is important, will complex information also be provided face to face by an appropriately trained and experienced person*?

In genetic testing there are frequently complex and sensitive issues that require discussion, rather than simply provision of information. While not all such issues require involvement of specialist genetics services, these have an important role when they are complex and time-consuming, or when they involve members of the extended family.

Where necessary, the REC may wish to consider whether appropriate arrangements are in place to ensure that research subjects are suitably informed. For instance, in specialist genetic practice, Genetic Nurse Specialists and other professionals play an important role in pre-test preparation and in post-test home visiting to ensure that necessary support is explored and that information has been received and understood.

CONSENT TO GENETIC TESTING

ACGT assumes that where an individual is able to give consent this will always be obtained before testing is undertaken. Consent should only be sought after the individual has been given information (see above).

7. Consent arrangements

7.1 Will written consent be obtained?

The main purpose of written consent is to provide documentary evidence that an explanation of the proposed procedure was given and that consent was sought and obtained. It also helps clarify for the research subject precisely what he or she is agreeing to. Written consent is not in itself a substitute for careful face to face explanation but is increasingly recognised to be good practice.

7.2 Will consent be specific?

New technology may make it possible to test for many genetic diseases at one time and could generate results relating to disorders that the individual was not even aware of, a situation which should be carefully avoided. If testing is for a group of allied disorders, this should be made clear when consent is being obtained. (see above).

7.3 Does the research involve children?

This is an area where considerable caution is needed. The Department of Health "Briefing Pack for REC Members" (1997) gives general guidance on the issues raised which are equally valid for research involving genetic testing.

ACGT takes the view that presymptomatic genetic testing of children for disorders not currently influenced by therapy is unjustifiable in the context of research.

Requests to test children in the context of research for genetic disorders that may affect them during childhood require full and sensitive discussion with the parents and professionals who are responsible for the care of the child or children in question. Testing should not be simply accepted or declined on ground of general policy, however it is clear that researchers must demonstrate that the participation in research is in the child's best interest.

When assessing a child's best interests consideration should not be limited to "best medical interests". Other factors that may be considered include: psychological health, well being, quality of life, ethical, moral, spiritual and religious welfare, relationships with other family members and financial interests.

In assessing the best interests of the child, the separate and potentially conflicting interests of children, parents and other family members should each be given careful consideration. Where there is particular concern over what is in the interests of a child in certain circumstances, including where there is any dispute between those with parental responsibility for the child, there must be serious doubt over the wisdom of recruiting that child.

When research involving testing is to be carried out in children, ACGT recognises that especially in young children, it may be acceptable, with appropriate consent, to go back to stored specimens rather than to take fresh samples, but issues such as the quality of the banking should be considered carefully.

7.4 *Does the research involving genetic testing of adolescents*?

Subject to the points raised in 2.2, 2.4, 5 and 6.1 above, requests from adolescents who are capable of giving informed consent themselves to participate in non-therapeutic research deserve full and sensitive discussion. Account should be taken of the views of the individual and, where appropriate, their family. However in many cases, it may be best to defer the decision until the age of majority is reached.

ANNEX A

Members of the Advisory Committee on Genetic Testing

Rev Dr John Polkinghorne KBE FRS	Chairman
Professor Kay Davies	Dr Lee's Professor of Anatomy and Head of Department, Department of Human Anatomy, University of Oxford.
Professor John Durant	Assistant Director, The Science Museum, South Kensington.
Professor Peter Harper	Professor and Consultant, Institute of Medical Genetics, Cardiff.
Dr Hilary Harris	General Practitioner, Manchester.
Professor John Harris	Sir David Alliance Professor of Bioethics, University of Manchester.
Miss Wendy Johnston	Specialist Health Visitor in Genetics, Belfast City Hospital
Mrs Christine Lavery	Director of the Society for Mucopolysaccharide Diseases and founding trustee of the Genetic Interest Group.

Professor Sally Macintyre	Director, MRC Medical Sociology Unit, University of Glasgow.
Mr Matthew Parris	Journalist, The Times.
Professor Marcus Pembrey	Mothercare Professor of Paediatric Genetics, Institute of Child Health, London.
Dr Sultana Saeed	Formerly Lecturer in Law, University College London.
Mr Philip Webb	General Manager, Zeneca Diagnostics, Abingdon, Oxfordshire.

ACGT's Terms of Reference are:

i. to provide advice to Ministers on developments in testing for genetic disorders;

ii. to advise on testing individuals for genetic disorders, taking account of ethical, social and scientific aspects; and

iii. to establish requirements, especially in respect of efficacy and product information, to be met by manufacturers and suppliers of genetic tests.