The Malaysian Medical Association's Position Paper on Molecular Medicine: Genetic Testing and Editing

By Dr Gayathri K. Kumarasuriar

Genetic testing focuses on a single gene or part of a DNA, while Genome Testing covers the whole DNA. On 31 March 2022 the Human Genome project produced the first complete blueprint of the human genome sequencing since it first started in 1990. At the project's conclusion in 2003, **the number of identified disease genes had risen to more than 1,400**.

There are 3 major types of genetic testing today:

i) Cytogenetics: to examine the whole chromosome
ii) Biochemical Genetic Studies: to measure the proteins which are produced by the genes
iii) Molecular: to look for small DNA mutations

Molecular Medicine is no longer limited to just getting one's genes tested to find out a cause of a disease or to take preventive measures should one have a faulty gene. While this gives researchers wider opportunities towards diagnosing, preventing, and treating complex as well as common diseases, this knowledge also opens a plethora of potential ethical, social and legal issues.

Genetic testing is the main door to a huge mansion of new technologies in genetic medicine which is growing at an exponential phase in today's world. Just having basic awareness about genetic testing alone is not enough. Medical practitioners must update themselves with the knowledge of current genetic technologies and interventions so that we are equipped to educate and guide our patients to make informed decisions about their health and the care they choose to receive. To avoid unwittingly crossing ethical boundaries, a constant reminder of the main goals of medical genetic screening and testing will keep medical practitioners on the safe side of the law.

The main goals of medical genetic testing and screening are:

i) For prevention of diseases or
ii) For early diagnosis and treatment of an illness
iii) To help and guide patients in prevention of a disease example, cancer and the treatment plan

Genetic Testing in Malaysia

In 2019, we described the progress of DNA profiling and DNA data banking in Malaysia for the first time. **The Guideline on Ethical Issues In the Provision of Medical Genetic Services in Malaysia published in December 2019** is an excellent source of reference for healthcare providers. It can act as a guide to good ethical practice in the delivery of healthcare and genetic testing services.

The Deoxyribonucleic Acid (DNA) Identification Act 2009(Act 699) and the DNA Identification Regulations Act 2012 were enacted on 3 September 2012 to establish the Forensic DNA Databank of Malaysia (FDDM). The Deoxyribonucleic Acid (DNA) Identification Act 2009(Act 699) is the only statute that empowers the court to order an individual to undergo DNA test in Malaysia. This act only applies to criminal proceedings and even then, still requires individual consent before DNA samples can be taken for examination. Medical indications for genetic testing also need informed consent.

The most common form of genetic testing is Polymerase Chain Reaction (PCR). PCR based STR (Short Tandem Repeats) analysis is a more modern approach to DNA typing. STR is a genetic marker found on the human genome.

Indications	**Screening**	**Diagnostic**	**Disease Prediction**	**Prognostic and Choice of Treatment**	**Research**
Genetic Testing	Individuals at higher risk for genetic disorders so that early diagnosis and treatment are available	To confirm the diagnosis of genetic treatment	Helps to determine if a healthy individual with or without family history of certain genetic disorder develop the disease	May help with the prognosis and treatment if certain diseases are revealed	To identify and understand the mutations and variants found in the human genome.

**From Guideline on Ethical Issues in the Provision of Medical Genetic Services in Malaysia*

CRISPR/Cas9 Gene Editing

Clustered Regularly Interspaced Palindromic Repeats known as CRISPR/Cas9 gene editing, is a decade old genetic engineering technique. The CRISPR/Cas system has emerged as a powerful tool for genome editing in metabolic engineering and human gene therapy. The genomes of living organisms are modified by cutting DNA and letting natural DNA repair process take over by directly targeting the defective gene. It uses the Cas9 enzyme and an RNA guide sequence to target a specific gene sequence, eliminate the faulty segment and either repair the defect or insert a new gene. It is said to be the most precise and efficient method of gene editing. Currently it is being utilized by scientists to monitor progression of diseases like cystic fibrosis, cancer, heart diseases and neurodegenerative disorders. It has the potential to prevent, treat or even cure certain inherited disorders. To refine this technique further, CRISPR-COPIES has been developed to help locate optimal sites on the DNA for genome editing.

On the other end of the spectrum, there is also a huge potential for this technique to be misused.

Eugenics is the advocacy of controlled selective breeding of human populations to improve the specific race or population is an area for potential misuse with gene editing. It is based on the concept of retaining positive traits and removing the negative ones. There is a potential for parents wishing for the 'perfect offspring' or a specific gender to resort to such choices in the future. This would be tampering with nature and may result in disastrous consequences.

Somatic Genome Editing involves alteration of non-reproductive cells and can be used to edit disease causing DNA. Germline Genome Editing on the other hand refers to genetic editing in the germ cells, modifying the genetic structure of the embryo and has a potential of passing these modifications to their off springs.

Heritable Genome Editing(2020), a consensus study report by the National Academy of Medicine; National Academy of Sciences; The Royal Society; International Commission on the Clinical Use of Human Germline Genome Editing following the birth of the reported CRISPR babies in China. This incident brought to light the absence of both societal acceptability and scientific evidence that these procedures could be done safely.

New technologies and advancement in this field are inevitable. Lately, there has been a breakthrough on a new CRISPR system. A type -III CRISPR protein has been programmed to cut RNA containing mutations. Time will tell how the type-III CRISPR will benefit the medical field.

Potential ethical concerns associated with the screening and diagnostic application of genetic testing:

i. **Privacy:** Can they maintain their privacy once they undergo genetic testing? Privacy includes the right to make an informed, independent decision about whether and who may know details of their results. Will withholding their results from employers and insurance companies have legal implications?

ii. **Mental health concerns:** Undue stress to a person whose results may not indicate a definitive disease but a potential risk to develop a disease. Some patients may develop severe psychological distress and worry about their risks of developing a potential disease. This may eventually escalate into more severe mental disorders for example Generalised Anxiety Disorder, Mixed Anxiety and Depression or Illness Anxiety Disorder.

iii. **Health Insurance:** Insurance companies may deny patients with unfavourable genetic testing results a policy or even terminate existing ones. Those who are deemed high risk by the genetic testing might also meet the same fate. Would these people be deprived the right to health care? This becomes a challenge as well when medical practitioners are requested by the second group not to mention the genetic test results when they fill insurance forms.

iv. **Confidentiality:** Genetic conditions are family health issues. Results of genetic testing reveals potential disease or other risks to the patient, and potential risks to the person's children and blood relatives. Does a medical practitioner breach confidentiality here? What about *Duty of Care*? If they break confidentiality, would they be causing psychological harm if they provide information for which there is no beneficial action the family can take? What about breaking this information to a partner or spouse especially if the couple are planning to have children?

v. **A child patient:** whose genetic testing results show high risk of developing a disease, but the parents refuse interventions of any sorts.

vi. **Prenatal testing:** What if the foetus's genetic testing result reveals a disease? What is the next step?

vii. **Risks:** Risk of miscarriage through small in amniocentesis and chronic villous sampling. Are we doing more harm?

viii. **Equity:** Can a person be prevented from taking up a job even though they are qualified and capable of doing the job just because they have a genetic disease?

ix. **Life altering decisions**: Patients may make decisions that will not just affect their lives but also of those of their loved ones.

x. **Choice of gender:** To balance the gender of children in the family. How ethical will this be?

Examples of Case scenarios: These cases do not reflect any general practitioners or patients specifically but were created based on discussions on genetic testing.

Case 1

A couple who had been married for 4 years where the wife who had suffered numerous miscarriages, managed to conceive successfully was in her 5th month of pregnancy. They decided to do genetic testing on the fetus based on some information they had read on the internet. The results indicated the fetus was having Down Syndrome (Trisomy 21). They wanted to have a consultation with their general practitioner as they were distraught and thinking of terminating the pregnancy

The General Practitioner validated their emotions and explored their concerns and fears. He enlightened them about the laws of abortion in Malaysia when they asked if an abortion might lessen the distress of their potential child and themselves. They were concerned about the other conditions that are often associated with children who have Down Syndrome like Fallot Tetralogy and Epilepsy. They expressed that they had no confidence in themselves to take care of a child with special needs and did not know what to do. He advised them to get more information from associations and support groups who work with children and parents who have children with Down Syndrome and start preparing themselves for their special child. He advised them to also discuss their concerns with her Obstetrician and get a second opinion if they wished. He also advised them to see a Psychologist or Psychiatrist to help them sort their emotions and distress.

Discussion:

The general practitioner listened to their concerns, advised them, the guided them to get more information. He had some knowledge on Genetic Testing, the law on abortion in Malaysia and directed them to the experts and support groups so that they could make an informed decision on the fate of their unborn child.

Examples of how he upheld the tenets of ethical principles:

Autonomy:

i) He affirmed their right to do the fetus genetic test and validated them on that when they expressed regret for having done it.
ii) They had the right to seek a second opinion from another obstetrician if they wished to

Beneficence: Guiding them towards support groups so that they can meet parents of children with Down Syndrome and hear from them firsthand on their experiences.

Non-Maleficence: He never offended them or gave them any ideas to harm the fetus.

Justice: He directed them towards the organizations and healthcare professionals who could help the patient get fairness and equity in access to health care.

Case 2:

Following the actress Angelina Jolie's decision to undergo a prophylactic double mastectomy when she discovered she was a carrier of the *BRCA1* gene, many women all over the world started panicking especially those who had family history of either breast or ovarian cancer. Angelina Jolie's mother died of ovarian cancer at the age of 56. The *BRCA1* gene significantly increases the odds of developing breast or ovarian cancer. The *BRCA2* gene also increases the chances of developing breast cancer.

A) A woman and her partner visited their GP to ask for his advice if she should get genetically tested for the BRCA1 and BRCA2 gene. She has a strong family history of breast cancer- her mother, maternal aunty and eldest sister all passed away from breast cancer. She also asked him if she could just opt for a prophylactic double mastectomy as well as a total hysterectomy with bilateral oophorectomy instead of going through the genetic testing as she was convinced that she was going to have either one of the cancers soon.
B) In an almost similar case, an unmarried lady in her 50s visited her general practitioner with the same concerns. She had lost her mother to Breast Cancer. She was keen to get herself tested for the BRCA1 gene and ready to do a prophylactic double mastectomy if her test turned out positive. She consulted her general practitioner for an expert opinion.

In both the cases, the General Practitioners advised them to see a breast surgeon and if needed an oncologist so that they could make an informed decision.

In case A, the general practitioner also advised her to consult a Gynae Oncologist who would be able to give her a better opinion about her concerns. He informed that he was not an expert on these matters, but as a rule doctors will not perform operations of these nature without evidence that a patient's life would be in danger.

In case B, it was straight forward, the general practitioner after listening and discussing with her, referred her to the Breast Surgeon for further management.

Discussion:

In both cases, all the 4 principles of ethics were adhered to by both the medical practitioners.

The patients were enlightened with further information by the general practitioners on the BRCA1 and BRCA2 gene and the risks.

Autonomy: The patients' right to decide was not taken away. Both the patients were given an explanation about their concerns, and they were referred to the experts who could help them make an informed decision.

Beneficence: By spending time explaining to the patients, both the General Practitioners showed that they had the patients' best interest at heart . By referring them to the right experts, they continued to uphold the principles of beneficence.

Non-maleficence: Both the General Practitioners demonstrated the principle of nonmaleficence when they did not just refer their patients straight to a surgeon for mastectomy. They advised the patients to the best of their knowledge and referred them for expert consultation to further guide them in their decision making.

Justice: The principle of justice was adhered to as both the patients were offered fair and equitable treatment.

Many Medical Practitioners, especially General Practitioners in Malaysia will eventually see these developments impact on their practice. Many will inevitably become more involved in the genetic management of families as testing becomes more widespread as the General Practitioner is normally the first point of contact for many patients and their families therefore it is preferable for them to have some skills in Genetic Counselling. Genetic counselling is important both before and after genetic testing so that all the implications of having a test can be understood. A General Practitioner will need to have the knowledge on how to navigate situations in which patients present self-obtained genetic screening results, along with an exploration of the implications for patient care, informed decision-making, and ethical considerations.

As medical practitioners, we have a responsibility to make sure that ethical practice of molecular medicine is upheld. The four pillars of medical ethics: Autonomy, Non-maleficence, Beneficence and Justice can easily be cast aside for financial gains and inducement by overzealous commercial companies. At the end of the day, it is our responsibility to make sure our patients do not become the victims of the commercial aspects of these technologies.

Genetic Testing and Editing in Malaysia

Malaysia is at a very young stage where genetic testing for medical purposes is concerned. To start off, we must have in place strict guidelines, legal framework and ethical standards before gene testing and gene editing can be applied here. As a nation, we will be left behind if we do not give importance to this area of medicine.

Conclusion

As much as genes influence our health, the environment plays a role as well. Patients must be made aware that there are limitations to genetic testing. While a variation in a gene may point to a higher risk of developing a disorder, it cannot tell us the severity of the disorder or when the disorder will manifest. The ethical implications, social justice and equal access to care for all are areas that must be examined scrupulously before these services are offered to the public. Dalai Lama in his book "The Universe In A Single Atom" wrote that he believes ethics has a place in science but it is the state of mind of the person wielding the instrument that determines the outcome.

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