Review Article

# Ethics of genomic research

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## INTRODUCTION

Ever since the discovery of Mendel's laws of inheritance and subsequently the double helical structure of DNA by Watson and Crick, genomic research has made great strides to an extent that genomic era is a real possibility in the near future.[1] Genomic research is an upcoming field which is fast emerging after the results of human genome project were made publicly accessible. It involves the study of genes which code for a protein, enzyme, or a transporter in a particular individual, and to find out if there is any mutation, single nucleotide polymorphism, or copy number variations which may determine the susceptibility of the individual to a disease or the response to drugs. Advances in technology and ample funding opportunities, both national and international, increase in commercial interest, more public awareness on personalised medicine (yet to evolve in a big way in India), and media coverage have increased genetic research as well as whole genome research. These developments have raised many ethical issues associated with genetic research. The two main tools which ensure protection of the participants of any clinical research in general are written informed consent and ethics committee (EC) review.[2] The ECs have a major role in ensuring that the rights of the subjects involved in clinical trials are preserved. This is a major concern in India given the fact that very few ECs in India are properly constituted and functioning and there is no legal requirement for the members of the ECs to declare conflict of interest.[3]

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## ETHICAL ISSUES IN GENOMIC RESEARCH

It is the duty of the researcher to disclose the results of genomic research to the individual participating in the research. This could be a cause of anxiety or depression to the individual and his/her family when the results predict the risk of development of cancer or a chronic disease in future. The individual and the family could be subjected to unnecessary psychosocial harm because not all subjects with genetic susceptibility can be expected to develop the disease in future. On the other hand, when this information is not revealed and the individual or his/her siblings develop the cancer that is detected only in late stages, then this is ethical injustice and could hurt public trust. Then, there is the issue of social stigma and discrimination. When the genomic data are publicly accessible, there is a risk of discrimination during enrollment for a job or obtaining health insurance. Individuals could be denied a job or an insurance policy based on the genetic information which suggests the risk of susceptibility to any chronic disease or cancer.[4] Some ethical questions which have arisen recently that require further research and analysis are as follows:

- Does a subject have a right to withdraw from the study at any time after the sample has been provided to the researcher? Will all the results be returned back to the subject and all electronic and paper records containing the genomic data destroyed?
- Both primary and secondary investigators could be involved in the genomic research and analysis of data obtained from same set of samples. In such instances, who is responsible for return of results, if a subject who has given his/her sample wishes to withdraw from the study?
- Will the subject be informed about the risks and benefits of data sharing among investigators through the open access web?
- Other factors besides genetics could predispose

an individual to cancer or other diseases. In these circumstances, how much information needs to be provided and explained to the subject by the researcher?

Besides issues on privacy, confidentiality, and informed consent, other issues in genomic research include withdrawal from research, return of research results, public data release, commercialization, patenting, benefit sharing, and the possibility of genetic discrimination.[5]

Only some of these issues about which the authors have firsthand experience are going to be discussed in this paper.

## EXISTING GUIDELINES AND RECOMMENDATIONS

There are only a few clear-cut guidelines or recommendations which address the ethical issues in clinical research. In general, the ethical principles which govern clinical research hold good for genomic research also. The Helsinki declaration that was first accepted by World Medical Assembly in 1964 and has undergone many revisions since then clearly states that informed consent is the key component of all research on human subjects. In India, the Guidelines for Good Clinical Practice (2001) emphasizes upon the principles which govern the ethical code of conduct, namely, non-maleficence, beneficence, institutional arrangement, risk minimization, ethical review, voluntariness, and compliance.[6] It states that the staff engaged in biomedical sciences or research should be aware of their ethical responsibilities and comply with the ethical principles. ICMR has provided comprehensive guidelines for Indian researchers working in genomic area, and a separate chapter has been included in the 2006 issue of "Ethical guidelines for biomedical research on human subjects."[7] In this chapter, ethical issues raised by genetic research both in terms of the individual and the society at large have been discussed.

## SOME SOLUTIONS TO ETHICAL DILEMMAS IN GENOMIC RESEARCH

In any clinical research or trial, the participation of the subject is based on the trust in the researcher and the medical science. Safeguarding the trust of the participants forms a major lynchpin of ethical research. Adequate care needs to be taken in recruiting participants for a genetic study, in obtaining informed consent, and maintaining confidentiality of research findings, more than in any other field of research. All necessary information that will be provided to the subjects enrolled into a genomic study should be documented in consent form and submitted to the EC for review.

### Informed consent

Informed consent involves explaining to the research participant about the research activity, the expected results of the research, the beneficiaries of the result, the risk and benefits of participation. This can enable the participant to make a voluntary decision about participating in the research. However, the implementation of the "real" informed process is difficult to achieve unless the investigator takes extra effort to clearly explain in simple language about the benefits and risks of participating in the research. Even then, the decision to participate or not will depend upon the type of illness a patient is suffering from, the anxiety associated with the illness, the expectations from the treatment, and the most important of all in a country like India, the implicit trust in the doctor.[8]

Genetic research involves sample collection, genotyping, sequencing, data analysis at various levels, and use of samples or data for future research projects which may or may not be known at the time of sample collection. The data obtained could be deposited into scientific databases which are publicly accessible. The privacy of the subject and autonomy pose many challenges under these circumstances. All of these issues need to be incorporated into the consent process. The subject must be given the choice of deciding for or against the future use of data. The subject could also opt for re-consent during the planning of future research. A flowchart of the consent process pertaining to the genetic research is shown in Figure 1. This can help the subjects to understand the pros and cons of participating in genetic research, thus aiding them to exercise autonomy in participating in the research

### Withdrawal from research

A subject must be allowed to withdraw from research at any time of the study. This information needs to be mentioned during informed consent process. When a subject decides to withdraw from the study, it is implied that he/she wants all the samples to be destroyed and all results if obtained to be destroyed both in the electronic and print form. It may be impossible to destroy data that has already been released into public domain, especially in places where efficient data release policy is prevalent due to advances in technology. In such situations, consent for public release of data should be obtained.

### Addressing incidental findings in genomic research

Lots of information can be gathered during whole genome analysis about the subject's genetic profile. This information could either relate to the phenotype under study when it is pertinent information or it could be additional data relating to a new health problem, an incidental finding. Questions may arise as to whether to disclose such information to the participant or not. As

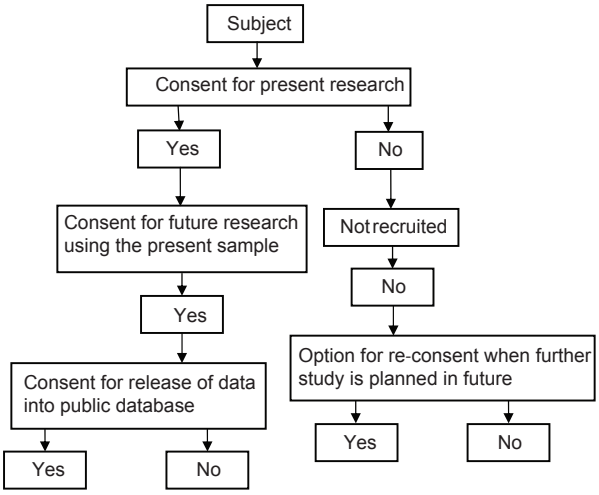


**Figure 1:** Flowchart of the consent process for genomic research

a consequence of enrolling into a genome-related study, should the subject need to know all the results or only what is important? Could the information on future health problems affect the mental peace of the subject or could it have a negative influence on the individual's job prospects? The physician or the researcher's ethical responsibility would be to preserve the confidentiality and privacy of the subject and at the same time to minimize harm to the family and society. The subject has the right to know the results of genetic testing – both the pertinent and the incidental findings. In India, the researcher has the additional responsibility of putting across the results in a simple and understandable language taking into consideration the moral, religious, and cultural beliefs of the population to which the research subject belongs. As with any other medical research, the disclosure of incidental findings in genomic research must ensure preservation of beneficence while making sure there is no therapeutic misconception.[9]

## Role of ECs

The role of ECs in genetic or genome-related studies is no different from that of other clinical research. ECs should ensure protection of research participants in general. They should ensure that all the information pertaining to future use of sample and data sharing has been provided to the subject before obtaining blanket consent. With expanding research in the field of genetics, the only way to ensure good-quality conduct of ECs is mandatory registration and an accreditation process. Some ECs in India have been accredited through the Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP) and the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRP).[10] In addition, routine on-site monitoring of research is essential to ensure ethical conduct of studies.[11]

## Biobanks and data abuse

Biobanks are private or public structured resources that contain long-term collection of human tissue and/or other medically relevant data and information connected to the collected tissue. With the expanding genomic research and its applications, biobanks have been established in many developed countries. While some biobanks collect their own data and samples, others rely on primary researchers and collectors at multiple sites to perform collection of samples and they are then aggregated in the biobanks.[12] The concept of biobanks for research purposes is still in its infancy in India, but with expanding genetic and genomic research the growth is likely to increase in the future. The data in these biobanks are likely to be used for purposes other than research, such as employment decisions, insurance calculations, and forensics. The utilization of this data for forensic purposes by governmental sources can lead to its abuse for political purposes to control and punish citizens or distinct segments of the population. Biobanks are also essential for genetic and genomic research because it is possible to study rare genetic variants or those with modest association with phenotypic traits or the effect of combination of genetic traits from the large size of data available in these banks.

## Compensation for participants

ICMR guidelines[7] in chapter VI on genomic research state that "undue inducement through compensation for individual participants, families and populations should be prohibited. This prohibition, however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care or of information infrastructure, reimbursement costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes." The Schedule Y1 of 2005[13] has specified the need for provision of compensation of participants for research-related injuries as an essential element of the Informed Consent Form (ICF). The Indian Good Clinical Practice (GCP)[14] recommends that research participants who suffer physical injury as a result of their participation are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability. In case of death, their dependents are entitled to material compensation. Unfortunately ICMR guideline states very clearly that in genetic research, the harm may not only be physical, but also psychosocial which may produce anxiety and depression or damage familial relationship. Hence, it may not be easy to assess the quantum of compensation to be given to an individual for participation in genomic research unless there is a physical injury when the individual can take recourse to the existing clauses in regulations.[15] Adequate counselling should be looked at as a part of

participant compensation in case of harm accrued during genetic research.

### Sharing the benefits of human genetic research

Biological Diversity Convention text states that benefits of genomic research can be thought of as those arising from the use, whether commercial or not, of genetic resources, and may include both monetary and non-monetary returns to the individual or the society.[16] Schroeder [17] states that there are essentially four different justification models that cover the main possibilities with regards to benefit sharing in genomic research:

- The outcomes of human genetic research are sufficient benefits for both cooperators and the public at large.
- Cooperators who cannot benefit directly from genetic research (e.g. donors of DNA samples for large-scale studies) qualify for some form of additional benefits, whereas cooperators who can benefit directly (e.g. recipients of experimental drugs in pharmacogenetics trials) do not.
- All cooperators qualify for additional benefits (owing to the risks involved or because their property is being used).
- Altruism should be the guiding principle for contributors to human genetic research.

The two main advisory reports on healthcare research in developing countries have failed to deal with the issue of benefit sharing. The Nuffield Council Report on "The ethics of research related to healthcare in developing countries" set the issue of benefit sharing aside, noting that it will require attention in the future.[18] The US National Bioethics Advisory Commission's report on "Ethical and policy issues in international research: Clinical trials in developing countries" only quoted the Human Genome Organization EC statement.[19] The Informed Consent section of the ICMR guidelines states that one of the components of the ICF/patient information sheet should be unambiguous information about benefit sharing in the event of commercialization of the research findings. The guideline also further discusses the issue in context to tissue/biobanking where benefit sharing to the individual or community in the form of appropriate written benefit-sharing agreement should be considered. As genetic research in India leads to potential products worthy of commercialization or medical use or patent protection, the time may arise for renewed interpretation of nationally accepted definitions or criteria for benefit sharing.

## CONCLUSION

Genetic and genomic research is fast expanding and newer ethical issues keep arising with the advance of science and associated technologies. An attempt has been made to discuss from an Indian context, some of the ethical dilemmas in topics related to obtaining informed consent, withdrawal of results, addressing incidental findings, the role of ECs in ensuring smooth and ethical conduct of genomic research, compensation, and sharing benefits of genomic research. As we move towards the era of personalized medicine, there is a real need to provide more clarity and also to build upon the different guidelines and regulations with regards to ethical issues surrounding genomic research in India.

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