ejpmr, 2023, 10(12), 107-117

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ETHICAL CHALLENGES AND IMPLICATIONS OF CLINICAL GENETIC AND GENOMIC RESEARCH AND DEVELOPMENT FOR THE LOW MIDDLE INCOME COUNTRIES

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Article Received on 06/10/2023 **Article Revised on 26/10/2023** **Article Accepted on 16/11/2023**

ABSTRACT

Rapid advances in genetic research during the past two decades have challenged scientists, health care professionals, ethicists, government regulators, legislators, and consumers to reflect on new developments. A constant update with the scientific advances and their implications is important for all stakeholders involved in making informed decisions about the ways in which genetic research and information will affect the lives of current and future generations. The potential benefits and risks associated with genetic and genomics research is different from the types of potential benefits and risks associated with other types of health research like clinical trials and biomedical research involving human subjects. Unlike most potential risks associated with biomedical research or clinical trials are in most cases biological in nature, potential risks associated with genomic research are mostly socioeconomic in nature. Although the peculiarity of some of the aspects of genetic research and the complexity of the science involved are identified, the extent to which these characteristics hinder issues of disclosure of information is a practical challenge that tends to be hyper in most situations. Genetic and genomic research since the unraveling of the human genome has the potential for drug discovery and development of new drugs and biologics like vaccines for the poverty related diseases of developing nations. This write up presents the various types of challenges and implication of genetic and genomic research for low middle income countries, and gives an insight to illustrate some ethical issues, followed by proposal on possible ways of managing genomic studies as some of the major challenges in emerging countries.

KEYWORDS: Genetics, genomics, ethical issues, drug development, clinical research.

1. INTRODUCTION

Rapid advances in genetic research during the past two decades have challenged scientists, health care professionals, ethicists, government regulators, legislators, and consumers to stay abreast of new developments. Understanding the scientific advances and their implications is critical for everyone involved in making informed decisions about the ways in which genetic research and information will affect the lives of current and future generations.[1] The pivotal importance of these societal decisions was underscored by the allocation of 5% of the budget of the Human Genome Project for the study of ethical, legal, and social issues related to genetic research. (The Human Genome Project was a thirteen-year study completed in 2003 conducted by the U.S. Department of Energy and the National Institutes of Health [NIH] that set out to, among other things; identify all of the genes in human DNA.) Till date, consideration of these ethical issues has not produced simple or universally applicable answers to the many questions posed by the increasing availability of genetic information. Ongoing public discussion and debate are intended to inform, educate, and assist persons in every walk of life to make personal decisions about their health and participate in decisions that concern others.[2]

As researchers learn more about the genes responsible for a variety of illnesses, they can design more tests with ever-increasing accuracy and reliability to predict whether an individual is at risk of developing specific diseases. The ethical issues involved in genetic testing have turned out to be far more complicated than originally anticipated. Initially, physicians and researchers believed that at-risk families would welcome a test to determine in advance who would develop or escape a disease.[3] They would be able to plan more realistically about having children, choosing jobs,

obtaining insurance, and living their lives. Nevertheless, many people with family histories of a genetic disease have decided that not knowing is better than anticipating a grim future and an agonizing, slow death. They prefer to live with the hope that they will not develop the disease rather than having the certain knowledge that they will.[4]

The discovery of genetic links and the development of tests to predict the likelihood or certainty of developing a disease raise ethical questions for persons who carry a defective gene. Should women who are carriers of Huntington's disease or cystic fibrosis have children? Should a foetus with the defective gene be carried to term or aborted? Serving as an example of this issue's complexity, one health insurance company agreed to pay for prenatal cystic fibrosis testing for a mother who already had one affected child, but the company insisted if the baby was affected, the mother would have to terminate the pregnancy or it would not cover the child's future medical bills.[5]

There are also concerns about privacy and the confidentiality of medical records, and the results of genetic testing leading to possible stigmatization. Some people are reluctant to be tested because they fear they may lose their health, life, and disability insurance, or even their jobs, if they are found to be at risk for a disease. Genetic tests are sometimes costly, and some insurers agree to reimburse for testing only if they are informed of the results. The insurance companies feel they cannot risk selling policies to people they know will become disabled or die prematurely.[6]

The fear of discrimination by insurance companies or employers if they learn the results of genetic testing is often justified. An insurance carrier may charge someone a higher rate or disqualify an individual based on test results, and an employer might choose not to hire or to deny an affected individual a promotion. The American Society of Medical Genetics and most other medical professional associations agree that people should not be forced to choose between having a genetic test that could provide lifesaving information and avoiding a test to save a job or retain health insurance coverage.[7]

1.1. Ethics in genetic research practice

1.1.2. Genetic screening and testing

Essentially, the screening process may be divided into three phases - the preparation of the participant or patient; the analysis of the genetic material; the interpretation of the analysis coupled with ensuing support programmes.[5] It is useful to distinguish between these three phases in a discussion of the ethics of genetic screening and testing. During the preparatory phase, ethical considerations revolving around informed consent must be addressed. The analysis phase raises familiar issues such as adequacy of procedure and confidentiality with respect to the participant or patient.[6] The final phase raises ethical concerns relating to the management of genetic disorders and the subsequent impact of the screening process on the individual and his or her family.

Genetic screening should be distinguished from genetic testing at the outset. The terms are often used interchangeably, although they represent two different forms of genetic practice. Genetic screening is carried out on groups of people, which could consist of a section of the population defined by age, sex, other risk factors, a subgroup within the population, or within broad groups in which genetic factors may be responsible for certain disabilities.[6,7] Genetic screening may be defined as a search in a population to identify individuals who may have, or be susceptible to, a serious genetic disease, or who, though not at risk themselves, as gene carriers may be at risk of having children with that genetic disease.[1,6]

Genetic testing, on the other hand, leads to a definitive diagnosis in individuals, and is defined to be:"the analysis of a specific gene, its product or function, or other DNA and chromosome analysis, to detect or exclude an alteration likely to be associated with a genetic disorder.[7] Individuals may desire testing where there is a family history of a specific disease, if they exhibit symptoms of a genetic disorder; or if they are concerned about passing on genetic disorders to their children.[2,7] In addition, genetic testing in individuals is used as a 'fingerprint' in forensics. The areas of focus for genetic testing at present are thus carrier and susceptibility testing, prenatal diagnosis, newborn testing, and forensic testing.[8]

Screening programmes play a useful part in public health care systems by identifying potentially serious risks that can be prevented by timely treatment. Genetic testing allows couples the possibility of making informed choices about parenthood and, possibly, in identifying genetic susceptibility to common serious diseases.[9] Three goals have been identified for genetic screening;

1. To contribute to improving the health of persons who suffer from genetic disorders;
2. To allow carriers for a given abnormal gene to make informed choices regarding reproduction; and
3. To move towards alleviating the anxieties of families and communities faced with the prospect of serious genetic disease.
4. A fourth goal could be added to this list - the reduction of public health costs. Genetic screening is an attractive option for those institutions seeking to manage their public health exposure. It is feared that the greater our ability to predict the costs of heritable diseases, the greater the public pressures on adults not to pass on genes that are associated with particularly bad outcomes.[9] Pressure may also be brought to bear on individuals to be tested for genetic predispositions and to act "to save society long- term costs resulting in new eugenics based, not on undesirable characteristics, but rather on cost-saving.[10] However, some consider any aspirations to a 'healthy public' to be misguided because genetic

control of the human population, or any form of 'genome cleansing' could easily slide into eugenics.[11] Others hold the view that genetic screening at embryo level will take place in developed countries, and if this is not done in developing countries the discrepancy between the two will widen even further.

1.1.3. Scientific basis: Inheritance is determined by the genes, of which there are an estimated 32 000 in the human genome. Genes are large molecules made up of a substance, DNA, whose double helical structure allows both copying and division. The particular sequence of individual chemical sub-units in a gene serves as a molecular code to specify the manufacture of a particular protein. An alteration (mutation) at even a single position of the DNA sequence may cause serious malfunction of the resulting protein. Modern advances in genetics are due to the ability to study DNA directly. At present we have, at best, information on only one-third of the genes.

The genes are arranged in a fixed order on the chromosomes. Chromosomes are elongated strings of DNA and protein that occur in the nucleus of every cell in the body. Unlike genes, chromosomes can be seen through a light microscope, especially when they become compacted during cell division. In the normal human there are two sets of 23 chromosomes, 46 in all, one set having been inherited from the father, the other from the mother.[8] The members of 22 of the 23 pairs appear identical: these are the autosomes. The remaining pair, the sex chromosomes, differ between males and females; females have a pair of X chromosomes whereas a male has one X chromosome (inherited from his mother) and one Y chromosome (inherited from his father).[12]

Medical genetics is part of the human genetics concerned with the role of genes in illness. Traditionally, the analysis of the genetic contribution to illness and human characteristics has been divided into:

1. Disorders due to changes in single genes;
2. Disorders influenced by more than one gene (polygenic); and
3. Chromosomal disorders.

In addition to the genetic contribution, the environment often plays an important part in influencing both the onset and severity of disease, particularly in the polygenic disorders.

1.2. Single gene diseases

Inherited single gene diseases may show three common types of inheritance patterns.

1. Autosomal dominant: such diseases (Huntington's disease, for instance) result from one of a pair of matched autosomal genes having a disease-associated alteration, the other being normal. The chance of inheriting the altered gene from an affected parent is 1 in 2 in each pregnancy. Autosomal dominant diseases commonly affect several individuals in successive generations.[2,11]
2. Autosomal recessive: these diseases (such as cystic fibrosis) require the inheritance from both parents of the same disease-associated abnormal autosomal gene. The parents are usually themselves unaffected, but are gene carriers. When both parents carry the same altered gene, the chance of inheriting two altered genes and thereby of having the disease is 1 in 4 in each pregnancy. Autosomal-recessive diseases usually only affect the brothers and sisters within a single generation; the incidence of the disease in individuals in previous or subsequent generations is usually very small. Hence diseases with this form of inheritance tend to occur 'out of the blue'.[12]
3. X-linked: diseases due to genes on the X chromosome (such as haemophilia) show a special inheritance pattern: they are also known as sex-linked disorders. Most X-linked conditions occur only in males who inherit the abnormal gene from their mothers. These mothers are carriers of the altered gene but are usually unaffected themselves, because their other X chromosome has the normal gene (as in auto-somal-recessive disease). Females may occasionally show some features of the disease, depending on the condition. An affected male never transmits the disease to his sons. When the mother carries a gene for an X- linked disease, the chance of inheriting the altered gene is 1 in 2 in each pregnancy for both boys and girls, but only the male offspring will be affected. X- linked diseases may thus give rise to the disease in males in several different generations, connected through the female line.[6,13]

1.2.1. Polygenic disorders

Many common diseases with a genetic basis result from abnormalities in more than one gene. The inheritance pattern is complicated because of the larger number of different genetic combinations and uncertainties about how the genes interact. Environmental factors frequently play a major part in such disorders, which are more often known as multifactorial diseases.[13] Because of this, screening can yield results that are less clear-cut. At the same time, as we advance our knowledge of all the environmental and genetic factors involved, it will become possible to identify individuals who are at increased risk of a disorder and who would benefit from advice on how to minimize the risk. This could lead to screening for genetic predisposition to common diseases, such as coronary heart disease, diabetes and some cancers.[2,14]

1.2.3 Chromosomal disorders

Chromosomal disorders fall into two broad categories.

1. Where an entire chromosome is added or is missing. For example, in Down's syndrome there is an extra (third) copy of chromosome 21 found in the cells of affected individuals (hence the technical term for it,

Trisomy 21). In Turner's syndrome, one of the X chromosomes in girls is missing. This type of disorder is not inherited but occurs during the production of a gamete (egg or sperm).[15]

2. Rearrangement of chromosomal material. If this involves either net loss or gain of chromosomal material, harmful clinical effects are likely. On the other hand, if a simple exchange occurs between chromosomes (translocation) or within them (inversion), the chromosome make-up may be 'balanced', and serious clinical effects are much less frequent.[3,16]

1.3. Types of genetic tests

All forms of genetic tests aim at identifying particular genetic characteristics but approach this in different ways.

1.3.1. Chromosomal tests (cytogenetics)

Microscopic examination of chromosomes from cells in blood, amniotic fluid or foetal tissue may be used to detect the chromosomal changes mentioned above. Until recent years it was possible to detect only large alterations on a chromosome involving many genes, but new techniques are making it possible to detect much smaller defects, allowing recognition of disorders involving only a small amount of genetic material.[10]

1.3.2. Tests for disorders involving a single gene

Genes cannot be seen through the light microscope, so tests for single gene disorders have been largely indirect, involving what the gene produces (protein), or another substance affected by it, rather than the gene itself. The protein is still unknown for the majority of genes, so testing for single gene disorders has been very limited until recently.

1.3.3. Direct tests. Various techniques have been developed for identifying important human genes directly. The two main approaches are:

1. The gene may be isolated if the product (protein) it normally produces is known. This approach was used for the genes involved with the main blood cell protein, haemoglobin (important for tests involving sickle cell disease and thalassaemia). The genes causing some metabolic diseases, where a specific chemical defect involving an enzyme was already known, have also been isolated in this way.[4,15]
2. The gene may be isolated if its position on a chromosome is known (positional cloning). This approach is increasingly successful in allowing genes to be isolated even when we know nothing about their function or what protein they normally produce. One reason for this success is that detailed genetic maps of the different chromosomes are being produced. This approach not only pinpoints the chromosome region where the gene lies, but can provide genetic markers (identifiable pieces of DNA) which lie close to the gene, and enables an accurate test for a genetic disorder to be made even before the gene itself is isolated.[16]

Once the gene responsible for a disorder has been isolated, it is possible to study its different changes (mutations) that may result in disease. These range from complete absence of the gene to faults in a single chemical subunit of the gene. A single gene disorder may be caused by many different changes in the gene responsible. By careful study of particular populations of people, it may be possible to determine which mutations for a disease are the commonest and most important, and to design a test programme accordingly.[17]

Direct genetic testing by DNA techniques differs in several important respects from most other forms of medical testing. Any body tissue can be used since genes are present in almost all cells. Although blood is most commonly used, cells obtained by mouthwash are proving especially suitable for some screening programmes. Since genes do not usually change during life, a DNA test can be performed at any time from conception onwards. This is a practical advantage for tests in early pregnancy, as it allows the detection of a serious genetic abnormality that, otherwise, would not show itself until after birth. However, this raises difficult ethical problems, especially in relation to diseases that do not appear until later childhood or adulthood.[18]

Major scientific advances have occurred in the sensitivity of genetic techniques, allowing minute amounts of DNA or protein products to be analyzed. A particularly important advance has been the polymerase chain reaction (PCR), which allows a single copy of a small part of a gene to be amplified many thousand times. Testing of single cells may make preconception testing of a single egg feasible, and may also allow testing of foetal cells in the mother's blood during early pregnancy. The dried blood spot taken onto filter paper from all babies in the newborn period can be stored and used for a wide range of genetic tests. New techniques increase the potential impact of genetic testing, because they are often suitable for mass population screening.[11,18]

An important discovery is that many stretches of normal DNA vary between different people and together provide a pattern that is unique for every individual (apart from identical twins). This powerful technique, known as genetic fingerprinting, has many applications, especially in legal cases. There are important ethical issues as to when and how it should be used.[9]

1.3.4 Indirect (biochemical) tests

These tests do not detect the gene itself, but some aspect of its function. The most nearly direct tests are for the specific protein that the gene produces. In a genetic disorder, tests may show that the protein is not being made or is present in reduced amounts; or that it may be altered so that it does not function adequately. Such tests are important; for example, for detecting abnormalities

of haemoglobin (in thalassaemia or sickle cell disease).[19]

Where the gene or its product cannot easily be tested, it may be possible to measure some other substance that is altered in the disease. Thus, the screening test for the disorder phenylketonuria (PKU), commonly used in Britain and South Africa on all newborn babies, is based on measuring the amino acid, phenylalanine, which builds up in the blood of affected persons.

1.3.5 Ultrasound

A quite different but very important technique is ultrasound imaging, which gives a virtually risk-free method of identifying structural and some functional abnormalities that may result from genetic disease. This technique is widely used during pregnancy for the detection of foetal malformations, some of which are genetic in origin. Some early manifestations of serious genetic disorders that may develop in later life, such as polycystic kidney disease (enlarged kidneys with cysts) or certain types of cardiomyopathy (heart muscle disease) may also be detected.[20]

2.0. CURRENT SCREENING PROGRAMMES

In reviewing existing screening programmes, some of which are well established and others barely beyond the pilot stage, various ethical problems may arise. Screening programmes are broadly divided into four groups, depending on the timing of the testing. These are:

1. Neonatal (in the newborn);
2. Older children;
3. Testing of couples or individuals before pregnancy (adults); and
4. Antenatal (during pregnancy).

There may be no single stage of life at which genetic screening is most suitable. Screening may best be offered in a variety of ways, and the optimal approach may change as the community becomes better informed. For example, genetic screening for thalassaemia in Cyprus and Sardinia (countries where this disorder is particularly common) has progressed from the antenatal stage to the premarital stage and towards screening in schools.[22] This type of progression may prove to be a common pattern as genetic screening becomes a more established component of primary health care.

2.1. Neonatal screening

The blood spot test for phenylketonuria (PKU) has not created any major ethical problems. Likewise, the test for congenital hypothyroidism, which is carried out on the same sample, does not appear to have raised any major ethical problems. This may be partly because both diseases are severe and can be adequately treated if detected.[9,23] Nevertheless, there is evidence that many women do not understand the purpose of the test. A study in Britain of new mothers' knowledge of the blood test for PKU and hypothyroidism, showed that two-thirds said that the test had been fully explained. Most, in fact, did not know what the test was for, and many incorrectly believed that it also detected other disorders.[24] Such results clearly challenge any notion that women are giving informed consent for their babies to be tested, although they believe themselves to be informed. There is no reason to believe that South Africa would be any different.

Some laboratories carrying out neonatal screening for PKU and hypothyroidism, in Britain and in other countries, have chosen to add tests for other serious conditions. It is not always clear to what extent parents are fully informed about these tests. A neonatal screening programme in Pittsburgh, USA, has chosen to employ 'informed dissent', where parents are required to express a wish to opt out if they so desire.[2,25]

The present method of screening for PKU, which is recessively inherited, is indirect and does not identify the genes involved. If direct gene testing were introduced, so that carriers as well as affected individuals were identified, a different order of ethical issues would arise. The finding of a carrier child has no disease implications for the child, but may become important to that child in later life, when reproductive decisions are being made. How and when the child should be told would require careful consideration.[26]

All newborn babies have a physical examination which may detect congenital disorders, some of which may have a genetic component. Examinations are often carried out in the presence of the mother, and the parents are informed about any abnormalities and their implications.[3,9]

2.2. Later childhood screening

As part of routine child health surveillance, all children have a physical examination for a variety of diseases that may, in part, have a genetic basis. For example, hearing defects may be detected. Programmes of screening for specific genetic disorders are in the pilot stage. These need to adhere to the principles of informed consent.[15,27]

2.3. Adult screening

Screening of adults may be carried out to detect existing disease or predisposition to a disease, or it may identify carriers with a reproductive genetic risk. Most pre-symptomatic testing for late onset genetic diseases (such as Huntington's disease) is currently offered to family members at risk. Increasingly, general screening for such late-onset genetic diseases is becoming technically feasible, although not necessarily desirable.[11,28]

The general screening of individuals who may be carriers of inherited disease genes is currently used only as a service to those in an ethnic group known to have a high incidence of an inherited disease; for example, the haemoglobin disorders in people of African,

Mediterranean and South East Asian origin and Tay-Sachs disease in Ashkenazi Jews.[28]

2.4. Pre-pregnancy and premarital screening

Testing before pregnancy is not systematically practiced to any extent in Britain or South Africa. Screening for carriers of the haemoglobin disorders may be offered through family planning clinics and general practice. Insufficient information is available to evaluate these programmes.[3] In Cyprus, antenatal screening for thalassaemia has been almost totally superseded by premarital screening. The religious authorities had ethical objections to screening during pregnancy, on the grounds that it excluded most options other than termination of affected pregnancies.[29] The church in Cyprus therefore insists on testing as a formal prerequisite to church weddings. The certificate required states merely that the partners have been tested and appropriately advised. In this way the confidentiality of the test result is preserved and the couple can exercise an informed choice about reproduction.

2.5. Screening during pregnancy

Screening during pregnancy may be carried out on the mother, on the foetus, or on both. If, through screening, a woman is found to be a carrier of a gene for a recessive disorder, her partner may be offered genetic testing to find out whether the couple is at risk of having an affected child. If both parents carry the gene for a recessive disorder, if the mother carries the gene for an X-linked disorder, or if either parent has the gene for a dominant disorder, tests may be done on the developing foetus.[30] There are several methods of obtaining samples for genetic tests on the foetus, the most common being amniocentesis and chorionic villus sampling (CVS). Genetic diagnosis can be achieved before 12 weeks' gestation with CVS, compared with about 16-20 weeks by amniocentesis. However, the risk of miscarriage is slightly higher for CVS (about 1-2% in excess of expectation at this stage of pregnancy) than for amniocentesis (0.5-1%).

In Britain, antenatal screening tests are carried out on all women for a predisposition to rhesus haemolytic disease of the newborn and rubella (German measles). Rubella screening was the first screening programme undertaken with the objective of offering detection and abortion of potentially affected foetuses. Severe congenital disorders may result from rubella infection during pregnancy. Both rhesus and rubella screening appear to be well accepted. Whereas the finding of a rhesus negative blood group results in preventive treatment, a positive rubella test gives rise to the need for very painful decisions, including the termination of the pregnancy.

The offspring of women with insulin-dependent diabetes mellitus have an increased risk of still birth, neonatal ill health and major congenital malformations, especially if their diabetes is poorly controlled. In many women with diabetes the diagnosis will already be known, but all women are screened early in pregnancy by blood and urine tests to detect undiagnosed cases. Expert foetal anomaly scanning by ultrasound is offered to all pregnant diabetics.[16]

In many areas, screening is carried out to detect neural tube defects (spina bifida and anencephaly). Maternal serum alpha-fetoprotein (AFP) determination is now offered routinely to all pregnant women between 16 and 18 weeks of gestation, but in about half of all pregnancies with a raised maternal serum AFP, no cause can be found, either pre- or postnatally.[22]

Antenatal screening is offered to women in specific risk groups. All women over an age that varies by area between 35 and 37 are offered testing by chromosome studies for the presence of Down's syndrome in the baby. Down's syndrome occurs in approximately 1 in 600 of all births; but is much less common in children born to younger women (1 in 1 500 at age 20). Its birth incidence increases with maternal age, being about 1 in 350 at age 35, and as high as 1 in 100 at age 40.

3.0 PRACTICE IMPLICATIONS

Health professionals must recognize women's fears that the unborn baby might have a serious abnormality and their need for information about the implications where such a diagnosis is confirmed. Further, protocols concerning the implementation of screening programmes should include adequate psychosocial support for participants.[17]

3.1. Counselling, providing information and obtaining consent

Genetic counseling is the provision of accurate, full and unbiased information that individuals and families require to make decisions in an empathetic relationship that offers guidance and assists people to work towards their own decisions.[12] The information should include a full description of the risks, diagnosis, symptoms and treatment of the disorder in question. Information about financial costs, emotional costs, education, and both positive and negative effects on the marriage and family unit should be included, as well as available social and financial supports for persons with genetic conditions.[14]

It is fundamental that actual knowledge or understanding on the part of the patient, or person consenting on behalf of the patient, is achieved. It is not sufficient for the practitioner to have reasonably explained the information. Informed consent is valid only when it represents true understanding.[14] This rigorous test of consent is linked to the patients' right to be so informed that they understand the proposed test or procedure, the possible alternatives and any associated risks, to enable them to make a balanced judgement on whether to continue with the test or procedure or to withdraw.[14] Evidence suggests that the combination of written information supplemented with face-to-face interaction is the most desirable method of ensuring that patients

receive sufficient information to empower them to make this choice.[2,18] It is recommended that the following ethical principles should be applied to genetic counseling:

1. Respect for persons, families and their decisions according to the principles underlying informed consent;
2. Preservation of family integrity;
3. Full disclosure to individuals and families, of accurate, unbiased information relevant to health;
4. Protection of the privacy of individuals and families from unjustified intrusions by employers, insurers and schools;
5. Informing families and individuals about possible misuses of genetic information by institutional third parties;
6. Informing individuals that it is their ethical duty to tell blood relatives of the genetic risks to which they may be exposed;
7. Informing individuals about the wisdom of disclosing their carrier status to a spouse or partner if children are intended, and the possibility of harmful effects on the marriage from non-disclosure;
8. Informing people of their moral duty to disclose a genetic status that may affect public safety;
9. Unbiased presentation of information, in-so-far as this is possible;
10. Adopting a non-directive approach, except when treatment is available, although the person being counselled may still decline treatment;
11. Involving children and adolescents whenever possible, in decisions affecting them; and
12. Observing the duty to re-contact if appropriate and desired.[32]

Informed consent is an accepted norm in the clinician-patient relationship, implying the patients' knowledge of the major characteristics of their medical disorder, an understanding of the test or procedure they are to undergo, the limitations of the test or procedure, and the possible consequence of their participation in the test or procedure followed by their agreement, or not, to undergo the test or procedure.[12,14] This term includes a right on the part of the participants or patients to be informed of risks not actually related to the medical impact of the test or procedure, including:

It is recommended, further, that information to be given to any patient undergoing genetic screening should include:

1. The seriousness of the condition to which the genetic disorder may give rise and how variable its effects are;
2. The therapeutic options available;
3. How the disorder is transmitted, the significance of carrier status and the probability of development of the serious genetic disease;
4. The reliability of the screening procedure and the results of the test;
5. Information detailing how the results of the screening test will be passed on to the patient, and what will be done with the samples;
6. The implications of a positive result for their future and existing children and for other family members;
7. A warning that the screening test may reveal unexpected and awkward information; for example, about paternity.[26]

3.2. Genetic screening - the law and public policy

The negative impacts of genetic screening may be separated into two categories of harm. The first is the effect on the personal choices and mental well being of the individual, and the second is the effect on the interaction of that individual with society at large. The first category of harm may include increased personal anxiety about health, decisions related to the termination of pregnancy, and deciding whether to pass on genetic information to spouses, partners or family members.[16] The second category involves more powerful ethical considerations with regard to eugenics, employment prospects and access to life insurance and other benefits. It is with this second-category harm that we are primarily concerned in these guidelines.

4.0. RESULTS OF GENETIC SCREENING AND CONFIDENTIALITY

Genetic information can be effectively used to reduce the health-related cost of labour. This simple fact is the most powerful reason for employers and insurers to be interested in genetic screening and testing. On the other hand, the dissemination of genetic information to employers and insurers may be linked to the dangers of "isolation, loss of insurance, educational and job opportunities for persons diagnosed with incurable and costly disorders.[28]

Dangers associated with genetic screening differ from those associated with genetic testing. Genetic screening is carried out at the instance of the State or large institutions, while genetic testing is done at the instance of the individual being tested. Guidelines related to genetic screening should also govern the scope and aim of screening programmes and ethical aspects relating to the use, storage and registration of data and follow-up procedure.[2,21] while guidelines for genetic testing should be more focused on aspects pertaining to the individual and the protection of his or her rights.

4.1. The scope and aim of screening programmes

The reports on genetic screening and discrimination suggest several areas of sensitivity as follows:

1. The workplace, where employers may choose to test job applicants, or those already employed, for susceptibility to toxic substances or for genetic variations that could lead to future disabilities, thereby raising health or compensation costs. In terms of Section 7 of the Employment Equity Act, No. 55 of 1998, medical testing of employees or job applicants by employers is prohibited in South Africa unless legislation permits or

requires testing, or it is justified in the light of medical facts, employment conditions, social policy, the fair distribution of employee benefits or the inherent requirements of a job.

4.2. Test results, privacy and data protection

Every individual undergoing either genetic screening or genetic testing has the right to be fully informed of the results concerning a suspected disorder.[3] A difficulty arises where an individual is to be informed of results that are "unexpected, unwanted, and have not been covered by consent. 'Everyone has the right to respect for his private and family life, his home and his correspondence'. The right to private life, or to privacy, clearly includes the right to be protected from the unwanted publication or disclosure of intimate personal information. The South African Constitution clearly protects each individual's right to privacy. Section 14 of the Constitution and the common-law right to privacy include privacy of information; that is, the right to determine for oneself how and to what extent information about oneself is communicated to others.[11]

The case for confidentiality in medicine applies with equal force to genetic screening. Individuals agreeing to be screened need to be confident that no results will be made available to anyone other than themselves and their medical advisers, without their explicit consent. Otherwise, people may be reluctant to participate, perhaps with damaging implications for themselves, their families and, potentially, other third parties. If clinicians were to break the confidence relating to genetic information, there would be adverse implications for other areas relating to the care and treatment of the patient. The patient would fear that other medical information was being disclosed to a third party.

4.3. The ethical dilemmas

It is important to discuss first the responsibility of the individual in resolving the dilemmas, and then, the role and responsibility of the clinician or other professional adviser. The main ethical dilemma arises from a conflict between the right of the individual to personal privacy, and the reasonable desire of family members to be fully informed.[30] The information, after all, might play a part in important decisions about their lives. A balance needs to be struck between the two. A further complicating factor, though, is that some family members may prefer not to be presented with the information. This would become a much more serious problem if widespread screening were introduced for X-linked or autosomal dominant diseases.

4.3.1. The individual's responsibility

The question of responsibility has at least two dimensions here. The first is the responsibility of the individual to pass on relevant information to other family members, and the second is the responsibility of the other family members to receive the information.[6] We adopt the view that a person acting responsibly would normally wish to communicate important genetic information to other family members. These members may have an interest in the information, and a responsible person would probably wish to receive it, particularly where it might have a bearing on decisions that he or she may take in the future. It is strongly agreed that the primary responsibility for communicating genetic information to a family member or other third party lies with the individual and not with the clinician, who may, however, do this at the request of the person concerned.[12]

The best way to ensure that genetic findings are appropriately shared with family members (and occasionally with other third parties) is through information and counselling procedures. Disclosure to other family members ought not to be made a condition of participation in a screening programmes. Inevitably some individuals will refuse to allow disclosure and this may present the clinician or other health professionals with an ethical dilemma.[25]

4.3.2. The clinician's dilemma

Just as it is not accepted that there should be a legally enforceable duty placed on people who have been screened, to inform family members or other third parties of the results, so do we reject the idea that clinicians should be placed under a legal duty to reveal information against the wishes of the individual concerned. No such general duty is acknowledged by law in most developing countries,[21] although the position may be different in some developed countries. Privacy and confidentiality should be respected and maintained, but it should be accepted that there may be exceptional circumstances in which these might properly be overridden by the clinician; for example, where information is withheld out of malice. It is impossible to foresee all the circumstances in which a doctor might properly disclose confidential information to family members. It is recommended, therefore, that the following points be adopted as guidelines to disclosure, to families, of the results of a genetic screening programme:

1. "The accepted standards of the confidentiality of medical information should be followed as far as possible;
2. Where the application of such standards might result in grave damage to the interests of other family members, the health professional should seek to persuade the individual to allow disclosure of the genetic information. The potential seriousness of non-disclosure should be explained to the individual;
3. In exceptional circumstances, health professionals might be justified in disclosing genetic information to other family members, despite an individual's desire for confidentiality."[26]

4.3.3. Genetic registers

In the context of genetic screening, where large numbers of tests are undertaken, this may be recorded in the form of a genetic register or similar database. Special

consideration should be given to the implications for security of these grouped results.

A register may be defined as a systematic collection of relevant information on a group of individuals.[2,17] Genetic registers record information on individuals with specific genetic disorders, and may include relatives at risk of developing or transmitting the condition. The information may be recorded by hand, or may be held on computer. Genetic registers may be set up for a variety of reasons, including research on the disorder, the effective provision of services to those on the register, and the systematic offer of genetic counselling to family members. The amount and type of information recorded varies greatly, as does the presence of identifying details.

There are several general ethical issues concerning genetic registers. Mentioned here are some issues relating to genetic screening. They should be seen against the background of the following points:

1. A genetic register may be the starting point for genetic screening; for example, the systematic testing of relatives of individuals with fragile X syndrome or Duchenne muscular dystrophy;
2. Genetic screening may also be based on a register not specifically genetic in its basis; for example, registers of specific cancers or of those with severe learning difficulties;
3. A genetic register may be the product of a genetic screening programme; for example, a register of carriers of cystic fibrosis or sickle cell disease in a population screened for the purpose.

It is essential to obtain individuals' consent before placing their names on a register. It is also important that individuals know that they are on the register, and what use will be made of the information. Consent of individuals to long-term storage of information resulting from genetic screening had been emphasized earlier. However, if this is to form the foundation of a genetic register, separate and specific consent should be sought for subsequent tests or other measures, also for further use which may generate financial benefits for the investigator.

Confidentiality of all medical information is essential, and this is particularly the case with genetic registers, which may contain highly sensitive and potentially identifiable data on large numbers of individuals with, or at risk of, serious genetic disorders. Computer-based genetic registers are subject to the Promotion of Access to Information Act, No. 2 of 2000, but there is need for additional safeguards for all genetic registers, including secure storage of information, limitation of access to those specifically responsible for a register, and the removal of identifying information when data are used for research purposes.

4.3.4. Employment

Competition drives the players in the economy to reduce costs and increase efficiency. In the context of employment, genetic screening provides the employer with an opportunity to reduce the health-related costs of employment. An employer may want to screen candidates, to exclude those susceptible to occupational or non- occupational disease.[27]

"Healthy workers cost less: they are less often absent through illness, there are lower costs for hiring temporary replacements or for training permanent replacements, and there are fewer precautions which would need to be taken to deal with health and safety risks.[16]

The dangers of permitting employers to embark on their own screening programmes are self evident. The result would be restrictions on the employment of individuals who are at risk of genetic disease, and the creation of class orders based on genetic disposition. The employees and the public at large have an interest in reducing the incidence of occupational disease. It is accepted that employers may require employees to undergo screening for illnesses or conditions that present a serious danger to third parties.[24,31] Thus, genetic screening may have a limited role to play in employment. One way of achieving this is for the State to introduce screening programmes whereby individuals are made aware of their genetic disposition and are empowered to make informed decisions with regards to their employment and their health.

5.0. HEALTH INSURANCE

Insurance and risk management are two separate forms of practice. Risk management seeks to reduce the costs associated with risks that will certainly eventuate, whereas insurance is more like a gamble: it is unknown whether the event will occur or not.[14,32] The relevance of this to genetic screening is that at present the medical aid industry operates as a form of insurance. Insurers constantly try to determine the risk associated with potential clients, to better allocate the premiums and so attract the least risky clients.

The revolution in genetics allows insurers to reduce uncertainty about future events. This fundamentally changes the context of insurance. The more predicable the risk, the more accurately an insurer can apportion premiums. The repercussions for individuals with genetic predispositions to certain diseases are that they may not be granted health insurance at all, or may be charged higher premiums. Insurers have argued that using genetic information to predict risks is nothing more radical than an extension of their current practice. At present, insurers require people seeking insurance to provide information regarding their family medical history and lifestyle, to be able to predict the risks and thereby to determine an appropriate premium. Additional statistical information linking a given test result to the occurrence of some

disorder is also needed if a sound prediction of disease or of lowered life expectation is to be made on the basis of a genetic test result. Without information that links genetic test results to incidence of disease or death, they lack actuarial import.[2,18] Recommendations on the use of genetic screening and genetic tests by insurance companies arise from the following considerations:

1. The difficulty of assessing sometimes slender evidence on the genetic susceptibility of individuals to develop polygenic and multi-factorial diseases (for example, some cancers and some forms of heart disease);
2. An awareness that ordinary commercial practice will lead companies to be overcautious in their assessment of the risks derived from medical data; and
3. The possibility of abuses.

5.1. Children

There are well-founded reasons for testing asymptomatic children and adolescents for genetic diseases or carrier statuses. However, genetic testing of children raises ethical concerns over issues such as informed consent and disclosure to the child. The test is conducted only where it is in the best interests of the child; thus, the primary justification for the test should be of timely medical benefit to the child.[15] If the provider of the test is of the view that the potential harm of the test would outweigh the potential benefit, or if medical intervention would be of no benefit until adulthood, the test should be deferred until adulthood.

The assent of the child should be sought. Related to this right is the right to make an informed decision without interference from health-care providers, although this right can be limited where there are objective reasons to believe that a decision or action has significant potential for an adverse impact on the health or well-being of the child.[12]

The following recommendations of The American Society of Human Genetics and the American College of Medical Genetics Report.[30] in respect of family involvement in decision-making are endorsed:

1. Education and counseling for the parents and the child, according to the child's maturity, should precede genetic testing;
2. The test provider should obtain the permission of the parents and the assent of the child or the consent of the adolescent. In terms of the Child Care Act, No. 74 of 1983, a child above the age of 14 years may consent independently to medical treatment, which would include genetic testing from which the child could benefit directly;
3. The test provider is obliged to advocate the child's best interests at all times;
4. A request by a competent adolescent for the results of a genetic test should be given priority over the parents' requests to withhold information.

CONCLUSION

Rapid advances in genetic research during the past two decades have challenged scientists, health care professionals, ethicists, government regulators, legislators, and consumers to reflect on new developments. Genetic and genomic research provide important opportunities to clinicians to understand the evolution at gene level the emerging poverty related diseases in Africa and chances of addressing the important health needs.

A constant update with the scientific advances in genomics and their implications is important for all stakeholders involved in making informed decisions about the ways in which genetic research and information will affect the lives of current and future generations. The potential benefit and risks associated with genetic and genomic research is different from the types of potential benefits and risks associated with other types of health research like clinical trials and biomedical research involving human subjects.

The potential risks associated with genomic research are mostly socioeconomic in nature. It is important to note that the genetic and genomic research since the unraveling of the human genome has the potential for drug discovery and development of new drugs and biologics like vaccines for the poverty related diseases of developing nations.

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