

# Genetic Testing

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## INTRODUCTION

Genetic disorders are diseases that arise as a result of abnormalities in the chromosomes. The abnormalities could be due to the malfunction of a single gene (Mendelian disorder), numerical or structural defects in the chromosomes, or multifactorial as a result of the complex interaction between genetic and environmental factors. On the other hand, congenital abnormalities are birth defects that are not solely due to genetic abnormalities; they may be inherited, may occur during pregnancy or may be inflicted during childbirth.

Genetic disorders are common in childhood. Approximately 53 per 1000 children and young adults have diseases with an important genetic component. However, if congenital abnormalities are included, this rate can be as high as 79 per 1000. Genetic diseases and birth defects account for approximately 12 to 40% of all paediatric hospitalisations<sup>1</sup>.

Genetics is a relatively new branch of science that studies the principles and mechanics of heredity, or the means by which traits are passed from parents to offspring. In 1953, scientists James Watson and Francis Crick successfully deduced the three dimensional structure of DNA<sup>2</sup>. This enormous discovery led to better understanding of gene functions at the molecular level. In 1998, the Human Genome Project was initiated. It is a massive international research project involving several centres from different parts of the world, with the aim of elucidating the entire sequence of genes of all the human chromosomes. It is expanding our knowledge of the genetic basis of diseases at an incredible rate. Some of the most important discoveries that have been or will be derived from the project can be seen in Table 1.

### Genetic testing

Genetic testing is a DNA-based diagnostic procedure that can be accomplished at many differ-

ent stages of human development. It can be performed preconception, prenatal, neonatal, at school or during adult life, such as couple screening<sup>3</sup>. It can serve as a diagnostic tool in affected individuals or be used to identify healthy individuals who may be at risk of developing genetic diseases.

At present, genetic testing has already been used to screen for some treatable genetic diseases such as phenylketonuria (PKU). PKU is an inborn error of metabolism of phenylalanine, in which early dietary intervention drastically changes an affected individual's outcome from severe mental retardation to a normal healthy life. It can be performed a few days after birth via a simple heel prick blood test called the Guthrie test.

In general, genetic testing can be divided into several categories: diagnostic genetic testing, genetic screening, identification of carrier status, and prenatal diagnosis.

### Diagnostic genetic testing

The goal of diagnostic genetic testing is to confirm the diagnosis of a symptomatic patient, or to identify affected individuals who are at high risk because they are related to a symptomatic person with a genetic disease.

Genetic testing is the best tool to confirm a clinical diagnosis of a symptomatic patient. For example, in a baby who presented with peripheral lymphoedema at birth in the absence of other organic pathology. A simple chromosomal analysis on a few cells obtained from the buccal mucosa can lead to an accurate diagnosis of Turner syndrome.

If an individual is healthy and asymptomatic but is at risk due to a positive family history, such as in autosomal dominant conditions or an X-linked recessive inheritance pattern, early detection and diagnosis with genetic testing may confer a better prognosis.

Genetic testing provides the greatest medical benefits to the affected individual in genetic diseases that are fully penetrant and have available preventive or curative measures, such as in the case of retinoblastoma. Identification of these individuals allows targeted surveillance by frequent ophthalmological examination to minimise morbidity and mortality via pre-emptive treatment. In addition, clinicians can exclude unaffected siblings, thereby freeing them from further unnecessary medical surveillance. Therefore, the knowledge of gene function and pathogenic progression of diseases presents new approaches in treatment.

Haemophilia A is a disease that is fully penetrant in affected males. Although there is presently no cure for the condition, genetic testing in a child born to a known carrier female is favourable as early intervention can prevent injuries, and prophylactic factor VIII infusions may allow the patient

**Table 1:** Discoveries derived from the Human Genome Project.

1.	The discovery of individual genes and elucidation of gene function.
2.	Development of new technology for widespread, easily accessible genetic testing.
3.	Creation of new methods of medical interventions for genetic diseases.
4.	Accurate assessment of risks of developing diseases via DNA-based diagnostic procedures.
5.	Anticipation and treatment of affected individuals prior to the development of symptomatic disease (pre-emptive treatment).
6.	The potential to alter cellular expression of genes by gene therapy, inhibition of gene expression, and drug development.

Advantages	Disadvantages
1) Minimise uncertainty about having the disease	1) Affect patient's interaction with family, school, or even within themselves
2) Allow patient to understand his/her genetic condition	2) Psychological problems of knowing the prognosis of the future
3) Allow patient to plan a more suitable lifestyle	3) Guilt in unaffected siblings
4) Parental expectations for future of the affected child become more realistic	4) Parents may discriminate against the child and treat them as diseased/disabled
	5) Development of "vulnerable child syndrome"

**Table 2:** Advantages and disadvantages of genetic testing

to lead a relatively normal life.

Huntington's disease is an autosomal dominant disease characterised by a trinucleotide repeat expansion mutations. The hallmarks of this inherited disease are progressive chorea and dementia in middle life. Although the majority of patients (>95%) present in adult life, less than 5% may manifest the disease in childhood. It is a fully penetrant disease and there are no cures or preventive measures available. There are controversies regarding genetic testing in this situation. Is it justifiable to perform genetic tests on children based on their parents' requests? Table 2 summarises some advantages and disadvantages of performing genetic testing.

It is very important to weigh the benefits and risks of genetic testing in this situation as the psychological impact of the genetic information will affect not only the patient but their family as well.

Another clinical scenario in which the utilisation of genetic testing is debatable is in an incompletely penetrant genetic disease. In this case, inheritance of certain genes may only increase an individual's risks due to variable gene expression, and the affected individual is often asymptomatic. Researchers have shown that a positive *BRCA1* gene in an Ashkenazi Jewish woman with a positive family history has a probability as high as 85% of developing breast or ovarian cancer before the age of 65 years<sup>1</sup>. Parents may want to test their children because of a positive family history or due to increased awareness of the disease. However, this may produce more harm than good, since there are no preventive measures at the present time, although gene therapy may be beneficial in the future. One must bear in mind that a positive result may only indicate a person's increased susceptibility to a particular disease. It does not necessarily predict whether the disease will affect the individual, at what age it might present, how aggressive the cancer might be or how susceptible the cancer is to standard treatment. A false positive result may create a lasting burden and worry, while a negative result does not guarantee that the individual will not develop the disease.

#### Genetic screening

Genetic screening refers to testing a population who do not possess any pre-existing risk factors and it is usually carried out in the neonatal period. There are several criteria that must be fulfilled in a population-based, newborn screening programme:

- ♦ There must be clear benefits to those newborns who test positive.
- ♦ A system must be implemented to confirm the

diagnosis.

- ♦ Treatment and follow-up must be available for affected newborns.
- ♦ The condition should be frequent and severe enough to be a public health concern.
- ♦ The condition must cause a known spectrum of symptoms.
- ♦ The screening test should be simple and reliable, with low false positive and false negative rates.

Genetic screening confers significant medical benefits in some situations because early identification of affected individuals can reduce the morbidity and mortality via implementation of early interventions. A classic example is phenylketonuria as previously discussed. Some diseases may not fulfil all the criteria to warrant universal screening due to low prevalence and high cost determined by cost-benefit analysis. In this instance, genetic testing is only offered in selected, high-risk communities. An example of targeted population screening is Gaucher's disease in the Ashkenazi Jewish population<sup>1</sup>.

#### Identification of carrier status

In recessive traits, carrier testing provides medical benefits in term of reproductive decisions. However, it is controversial in cases where parents request testing for carrier status in children with respect to consent. Some of the advantages and disadvantages of testing for carrier status are shown in Table 3.

Based on the above disadvantages, carrier testing in children should only be performed following parental requests after appropriate counselling has been delivered.

#### Prenatal diagnosis

Carriers of a genetic disorder often choose

**Table 3:** Advantages and disadvantages of identification of carrier status in individuals

Advantages	Disadvantages
1) Easier for one to accept carrier status in childhood and incorporate into one's identity	1) Violation of the child's privacy and the right of not knowing their diagnosis
2) Genetic information might be useful for other family members	2) Parents may treat their child as diseased (genetic discrimination)

prenatal diagnosis because they have affected family members and fear having similarly affected offspring. In Sweden, researchers have shown that women who opted for prenatal diagnoses are among those who perceive haemophilia as a serious disease and have a positive attitude towards legal abortion<sup>4</sup>. Those who did not choose prenatal diagnosis often abstained from further pregnancies after the birth of a child diagnosed with haemophilia.

#### **DISCUSSION**

Perhaps one of the most controversial areas of genetic testing in children is consent. Traditionally, parents are presumed to be best suited to make decisions for their children. However, current attitude favours the child's autonomy since they are recognised as having significant decision-making capacity<sup>1</sup>. The affected child is also entitled to confidentiality of the knowledge. In spite of this, one must remember that the genetic information may have significant impact on the relatives as well, especially if the result is positive. Therefore, it is often difficult to ensure an individual's confidentiality when the genetic information has significant influence on the individual as well as their family.

Individuals who tested positive often encounter discrimination even though the disease may not be fully expressed. There is a fear that certain institutions such as insurance companies might exploit the genetic information in a discriminatory manner against the individual.

Most of the genetic tests are quite new and they are not infallible. Before the result of a test can be interpreted, many factors must be taken into account. These include the technical quality of the test, its predictive value, reliability and validity. A study carried out in Wisconsin investigated the positive predictive values (PPV) of some congenital endocrinopathies that were identified via newborn screening<sup>5</sup>. The researchers revealed an extremely low PPV, in the range of only 0.5% to 0.6%. In other words, on average, there are more than 50 false positive results for every true positive result identified through newborn screening in the United States.

A myriad of questions relating to the ethical, social, political and economical aspects of genetic testing have arisen in recent years, which may affect the implementation and utilisation of genetic knowledge and technologies. The Ethical, Legal & Social Implications (ELSI) division of the Human Genome Project has been established to evaluate the use and misuse of genetic knowledge and technology, before they are available in our society.

Genetic testing has decreased the incidence of some genetic diseases and this is attributed to accurate diagnosis, education and freedom of individuals to make reproductive decisions. Couples have more options in terms of reproductive planning, which include prenatal diagnosis, pre-implantation diagnosis of embryos, artificial insemination by

donor, *in-vitro* fertilisation, and embryo donation.

A controversial technique of reproductive planning still being debated is pre-implantation diagnosis of embryos. It is a very early form of genetic testing that involves testing of a few cells taken from an embryo. Following this, selective transfer of genetically desirable embryos for *in-vitro* fertilisation can occur<sup>6</sup>. This technique is only allowed in situations involving a high-risk conception of a serious genetic disease such as Fragile X syndrome or cystic fibrosis, with the advantage of excluding the necessity of a therapeutic abortion. From an ethical point of view, it is not justifiable to select desirable traits in reproduction.

Prenatal diagnosis may be beneficial in terms of knowing the genetic condition of the baby before delivery. Some couples that have a positive attitude towards elective abortion will choose to terminate the pregnancy to decrease the burden of having a child born with a genetic disease<sup>7</sup>. The moral sentiments and religious attitudes towards abortion cannot be understated. In Ireland, for example, abortion is not permitted by law based on the belief that the unborn foetus possesses a life from the moment of conception.

No doubt, genetic counselling plays an important role and is an essential component of medical genetics. A genetic counsellor often works hand in hand with an experienced paediatrician, and can help a family to understand the relevance of genetic information in terms of clinical and reproductive outcomes. Extensive counselling is needed to inform the parents about what genetic testing can and cannot do, and how some tests may only provide information about increased or decreased disease susceptibility rather than definite answers. In addition, genetic counselling also incorporates sensitive issues relating to child bearing, handicap and continuation of family. Hence, counsellors must have the technical knowledge, skills and clarity of purpose to carry out their tasks.

#### **CONCLUSION**

Genetic testing, may serve as a diagnostic tool, uncover disease risk, decrease morbidity and mortality, and reveal information that has relevance in reproduction. These advantages may be of incalculable value to medical advancement, provided that all the ethical and psychological implications of genetic information are taken into consideration. This includes consent and confidentiality of genetic information, morality of certain testing techniques, and the actual meaning of a positive result. Genetic counsellors and paediatricians play essential roles in providing guidance and clarifying all possible implications and repercussions of genetic testing. Further research regarding the implications of genetic information, especially the ethical aspects, is vital before the advancements in genetics presently occurring can be utilised.

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