Ethics in Genetic Research

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48.1 Why this Chapter?

The reader must be wondering about the need for this chapter in a book on pursuing academic medicine in developing countries, as the authors did when asked to write it. The foremost reason is that informing readers about ethics in a predominantly unethical world is not out of place. It is a reminder of the inherent good in man. Secondly, genetics, which was considered a luxury in developing countries has in recent years assumed importance in clinical practice. The completion of the project on the sequencing of the human genome also provided the impetus for the development of faster and cheaper sequencing technology, which came to be known as the next generation sequencing (NGS). To illustrate, the Human Genome Project (HGP) took 13 years to complete at a cost of US $2.7 billion (US contribution). It involved the sequencing of 3 billion base pairs. The same could be carried out in a few days for US 1500 in 2016 [1]. Indeed Hennekam and Bieseker (2012) have called NGS as 'the most powerful diagnostic tool developed in medicine since the roentgenogram. Its value and utility in clinical medicine will be enormous' [2]. Numerous perplexing disorders were unravelled by NGS, and in many patients it resulted in life-saving therapy, ushering in the era of precision medicine. Medical therapy, from a position of 'one size, fits all' changed to "the right size for each patient.

Secondly, genetics deals with DNA—the very stuff of life. Using genetic techniques we can manipulate DNA—alter it, duplicate, or delete it, or correct the errors that led to disease in the first place. It thus has tremendous power which can also be misused. It is now well-known that every disease has both a genetic as well an environmental component, although the contribution of the two factors varies, depending upon the disorder (Fig. 48.1). For example, in infectious diseases, the environmental component is greater while the genetic component is small. On the other hand diseases such as β-thalassemia have a greater genetic component while the environmental component is small. In the middle are disorders such as diabetes mellitus, coronary artery disease, hypertension etc. with almost equal contributions from both the factors.

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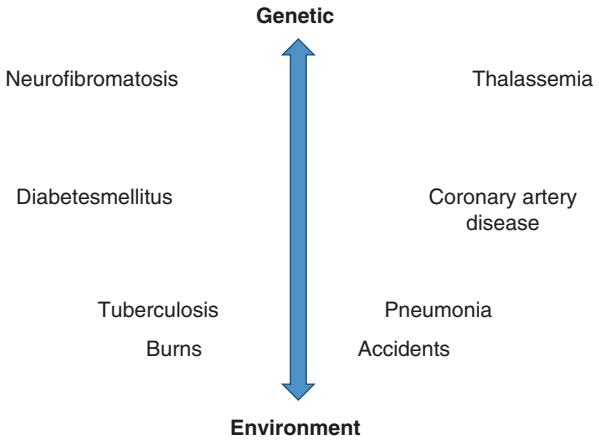

Fig. 48.1 Interaction of genes and environment

The implementation of widespread immunization programs, improvements in sanitation, and increase in incomes has led to significant control of infectious, nutritional, and parasitic disorders, and this, in turn, has resulted in the emergence of genetic disorders as important causes of morbidity and mortality. The WHO recommended that once the infant mortality rate falls below 40 (per 1000 births) the need for genetic services begins to be felt [3]. The developing world is now faced with a double burden—of infectious as well that of non-communicable disorders. Controlling the latter requires not only a change in the lifestyle and the 'environment' but also recognizing that genetic alterations have played a significant role in causing these disorders. The developing countries have a heavy load of genetic disorders as they have many communities that practice consanguineous marriages which increases the incidence of autosomal recessive disorders [4]. Cancer is also on the increase leading to genetic studies for delineating predisposition to cancer as well as the use of genetic markers in therapy.

48.2 Why Be Concerned about Ethics in Genetic Research?

Historically, genetics has been blamed to have been used as a tool for eugenics through prenatal diagnosis and termination of the pregnancy if the foetus was abnormal. Others have tried to create designer babies, or attempted to clone some individuals to generate 'perfect humans'. These misguided attempts to improve the human race have been frowned upon by the majority of people. As the cost of performing tests has come down this has led to mushrooming of genetic laboratories at times offering tests of questionable utility. The developing countries have lagged in enacting suitable legislation in controlling these laboratories to ensure the quality of the tests. Strict guidelines are needed so that genetic tests are performed adhering to ethical and professional guidelines, and create some mechanism to enforce these guidelines.

48.3 What Activities in Genetic Research Demand Special Attention to Ethical Principles?

Activities that require special attention are genetic testing which is of many types, genetic counselling, prenatal diagnosis, assisted reproductive technologies, manipulation of embryos and genes, and clinical trials for new therapies. The ethical problems arising in some of these will be discussed separately.

48.4 What are the Core Ethical Principles Worth Adhering to?

Most nations accept the following as core principles of medical ethics: respect for patient autonomy, beneficence (doing good), non-maleficence (avoiding harm), and justice (fairly balancing burdens and benefits across society). Of these, respect for autonomy has acquired a position of primary importance [5]. The conflicts arise because the law lays down the limits for the autonomy of the individual. Autonomy is not absolute and has to be within the law of the land. For example, currently, the law in India lays down that no termination of pregnancy can be carried out beyond 20 weeks of gestation. If a pregnant woman learns that the foetus has Down syndrome (that leads to mental retardation) at 22 weeks of pregnancy and wants an abortion the law does not permit this. It is apparent that the core principles are global but the action has to be as per local conditions.

The doctor is governed by the five core principles and has to work within the bounds of medical ethics (the Hippocratic Oath). The patient has to respect the culture, religion, the society, and the family norms; but above all is the law (Fig. 48.2).

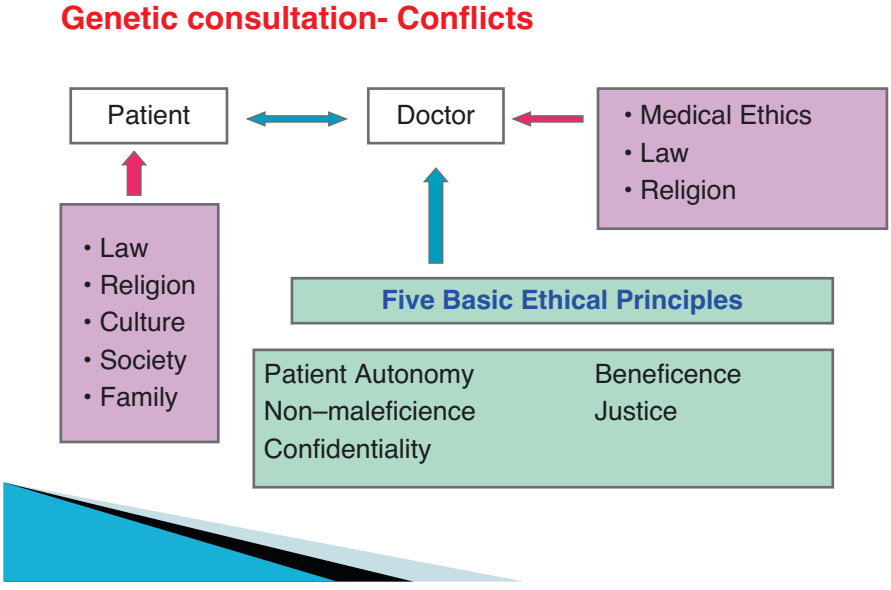

Fig. 48.2 Factors influencing actions of the doctor and the patient, and the core principles of ethics

48.5 What are the Types of Genetic Tests, their Utility, and the Ethical Concerns Raised by their Performance and Reporting?

Due to the cost of the genetic tests coming down as a result of next generation sequencing technology they are offered widely in India and are rapidly being set up and provided in other developing countries. Genetic testing may be done for diagnostic or research purpose [6]. Most commonly it is for diagnosis of a suspected genetic disorder in a symptomatic patient, which is similar to common tests in symptomatic patients, e.g., glucose testing in a case of diabetes mellitus. In such cases, it can be argued that consent is implicit in the patient coming to get the test done, and special consent may not be required. However, there is one big difference—the DNA can be used not only to diagnose a particular disease in an individual but also other disorders. It can also point to the occurrence of the disease in the family. Secondly, the leftover DNA can be utilized for the diagnosis of various genetic disorders or genetic predisposition to other characteristics. Therefore, it is advisable to obtain consent even in those subjects wanting a genetic test for diagnostic purposes The testing may be to make a prenatal or preimplantation genetic diagnosis, situations that have their ethical issues. It may be done in an asymptomatic individual to diagnose a disease before symptoms appear, or predictive testing in a young person for a disorder that occurs later in life, such as Huntington disease or Alzheimer's disease. In many countries, newborn screening tests are performed to detect disorders before they have caused serious problems or disorders that may lead to disability or death. Most hospitals require a formal consent for newborn screening as often this is mandated by the State or the Government, although the couple is given the chance to opt-out of the test if they wish. Lastly, in forensic genetic testing DNA can be used to identify persons from some remains of their tissues such as hair, blood, or semen at the scene of the crime. The test results may impact employment, insurance, or health coverage so that confidentiality of the results is of prime importance. The doctor or the laboratory cannot reveal the results of the test to the relatives without the permission of the patient unless the disorder involves a threat to life, and preventive measures can be undertaken.

48.6 What is the Revolution that Genetic Tests are Going Through?

The human genome project marked the complete sequencing of the human genome. This saw the sequencing technologies achieve unprecedented speed and at the same time reduce tremendously the cost. This was called next generation sequencing (NGS) and propelled the performance of genetic testing to unimaginable heights. Genetic tests that would earlier cost US 2000 to the US $3000 could now be done for the US $300. Instead of sequencing one gene, we could sequence a panel of genes varying from 10 to 1000 or more, the exome (all the protein-producing genes)

and even the whole genome (which including the non-coding DNA—the introns). This has led to the adoption of NGS in everyday practice in India in several fields, paediatric, adult, neurology, and haematology—literally in every field. A new era of precision medicine has dawned. Equally, changes have taken place in cytogenetic tests and karyotyping has mostly been replacing by microarray studies which can delineate much smaller changes in the chromosomes.

48.7 Ethical Issues in Next Generation Sequencing (NGS)

Exome or whole-genome yields a vast amount of information about the genes to be tested as well as other genes. Significant changes in the gene relevant to the phenotype have of course to be disclosed. What about changes detected in other genes? There is a consensus of the genetic societies that patients should be informed about changes in genes of high clinical importance such as that led to breast cancer or heart disease. List of these genes for which incidental findings should be disclosed has been generated. Another ethical issue associated with NGS data is that the patient has a right not to know the incidental findings, and such wishes should be respected. Disclosure of some results raises several sensitive human rights issues, such as the possibility of discrimination and social stigma for obtaining health or life insurance or employment [7]. Therefore confidentiality of the results is important. USA has enunciated in 2008 the Genetic Information Nondiscrimination Act (GINA) that forbids discrimination on genetic data [8], but such a law does not exist in most developing countries. In India, insurance companies even refuse health insurance or reimbursement of expenses if the disease in a person is of genetic origin. Another ethical issue is that the results may reveal information about other family members in addition to the person who is tested, and have to be handled with care. A common situation is the vast number of DNA variants that are revealed and need to be classified for pathogenicity. Despite the best efforts of the scientist's many variants remain classified as of unknown significance (VUS). At times the pathogenic variants may not be identified. All these limitations should be explained in the pre-test counselling session.

48.8 How Essential are Pre-and Post-Test Genetic Counselling?

In all genetic tests, it is good practice to provide pre-test and post-test counselling. This is especially so for prenatal tests or those that are complex or that have serious import such as for predisposition to cancer. In all such cases, the purpose and utility of the test should be explained to the patient, especially its limitations. The patient needs to be told about the cost and reliability of the test. In the post-test counselling session, the results are explained, with their interpretation, the options available, and implications for the patient and family members.

48.9 What Ethical Concerns Arise in Informed Consent for Genetic Tests?

It is essential to have consent for the genetic test to be performed from the subject being tested. The contents of the consent are very similar to the one employed in a medical test, albeit with some differences that raise ethical issues [6]. Commonly the genic laboratories store the DNA leftover after performing the test. This is used in an anonymized fashion for standardization or performance of tests to generate data for other research studies. So the consent form must specify what will be done with the DNA after the performance of the test. Will it be destroyed or used for anonymized tests for research? The ethical committees do not like to give bracket permission to store leftover DNA and perform any type of genetic research so that the investigator has to specify the nature of further testing that will be performed.

The biggest ethical issue that is faced while obtaining informed consent in developing countries is how to explain complex genetic issues to persons with little knowledge of science. One tries to be as simple as possible but even that may be beyond the comprehension of people who have very little knowledge of scientific principles. Another common misunderstanding the patients in developing countries have is that the research being done will provide treatment for the disorder that has eluded the patient so far. The scientist must remain ethical and should not provide any false promises that the results of the research will provide treatment for the patient's problems unless this happens to be true.

In general, informed consent can only be given by adults who are competent to make medical decisions for themselves. For children and others who are unable to make their own medical decisions (such as people with impaired mental status), informed consent can be given by a parent, guardian, or another person legally responsible for making decisions on that person's behalf. This is similar to consent for another medical test.

In developing countries, the language of communicating with a patient can be a barrier. Most doctors are fluent in the English language but in India and other developing countries, the patient may not understand English. The patient may understand the language of his ethnic group which the physician does not know of. A good translator is then required to make informed consent meaningful. Does the translator faithfully convey the purpose and procedure of the research study is always a moot point?

Acknowledgement that the person who is being tested has had the opportunity to discuss the test with a healthcare professional with the individual's signature, and that of a witness is essential. Verbal consent can never be accepted. Informed consent is not a contract, so a person can change his or her mind at any time after giving initial consent, and an ethical scientist will honour the wish of the patent. Informed consent from children or vulnerable groups does not have any special ethical concerns when performed for genetic research. This is similar to research in other subjects.

48.10 Informed Consent from Tribal Communities?

In developing counters there are many tribal groups and these are often subjects of research by medical anthropologists for genetic research or epidemiologic studies, and by medical geneticists for sickle cell disease and other haemoglobinopathies or other rare disorders. The tribal communities represent groups as they were before being 'civilized' and adopting modern habits and mores. These tribal communities often do not know written English or Hindi [9]. They cannot even sign their name and often their thumb impression is taken on the consent form. In the past, their thumb impression has been misused for purposes other than those explain to them, and in this way, their lands have been taken away fraudulently. When scientists approached them for research in sickle cell disease tribals are often reported as saying 'our lands have been taken away in the past and now you want to take our blood'. They are thus very suspicious of giving signatures or thumb impressions. Some anthropologists have suggested that their consent may be recorded on video. Often it is necessary to first convince their leader before the tribal people with agreeing to give a blood sample or sputum. It is the experience of the authors that scientists with good intentions usually do not have difficulty in getting consent from the tribals, who can easily judge what is good for them.

48.11 What are the Ethical Issues in Predictive Testing?

Predictive genetic tests are performed on subjects who are at risk of developing a genetic disorder based on their family history. This is termed as pre-symptomatic genetic testing when used to find out whether a person, who is currently asymptomatic, is carrying the mutation that causes disease. For example, if a child has Wilson disease and the mutations are known one may test the other siblings to find out if they are at risk of developing the disease. If they are positive for the mutation, treatment can be initiated to present the symptoms/complications of the disease. Another type of predictive testing is when it is performed for disorders for which no therapeutic intervention is available, e.g., Huntington disease, spinocerebellar ataxia, Alzheimer's disease, and other disorders of adult-onset. The subjects to be tested are in an ethical dilemma, should they get tested or take their chance. If they test positive, knowing that they may suffer from the disease in future, may cause depression and occasionally lead to suicide. If they do not have the mutant gene then this would mean they will not suffer from the disease and neither will their children be at risk. In India more people seem to opt for testing, the reason being that many live in a joint family system which provides a sort of buffer against bad news, and provides support. In developing countries many patients who are suffering themselves want their children to be tested for the reason that the child's life can be planned and the future career be decided accordingly. Generally, testing of children is permitted only if some therapy is available, not otherwise. The major reason for this is to let the child grow up and then decide for himself. As mentioned earlier this personal autonomy is less of an issue in India and other developing countries.

The issue of 'the right not to know' does get applied in developing countries too. Consider the situation where the grandfather has an adult-onset autosomal dominant disorder and his asymptomatic 'at-risk' progeny is married and the wife is pregnant. Such a person may like the foetus to be tested but not the person himself or herself. We do carry out such tests to honour the wishes of the individual.

48.12 What are the Ethical Issues in Genetic Counselling?

Genetic counselling involves providing necessary information to the patient with a genetic disease to cope with the disorder in the family and take informed decisions. In the West, it is customary and essential that the information be provided in a non-directive way and let the patient decide what should be done in a particular situation. In developing countries, non-directive counselling is very difficult to follow. Most patients when informed that they must make the decision on their own, albeit after getting the necessary information, appear uncomfortable, and will ask the doctor 'what would you do in my place'. I was once confronted with the statement 'doctor that is why we came to you, so you would tell us the right course of action to be followed'. In developing countries, most children—preschool, school, and college—are guided by the parents—what to wear, what to study, and whether to go to a movie. The children are not trained to take independent decisions. So in real-life situations or genetic counselling, they find it hard to decide on the action to be pursued. In such situations, the counsellors often say 'what others might do in your sort of situation'.

Another important principle followed in genetic counselling is the autonomy of the patient in choosing a particular course of action. The patient should be provided with the necessary information and should be given the autonomy to choose the course of action that is appropriate for his/her situation. One has to remember that this autonomy is not absolute, it is limited by what the law allows, or what the society permits. This is particularly applicable in prenatal diagnosis when a person would like to know the sex of their child (which is not permitted by law) or would like to terminate an affected foetus beyond the legally permitted gestation.

48.13 What is an Ethical Issue in Prenatal Diagnosis?

Prenatal diagnosis is easily accepted in developing countries such as India because it is a means for ensuring that a normal baby will be born. The expense of bringing up a baby with abnormalities and disabilities has to be borne from out-of-pocket expenses by the family, and most couples would like to avoid this. However, there are many ethical issues in prenatal diagnosis. The foremost in India is that the law forbids disclosure of sex of the foetus, as well as the performance of any test that may reveal the sex of the foetus. The doctor in charge of the foetal medicine specialist or the ultrasonologist has to maintain a register of every patient they see and certify that the sex of the foetus was not determined and not disclose to the patient.

For which disorders prenatal diagnosis can be permitted is an ethical question and the answer varies in different countries. In developing countries, prenatal diagnosis is sought for many disorders that may not form the basis of prenatal diagnosis in the West. The reason for this is that the socio-burden of having a child with a genetic disease is high. To illustrate, in India patients desire prenatal diagnosis for deafness or albinism as the burden of rearing an affected child is sufficient to persuade them to go for prenatal diagnosis. Another example is biotin deficiency. This causes seizures, deafness, and mental retardation. However, if the treatment is initiated before the onset of symptoms the patient remains normal. In Japan, they carry out newborn screening for biotic deficiency and treat in the presymptomatic stage and prenatal diagnosis is not performed. In India and other developing countries, couples at risk go for prenatal diagnosis for biotin deficiency as there are no newborn screening programmes for this disorder.

It is advisable to do a pre-test and post-test counselling in the presence of both partners. However, in developing countries, there is discrimination against women in many spheres and activities, who get a greater proportion of the blame for 'bad luck' issues such as having no babies or having babies with abnormalities. So the genetic counsellor has to be very careful in the presence of X-linked disorders (haemophilia A or Duchenne muscular dystrophy) in a family. Counselling is often sought by the at-risk woman accompanied by her parents or relatives. In such families very often the boy's side has not been told about the presence of X-linked disease. We, therefore, accede to the wishes of the at-risk woman and her family and do not disclose the information to the in-laws.

The disclosure of results of prenatal diagnosis in X-linked disease is also problematic due to the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Amendment Act [10], which forbids the disclosure of sex of the foetus. The laboratories report that the foetus is affected or unaffected. However, if the foetus is female the family wants to know if the foetus is a carrier or not. They desire not to have a girl who is a carrier due to the difficulties they encounter in arranging her marriage. Although a female carrier in most X-linked disorders is free of disease, this is unacceptable to them because of their own experiences and hassles they have to go through. However, the staff of the genetic centre have to follow the law of the land, because of the stiff penalties for disclosing the sex of the foetus.

48.14 Is Research on Embryos Permitted?

Many people have moral and religious objections to the use of human embryos for research. In USA, Federal funds cannot be used for any research that creates or destroys embryos. However, many bioethicists and scientists believe that research using embryos is important for various reasons, as scientific questions about human biological processes in embryos need to be answered, as long as the embryos are not used for reproductive purposes [11]. Some countries have already allowed research on non-viable embryos (those that would not result in a live birth), while others have approved research studies on viable embryos.

48.15 What are the Ethical Issues in the Genomic Editing of Embryos?

The discovery and use of CRISPR CAS 9 have highlighted the ethical debate of genome editing [12]. The common consensus is that editing of the germline human genome should not be permitted at present. The story of the two Chinese doctors who attempted germ-line editing, though for the noble cause of stopping the spread of HIV, is a reminder that one should abstain from germ-line editing, as the Chinese scientists were sent to jail. This may continue until the chance of introducing a change in the wrong place (off-target) is eliminated. Until that time preimplantation genetic diagnosis (PIGD) may be resorted to. Gene editing can indeed address issues not tackled by PIGD, e.g., when both the partners are homozygotes for an autosomal recessive disorder such as sickle cell disease. There is a total consensus by almost all countries that genome editing for purposes of enhancement of certain qualities should be forbidden. However, the moot point of how much right the parents have o interfering with embryos and foetuses will always remain. There is also the concern that genome editing will only be accessible to the wealthy and will increase existing disparities between the rich and the poor.

48.16 What Do the ICMR Guidelines Say about Ethical Practice in Genetic Research?

There are many international guidelines and documents on this topic, such as those issued by the UNESCO Bioethics committee, WHO [13], CIOMS, HUGO, European Commission, and Nuffield Bioethics Council. India is one of the few developing countries where guidelines exist for genetic service and research (Sect. 10) and for biobanking (Sect. 11) issued by the Indian Council of Medical Research entitled 'National Ethical Guidelines for Biomedical and Health Research involving Human Participants' [14]. It mentioned that a thin line exists between genetic testing for service and research, and both may be considered together. Some of the important clauses are as follows: For routine testing written informed consent may not be required, and the institutional policy for these tests may be followed. It emphasizes that the harm caused by genetic testing and research may be psychosocial, and that stigmatization and discrimination should be avoided at all costs. Confidentiality of information is critical. Breaking of families by information such as the revelation of non-paternity or carrier status for X-linked disease should not be disclosed. The commercial benefit accruing from samples collected from a group requires some return of benefit to the group. One should ensure that for samples collected for commercial purposes no coercion or inducement is used. Somatic cell gene therapy is permitted while germline therapy is not permitted. It does not forbid direct-to-consumer marketing of genetic tests but emphasizes that the results should be given out by a physician who is knowledgeable in these tests.

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