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Original papers

Ethical aspects of genetic research

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The double helical structure of DNA, specifies virtually everything about the form and function of all cells and all organisms. A knowledge of the genomic sequences gives physicians a unique opportunity to identify the genetic loci involved in human diseases. Over the past decade, developments in molecular genetics have allowed the mapping and isolation of a large number of genes for many human disorders. DNA analysis of specific mutations or of linked markers now gives the possibility of presymptomatic and prenatal diagnosis of the healthy heterozygous carriers and in some instances of inferring the severity of the disease from the nature of the mutation detected. Much of the research leading to these and other important advances have entailed the study of families with specific inherited disorders.

Ethical and practical problems may arise when samples from relatives who are healthy but at risk are included in such studies. New molecular transfer specific gene mutations may result in the detection of a genetic defect in relatives who had neither expected this possibility nor given specific consent for such testing. Problems may be created if banked samples were used for such detection. Therefore, patients and to a lesser extent healthy volunteers who participate in research are vulnerable to exploitation and must be protected.

Properly designed and conducted medical research studies that are ethically acceptable and benefit society should be encouraged and protected. Ethics of gene therapy research, use of fetal material, human fertilisation and embryology receives special attention but receives no mention in the recent in several reports on ethical issues in medical genetics[1]. Genetic research using stored tissue samples poses an array of benefits and risks to individuals, researchers and society[2]. Therefore, when using human subjects in genetic research, it is mandatory to protect human subjects involved in research as they do so for general good rather than for self benefit.

Several international agreements govern the protection of human subjects in biomedical research. Guidelines developed in their chronological order are given below[3].

- Nuremberg Code Published in 1949[4]
- Universal Declaration of Human Rights (1948) introduced by United Nations General Assembly
- Declaration of Helsinki (1964). In this the Fundamental principal of ethical and legal medical research enshrined in the Nuremberg Codes of conduct
- Declaration of Helsinki (1975) – Tokyo By World Medical Association
- Declaration of Helsinki (1983) – Venice By World Medical Association
- Declaration of Helsinki (1989) – Hong Kong By World Medical Association
- International Guidelines for Ethical Review of Epidemiological Studies (1991) Council for International Organisations of Medical Sciences and World Health Organisation.
- International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993) Council for International Organisations of Medical Sciences and World Health Organisation.
- Guidelines for Good Clinical Practice for Trials On Pharmaceutical Products (1995) by World Health Organisation.
- Declaration of Helsinki (1996) South Africa by World Medical Association.

The United States has developed several National Standards to maintain the ethical standards of genetic research.

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- Development of case law by American Courts since the 1957 decision of Salgo V. Leland Stanford Jr. University Board of Trustees[4]

- Office for Human Research Protection[5]

- Publication of the Beimant Report in 1978 by the National Commission for the protection of Human Subjects of Biomedical and Behavioural research[4].

A statement of the Association of American Universities which represent 61 institution of higher education states that the protection of Human subjects must be borne by the institute that performs the research through **Institute Review Boards** (IRB)[5].

Responsibilities of an investigator

It is essential that the investigators maintain public confidence in their work and their competence. The investigators should adhere to strict protocols and the highest ethical standards should be maintained[5].

Informed consent

Medical researchers and physicians are aware of the need to involve research participants and patients in a process of shared decision-making pertaining to their health and welfare. It is dishonest to use human subjects without their full knowledge and understanding to place them at a risk of identifying diseased genes. Amongst the acceptable guiding principles are that research on human subjects should in general undertaken only on the basis of individual consent. Informed consent is regarded as a process of communication in addition to signing a consent document. Signing a consent document is both an ethical and legal requirement in bio medical and clinical medicine[4]. The fundamental principle of ethical and legal medical research enshrined in the Helsinki Declaration and in the Nuremberg Codes of conduct states that no research should be conduct on human beings without appropriate consent. In addition, special arrangements should be made for those who cannot give valid consent such as children and those with mental incapacity. Such research should be subjected to approval by an independent, credible and publicly accountable Research Ethics Committee[6]. It is now possible with modern technology to store DNA. Therefore, it is possible to test, screen and analyse without informed consent each time when a new genetic research project is initiated. This is unacceptable since the definition of prior consent is different from informed consent, therefore, the ethical perspectives will change because informed consent was obtained on one occasion for a only one particular study. The DNA of a person is regarded as probabilistic future diary than a record of past events and what was written in it has not yet broken. For what, by whom and when it should be decoded is entirely a decision which should be made by the individual[7]. Therefore, the way to obtain informed consent will have to be reviewed and needs to be expanded to fit the context of DNA banking.

Many groups are involved in modern genetic research. The resources of genetic studies usually involve the probands affected with the disorder and volunteers who are unaffected but at risk. Most molecular studies of families with genetic diseases initially entail a genetic linkage approach by relying on a comparison of marker genotypes between affected and unaffected subjects to establish linkage with a particular marker. Once the gene is isolated, a comparative approach is again important to establish that any change identified in the gene is infact specific to affected subjects and not a harmless polymorphism or other coincidental change. Detecting such a gene may create problems due to uncertainties relating to consent when using banked DNA samples.

Adverse effects of an unexpected detection of genetic disorders

Fear of the potential clinical effects of the disease and genetic detection may cause psychological consequences in some of the participants. Unexpected detection of a genetic defect may have serious repercussions on marriage and family relationships. Findings from participation in a genetic study will have adverse effects on insurability and employment if it becomes available to third parties and social stigmatization can result if individuals are identified as carriers of genes that may cause certain conditions[8].

Advantages of detection of a genetic defect

The people with family history pre disposing to a particular genetic disorder may value the results of the detection of genetic defect because they can have knowledge of their own and their children's genetic makeup to reveal possible predisposition to the disease. This may enable them to improve their own health and the health of their relatives. Most importantly, this gives them an opportunity to make more informed reproductive choices.

Problems to investigator

When discovering a defective gene where no effective treatment is available, the investigators too will have to undergo difficulties. Will ignorance be bliss in the case of an individual who has untreatable genetic

disorder? Should the information given to the person who provided the sample? What if anything should be done and how?. Should their doctor be informed or the information be recorded in the persons medical record or should the investigator keep the information to themselves or destroy it?.

The situation may be different for samples from subjects affected by a known genetic disorder when specific information such as type or nature of a mutation may be helpful and valuable. Many may feel strongly that they should do everything possible to help those who take part in research and it is wrong to withhold information that could be important[8].

However, the outcome of any research project is uncertain. Therefore, it is preferable to make it clear to healthy member of a family from the outset that no result will be forthcoming either for themselves or for their doctor or medical record. This should resolve any later uncertainty.

Advantages of obtaining informed consent

Seeking consent from prospective subjects serves important societal interests. Obtaining consent will reassure the patients of their right to decide to participate in research and the community will benefit from the cooperative commitment of the participants knowing decision to participate in research[2]. This will reduce the risk of researches if the participants of the research will pursue legal actions when their expectations about the research are not met. In addition, the possibility of unhappiness and even litigation later on may be greatly reduced by early disclosure, discussion and the opportunity to refuse to participate.

Certificate of confidentiality

Most informed consent forms for data collection state that the information obtained will remain confidential. Investigators would not only lose credibility but would in effect breach the contract made with the study participants, if the identity of participants were subjected to review by insurance companies or employers. Breach of contract could also seriously affect the credibility with other family members and future potential subjects as well as with the institutional review boards and agencies from which the investigator receives funding. This certificate protects the investigator from revealing research data of the participant which would reasonably damage his financial standing, employability, reputation, and lead to social stigmatization or discrimination in any local civil criminal administrative legislative or other proceedings[8]. Disclosure of any data may require the consent of subject and permanent protection provided may remain even after the death of the subject.

DNA banking

Most of the genetic research studies now require isolated DNA from any nucleated cells from research participants. It is now possible to established DNA banks in many forms. This facilitates the investigators by providing a resource that can be used repeatedly for different research protocols that were not consented to at the time it was collected without having to cause discomfort or disturbances by taking further sample[7].

Possible kinds of DNA banking connected with genetic research projects[4].

1. Long term storage of one or more tissue samples (WBC, Extracted DNA). Isolated DNA is generally stored at -20°C or -70°C temperature.
2. Transformation of one or more tissue samples by laboratory techniques into immortalized cell lines, which are capable of infinite division. (Creation of lymphoblastoid cell lines by Epstein Barr virus (Cause of infectious mononucleosis, Glandular fever and certain tumors)
3. Long term storage of genetic data derived from the tissue samples and cell lines (allele types or DNA sequence data).

Categories of consent that should be present in documents seeking consent for DNA banking:

1. **Confidentiality and privacy –**

One of the **core ethical** features of the **genetic** research pertains to the **confidentiality and privacy** of research records, Stored biological materials and any genetic material derived from these stored materials especially if the stored DNA samples, cell lines or genetic information are identifiable or linkable to the sample source[9].

Research participants should be given laboratory specific information regarding procedures that will be used to protect the confidentiality and privacy of any **personal identification** regarding the source of a tissue sample or cell line[4], the risks and benefits of participation, under what circumstances if any they will be re-contacted[2]. It should contain the investigators plans for the physical security of the stored tissue sample, coding of the sample, striping of all identifiers from the samples (anonymizing)[9]. The subsequent investigators access to the cell lines should be included in the consent document. Such a disclosure statement

does not seem necessary if the DNA sample will be truly "anonymised" immediately in the laboratory so that no subsequent identification of or linkage to the sample source will be possible and the investigators anticipate no subsequent commercial possibilities for a transformed cell lines. A simple assertion in a consent document without any explanation that confidentiality and privacy would be maintained was not regarded as satisfactory[9].

2. Control and ownership

Research participants should be informed about the control and ownership of the biological materials when the tissue sample is in storage and in the event of its biological transformation in the laboratory to become an immortalized cell line[4] and commercial possibilities of immortalized cell lines[9]. A statement of the research participants and investigators as being sequential owners of the original tissue sample and subsequent cell lines and their ownership for a percentage of possible commercial profit should include. They also can include a statement in the consent document indicating a commitment to re-consent the sample source of identifiable biological materials if it turnout to be commercially valuable. A statement of subsequent investigators given access to the tissue sample or cell line derived from a sample source which remains identifiable or linkable to the cell line should be stated in the consent document and the concept of sequential ownership should be included[9] and not required if the samples are anonymized.

3. Right for subsequent withdrawal from a research study

Withdrawal from a genetic study is more difficult than from other studies as the research participant can continuously partake in family pedigree studies. Therefore, all research subjects have the right to withdraw from research project at any time[7].Participants should be informed both verbally and in the consent document about their right to withdraw from the study by requesting to destroy the stored biological material or to remove personal identification from the DNA samples (annonymization).

In genetic studies that involve future research on stored samples, the issue of withdrawal concerns not only the withdrawal of an individual from a study but also the decision by an individual to withdraw his or her continual contribution to or personal identification with an ongoing research project using banked samples. Withdrawal should involve the destruction of the DNA sample provided by the subject. To preserve and honour this right, the subjects should have the right to order their DNA sample destroyed at any time.

4. Information about the length of storage planned for the tissue sample and/or immortalized cell lines and/or genetic data derived from biological materials[4]

Information about number of years for DNA storage, length of the research project or whether samples will be stored indefinitely should be clearly indicated. Regarding the length of storage of the samples it is preferable to give a specific period planned for the storage of tissue samples rather than suggesting or giving no information at all about planned research time with the stored tissue samples. The anticipated length of time for DNA banking can be given to potential research participants in terms of an arbitrary number of years or the period funded for the research study. Investigators would convey a sense of certainty, structure, scientific goal and control rather than a sense of unplanned and unstructured guesswork about future research. If during the research period if investigators decided to convert the stored tissue samples to transformed cell lines they should get consent for such. Investigators planning at the outset to create transformed cell lines, should indicate such time limits in their consent documents. The necessary indefiniteness of research time an immortalized cell lines is different from the time limited research that is possible with stored tissues samples. When anticipating an indefinite length of time for research on one or more transformed cell lines, the consent could be obtained by giving brief statement regarding the scientific need and the possible benefit of extending research time through the creation of a cell line capable of indefinite division[9].

5. Future access to the information derived from the banked biological materials

The consent document should reveal the relevant information regarding the right of future access of the participants to any information relevant to them, gained through the study. Information that may be of clinical relevant to them or alternatively be told that such information will not be available in the future because the investigators plan to strip all personal identifiers from the stored samples, or if the identifiable codes still remains, the participants should be told by the investigators in writing whether they have access to personally relevant information

- In final results of the study
- Interim results of the study
- Incidental findings gained from the banked sample[4].

A statement of such will clearly state how and when the findings should be disclosed.

6. **Plans to handle future third party access to the stored DNA sample or genetic data[4]**

Research participants may like to withhold the research findings and access to the stored biological information from employers, Insurance companies, and governmental agencies. Some may restrict all third parties access including relatives and personal physicians. Their wish should be honoured.

7. **Secondary use:**

The principal investigator or numerous other investigators may use the stored DNA samples for other research studies secondary to the scientific purpose for which the tissue sample was originally collected. Possible kinds of secondary uses of the stored samples can be

- Use by the principal investigator for an other study
- Use by secondary investigators in the same laboratory for some other genetic study.
- Use by some other investigators in an other laboratory for the same genetic study.
- Use by other investigators in other laboratories for different scientific purposes[9].
- Commercial enterprises[2].

To assure the research participants regarding these issues, the consent document should state that there will be no secondary use of the stored biological material or they should be given the option of consenting now for future secondary use of the sample or should promise to contact them for additional consent in future if subsequent secondary use of the stored biological material. If not, it should indicate that all secondary uses will occur after striping off all personal identifiers.

Legal standards of disclosures for informed consent in bio medical settings[4]

The following standards of disclosures were formulated by various courts

1. Professional practice standard
2. Reasonable person or prudent person standard
3. Subjective or individual person standard

The first and least stringent **standards of disclosure** should disclose that patient in clinical settings and potential research participants be given adequate (quantity and quality) information that meets the professional practice standard and objective information that any reasonable or prudent person would want to receive in a particular clinical or research setting. Physicians and biomedical researches should also provide information to patients and research participants based on individual preferences.

Advantages of prudent person standard as the appropriate standard for disclosure in consent documents for DNA banking

In any biomedical setting particular person standard of disclosure is too high for genetic research protocols as most genetic investigators have limited knowledge about the preferences of the individuals participating in a study. On the other hand the professional practice standard sets the disclosure too low and unsatisfactory as little information is communicated to the research participants specially the content of the consent document pertaining to DNA banking and failing to disclose any information about the future use of stored tissue samples, cell lines or genetic data derived from the biological materials. Therefore, reasonable person standard of disclosure considered more appropriate standard of disclosure in consent documents for DNA banking[4].

The seven categories of consent listed represents the essential features of information that a reasonably prudent person would like to receive in the context of DNA banking.

Research based on archived information and samples

This involves the study of existing medical records for analysis of disease prevalence, biological samples that have been previously taken during the course of medical diagnosis or treatment, at autopsy, or for research, and are in excess of requirement for the original purpose.

International codes govern the protection of human subjects were governed in the context of intrusive research and no modification relating to non intrusive research has been made in the subsequent revisions of Helsinki Declaration[6]. Some in recommendations for research based on archived materials were put forward by the Royal College of Physicians of London (Annex 1). Emerging legislation or regulation designed to protect the rights of patients should not inhibit the conduct of some types of harmless research which have previously been conducted without difficulty and have formed the basis of important medical advances. Medical records based research is often done without individual consent under the assumption that the confidentiality is properly protected. Extension of the requirement for universal consent to the non-intrusive

research referred to above would bring to a halt all research on existing archived material some of which has been collected over decades and has been used and is being used to make important contributions to medicine. The resources of medical information and medical samples already in existence for which such consent has not been sought are enormous.

Removing identifiers from existing samples

Federal regulations in the USA currently permit investigators to take such samples by making them anonymous after removing identifiers, without seeking consent. However, some feel it is ethically unacceptable because the researchers had the opportunity to seek for consent but did not exercise it. Therefore, if doubt exists, the benefit of the doubt should always lie on the side of seeking appropriate consent and the Research Ethics Committees should have reviewed and agreed the research protocol to exempt the general requirement of individual consent[6].

The Institutional Review Boards should consider whether the information the researcher seeks can be obtained in a manner that allows individuals to consent (this includes the possibility of using tissue samples for which people had previously given permission for use in research), whether the proposed investigation is scientifically sound and fulfils important needs, how difficult it would be to re-contact subjects, whether the samples are finite and if used for research they may no longer be available for the clinical care of the source or his or her family and how the availability of effective medical interventions affects the appropriateness of pursuing anonymous research and in accessing research protocols that proposes to make the existing identifiable samples anonymous for use in research.

Disadvantages of seeking consent to use archived records or samples

Obtaining individual consent entails cost. Apart from that, obtaining the willing and informed participation may be too burdensome and may prevent the pursuit of desirable research[2] and attempt to contact very large numbers of people often long after the event in question is difficult. Moreover, seeking consent from large number of participants would be impractical and unethical since it involves a considerable and unexpected intrusion into people's lives. Furthermore, if the patients should have given the right to prevent use of their records for research, the selective removal of data could invalidate the research. Therefore, it is unreasonable to allow individuals to do this when the use of their records or data is at no cost or harm to themselves. These records can properly be used for research without explicit patient's consent if confidentiality is preserved.

Some states of the United States enacted laws that specifically allow the investigators within an institute to obtain medical records for research without seeking patient consent but this conflicts with the Federal regulations that protect private information.

a) Advantages of using archived samples

Archived samples have already been obtained. This prevent an additional hazards to the research subjects from physical intervention. The risk of psychological harm and invasion of individual privacy can be reduced if the samples were anonimised to keep collective confidentiality of the research subjects.

Studies involving large populations

Before conducting large-scale biomedical research on a population, it is considered important to obtain the consent of that population[10]. However, obtaining blanket consent is a tedious task from a large population. Therefore, countries like Iceland which have created population-based data bases, based on medical records of its population have collected them under the assumption of presumed consent. However, some argue that presumed consent is inconsistent with the right of individuals to decide for themselves and actually amounts to no consent at all. Obtaining broad consent indicates that the potential subjects cannot be informed in the same detail required by informed consent. Since genetic studies on populations have the potential to stigmatize the entire population, research should not be conducted on a population unless the benefits to the population are likely to overweigh the risks[10]. It may be possible to ensure anonymity while retaining some information about the individual sources such as ethnic origin, sex, age cohort or limited clinical data with the sample[2].

Use of samples obtained from people who have since died, for genetic research

According to the Federal regulations governing the protection of human subjects in United States, people are considered as subjects only when they are alive. But revealing of genetic information of such a person can bring a psychological harm to the living relative. Therefore, unless the person had previously consented it is appropriate to allow living relatives to consent to use linkable samples. The investigators should honour the wishes of the relatives, under cir-

cumstances where the risk is high, whether the samples should be even used for anonymous research though they have obtained consent from those who have died[2].

Use of tissue samples from children for genetic research

When using identified tissue samples from children, consent should be sought from the parent of the child and if appropriate must be sought from the child. The Parents' role here is to give permission but children are entitle to decide to proceed with the therapy or research as they grow older[2]. Therefore, care should be taken to not to enter the results into child's medical record unless strictly necessary for child's immediate medical care, to minimize the risk of disclosure to third parties.

Protecting human research subjects can never be a job for government alone. The never ending challenge of organisations that participating in research is to make sure that researchers and other personnel have thorough knowledge of their responsibilities. These include, communicating with institutional Review Boards, ensuring that procedures for informed consent have been followed, monitoring compliance with protocols and reporting safety issues.

Independent bodies like the College of Physicians need to take a lead in ensuing that guidelines are formulated for the institutions and individual researchers.

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Annex 1.

Recommendations from the RCP committee to use existing archived materials for research

- The material must be annonymised at the earliest possible stage. The minimum level of anonymisation is that which precludes identification of individuals from the output of the research.
- There would be no inconvenience or hazard, psychological or physical to the subjects.
- Where doubt exists the benefit of the doubt should always lie on the side of seeking appropriate consent from the research subjects
- The appropriate Research Ethics Committees should have reviewed and agreed the research protocol and specifically agreed to exempt the research from the general requirement for individual consent from each research subject.
- Research based on medical records or stored samples could be conducted without subject consent, with appropriate safeguards since it does not contravene any fundamental or human rights and obtain ethical approval when needed.

Recommendations on informing patients about the use of their health records in medical research and allowing **opting out consent** were made in 1985 and included in Department of Health guidance but not widely applied in health service. The Nuffield Council on Bio Ethics also urged the health service providers to consider the inclusion of consent forms for left over biological materials but not widely used.