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Unit No. 1

PRINCIPLES OF CLINICAL GENETICS AND THE ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

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ABSTRACT

Clinical genetics plays a pivotal role in genomic medicine and precision healthcare, offering insights into the understanding, diagnosis, and management of genetic conditions. This article explores the fundamental principles of clinical genetics that underpin the practice of genomic medicine. Here, we explain the genetic concepts relevant to the understanding, identification, and management of genetic conditions to equip primary care practitioners with a basic knowledge of genetics. Furthermore, as the utility of genetic testing for diagnosis continues to expand, many ethical, legal, and social implications associated with clinical genetic testing have been raised. Therefore, this article will similarly explore the ethical challenges, legal implications, and broader societal repercussions inherent to the use of genetic testing and its test results. An understanding of these current issues will give insight into the challenges individuals with genetic conditions face, and can help better integrate the practice of clinical genetics into primary care.

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Key words: clinical genetics, genetic conditions, ethical, social, legal

INTRODUCTION

Genetic conditions can affect any body system and any age group. To date, there are over 10,000 human genetic conditions caused by faulty genetic variation, also known as pathogenic variants or mutations. The field of clinical genetics focuses on the diagnosis, management, risk assessment, and genetic counselling of patients and their family members with genetic or inherited conditions. The practice of clinical genetics and genetic counselling aims to help patients and their family members manage their condition, empowering them with the information and resources to acclimatise and adapt to their genetic diagnosis.

Genetic conditions include, but are not limited to the following[1]:

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- Chromosomal: This type affects the structures that hold your genes within each cell (chromosomes). With these conditions, people are missing or have extra chromosome material.
    - These usually cause birth defects, developmental delays, and/or reproductive problems.
- Single gene disorders (monogenic) results from a single gene variant that is disease-causing (pathogenic).
    - Cystic fibrosis, muscular dystrophy, Huntington's disease, and sickle cell disease are common examples of this.
    - Most familial cancer and hereditary cancer syndromes such as hereditary breast and ovarian cancer syndrome, lynch syndrome, and neurofibromatosis type 1 are monogenic conditions.
    - Genetic cardiac conditions, which include arrhythmias, congenital heart disease, cardiomyopathy, and high blood cholesterol (familial hypercholesterolemia), can be monogenic as well.
- Multifactorial (polygenic): These conditions stem from a combination of gene variants and other factors such v as environmental and lifestyle (e.g., chemical exposure, diet, certain medications, and tobacco or alcohol use)

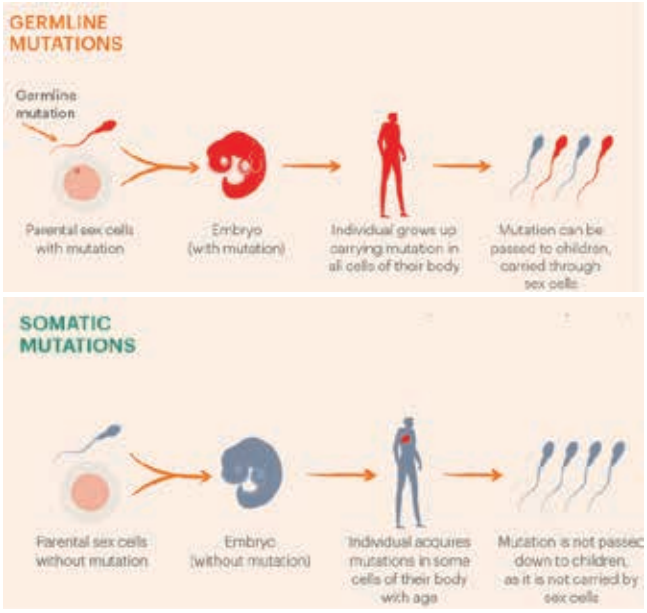
GENES, GENETIC VARIATION, AND GENETIC CONDITIONS

We have over 25,000 genes in our body that are inherited from our parents, half of which come from our father and the other half from our mother. These represent a mere 1-2 percent of the genome that our bodies need to carry out different functions.[2] Changes in our genetic material represent genetic variations and are known as gene variants, which can be identified through genetic testing. Some genetic variants are responsible for differences between people (e.g., blood type, eye colour) whereas other variants have little to no impact and can be considered common genetic variants. However, pathogenic variants can affect our health and development.[1] Health conditions that are caused by pathogenic variants are called genetic conditions. Many of these genes protect us from various diseases. For example, a cancer protection gene that is not working well (pathogenic) can increase our risk of cancer and result in a hereditary cancer syndrome.

GERMLINE AND SOMATIC GENETIC VARIANTS

There are two types of variants, namely germline and somatic variants. Germline variants are usually inherited from parents and can be passed down to the next generation. They are present in all the cells of an individual. Pathogenic germline variants are the cause of hereditary conditions. Somatic variants, on the other hand, are acquired as you age. They are not inherited from parents and are therefore not passed down to children. They are only present within tumour cells.

Figure 1. Germline vs. somatic variants. Germline variants are usually inherited and passed down to children and are found in all cells of the body. Somatic variants are acquired and not passed down to children and are only found within tumour cells.



IMPORTANCE OF FAMILY HISTORY

Family history taking, also known as constructing a pedigree to those in the field of genetics, is an important tool to facilitate clinical risk assessment of genetic conditions. A pedigree is essentially a family tree that depicts the different members (sex, age), their relationships and their medical conditions (if any). A three-generational pedigree is useful in capturing how family members are connected and how they are affected by any medical illnesses – it enables the visualisation of trends or clustering of disease/trait within the family.

In families with a genetic condition, an accurate pedigree will be important to establish the pattern of inheritance to guide differentials for genetic testing. A pedigree can also be used to exclude genetic diseases, particularly for common diseases in which lifestyle and environmental factors play an important role. Lastly, a family history can identify potential health problems and genetic conditions that an individual may be at increased risk of. For example, in Hereditary Breast and Ovarian Cancer (HBOC) Syndrome, which is an adult-onset condition, a clustering of breast, ovarian, prostate, or pancreatic cancer in family members on the same side of the family would suggest that it is hereditary or genetic in nature. Although most of cases of cancer are sporadic, about 10 percent are hereditary. Individuals with hereditary cancer syndromes like HBOC are recommended cancer risk management strategies that include earlier, more frequent screening and risk-reducing surgeries to manage and reduce their chance of developing cancer.

While family history can be used to define the occurrence of genetic conditions within a family, some genetic diseases are caused by spontaneous or *de novo* pathogenic variants. This is frequently observed in trisomy 21 (Down syndrome), cri-du-chat syndrome, 1p36 deletion syndrome, and hereditary cancer syndromes like Neurofibromatosis type 1[3] and Li-Fraumeni Syndrome.[4] Therefore, the absence of a family history alone cannot be used to rule out an underlying pathogenic variant for one's personal history suggestive of a genetic condition.

INHERITANCE PATTERNS OF GENETIC CONDITIONS

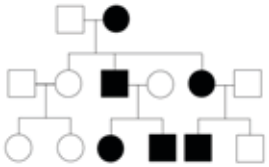
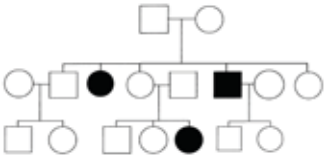
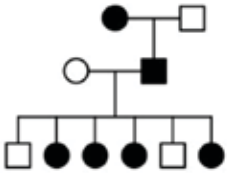
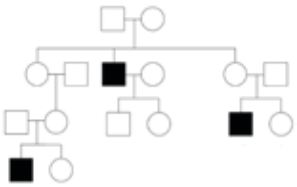
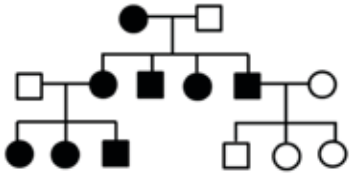
Pathogenic variants can be inherited in different ways, and understanding the ways they can be inherited or passed down affects clinical management of patients and their family members.

Variants are passed on in a Mendelian fashion and can be either dominant or recessive in nature.[1] Dominant variations are expressed when only one copy of the variant is present. Therefore, anyone who inherits one copy of the variant will have the genetic condition. Dominant conditions (refer to **Table 1**) are usually observed in every generation of the affected family, and each affected individual usually has an affected parent; all first-degree relatives have a 50 percent of inheriting the pathogenic variant. However, *de novo* or spontaneous pathogenic variants can also occur, i.e., acquired at birth. These are found in germ cells and can therefore be passed down to children. Recessive conditions (refer to **Table 1**) require two copies of the pathogenic variant, from mother and father, for disease to develop. This gives offspring a 25 percent chance of inheriting the two pathogenic variants. Recessive genetic diseases are typically not seen in every generation of an affected family. The parents of an affected person are generally carriers; these are unaffected individuals who have a copy of the pathogenic variant. If both parents are carriers of the same pathogenic gene and both pass it to the child, the child will be affected.

Genes are inherited differently on sex chromosomes (chromosomes X and Y) vs those on non-sex chromosomes (autosomes). This is because females carry two copies of the X chromosomes, whereas males carry one copy of the X and Y chromosome each.

X-linked conditions can be inherited in either a dominant or recessive manner. However, as males have a single X chromosome, any pathogenic variant on the X chromosome,

Table I. The types of inheritance patterns, its key features, pedigree, and disease examples.

Inheritance pattern	Features	Pedigree	Examples
Autosomal dominant	Each affected person has an affected parent. Occurs in every generation; both males and females can be affected.		Huntington's disease, neurofibromatosis, familial hypercholesterolaemia, hereditary breast and ovarian cancer syndrome
Autosomal recessive	Unaffected parents have affected child/children. May not be seen in every generation; both males and females can be affected.		Tay-Sachs disease, sickle cell anaemia, cystic fibrosis, phenylketonuria (PKU)
X-linked Dominant	Females are more frequently affected than males. Affected fathers will have affected daughters while affected mothers could have both affected sons and daughters.		Hypophatemic rickets (vitamin D resistant rickets), ornithine transcarbamylase deficiency
X-linked Recessive	Males are more frequently affected than females. Unaffected parents can have an affected son with his mother being a carrier. An affected father would have unaffected children.		Haemophilia A, Duchenne muscular dystrophy
Mitochondrial	Affected individuals have an affected mother as all mitochondria are inherited from the mother's egg. Affected fathers have unaffected children. Can affect both males and females.		Leber's hereditary optic neuropathy, Kearns-Sayre syndrome

whether dominant or recessive in nature, will result in disease. Females who carry two copies of the X chromosomes will not be affected by disease if they have a single recessive pathogenic variant on an X-linked gene. Females with X-linked recessive conditions have two pathogenic copies of the X-linked gene. Therefore, families with an X-linked recessive disorder often have affected males, but rarely any affected females. In dominant X-linked conditions, a pathogenic variant in one copy of an X-linked gene will result in the condition for both males and females. These families have both affected males and affected females in each generation.

Notably, fathers can pass X-linked traits only to their daughters but not to their sons as sons only inherit the Y chromosome from the father. In contrast, mothers can pass X-linked genes to both sons and daughters.

PHENOMENA THAT CAN COMPLICATE THE EXPRESSION AND HENCE THE MANAGEMENT OF GENETIC CONDITIONS

There are several principles that affect the way genetic conditions are understood, passed down, and/or expressed:

Expressivity: The degree that a particular genetic makeup (genotype) is expressed as a physical trait (phenotype) within an individual. Variable expressivity can happen where different members of the same family with the same genetic condition have different symptoms of varying severities.

Penetrance: The frequency (in percent) with which a dominant or homozygous recessive gene or gene combination manifests itself in the phenotype of the carriers. If some people with the pathogenic variant do not develop the condition, it is said to have incomplete penetrance.

Pleiotropy: Variants that result in the production of multiple, apparently unrelated, effects at the phenotypic level. For example, patients with phenylketonuria, caused by pathogenic variants in the *PAH* (phenylalanine hydroxylase) gene, have reduced hair and skin pigmentation in addition to mental retardation, resulting from toxic levels of phenylalanine in the blood.

Genetic heterogeneity: Occurs when a single genetic condition can be caused by several genes. Examples include tuberous sclerosis, which is caused by pathogenic variants in a gene on either chromosome 9 or chromosome 16, and retinitis pigmentosa, which has both autosomal

dominant and recessive and X-linked recessive forms. When considering diagnosis by gene tracking for a family, it is extremely important that genetic heterogeneity was excluded.

MOLECULAR GENETICS AND GENETIC TESTING

Advancements in molecular genetics have revolutionised the field of genetic testing. Techniques such as DNA sequencing, polymerase chain reaction (PCR), and microarray analysis have enabled the identification of specific pathogenic variants associated with various disorders. Sanger sequencing developed by Frederick Sanger in 1977 remains the gold standard for DNA sequencing[5]; however, Next-Generation Sequencing (NGS) is now largely used in view of its capacity for higher throughput, faster turnaround time, and increased cost-efficiency.[6]

The practice of clinical genetics has moved towards multi-gene testing, which presents a more time- and cost-efficient approach to obtaining a genetic diagnosis. However, more complicated cases may require exome and whole genome sequencing as part of their diagnostic journey. For example, exome and genome sequencing was able to detect pathogenic variants in 17 percent of adults and 56 percent of paediatric cancers cases that were otherwise not reported by gene panel testing.[7,8]

The use of multi-gene testing and NGS had led to the generation of vast amounts of data, which poses a challenge to process, analyse, and interpret accurately – leading to a bottleneck in variant curation and an increased incidence of variants of uncertain significance (VUS). These variants represent genetic changes that were detected through testing but whose significance is not yet known. Consensus guidelines have been published to help standardise the variant curation and classification process (refer to **Figure 2**). Possible misinterpretation of VUS results may impact clinical management. The lack of genetic literacy of clinicians and the variability of variant classification across institutions may further exacerbate the situation when a VUS is detected.[9] Therefore, in order to limit the detection of VUS, the American College of Medical and Genomics[10] recommends only testing genes that are clinically relevant to one's phenotype.

Chiang et al[11] studied the prevalence and frequency of VUS reclassification in patients of a cancer genetics service locally. They found that around 50 percent of patients receive VUS results. Reclassifications were only reported in 7 percent of cases over six years, of which 94 percent of the reclassifications were downgrades (i.e., VUS to benign/likely benign) and 6 percent were upgrades to pathogenic/likely pathogenic results. Actionable VUS upgrades and pathogenic/likely pathogenic variant downgrades that resulted in management changes occurred in 31 percent of patients. Their results emphasise the need for VUS result management to be personalised based on patient's personal history, family history, and variant details; particularly for VUS results that are clinically relevant and suspicious, follow-up is recommended every two years, as actionable reclassifications may be reported during this period.

Figure 2. Symbols used in pedigree drawing

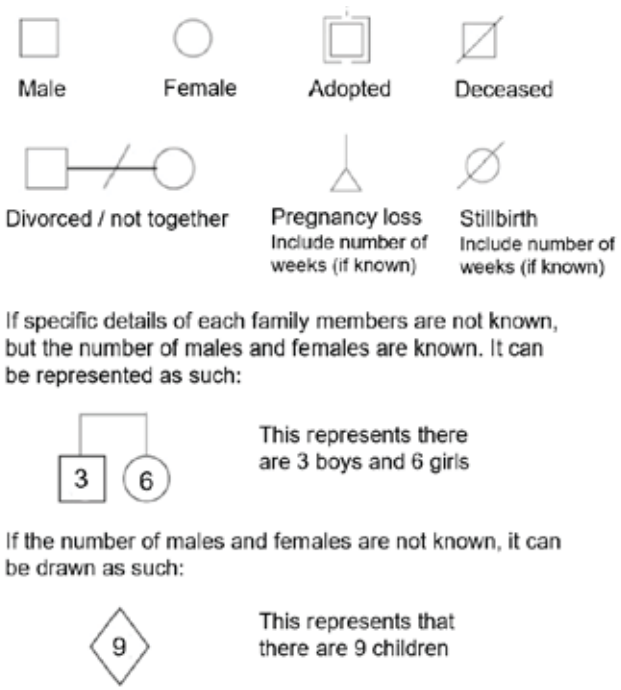
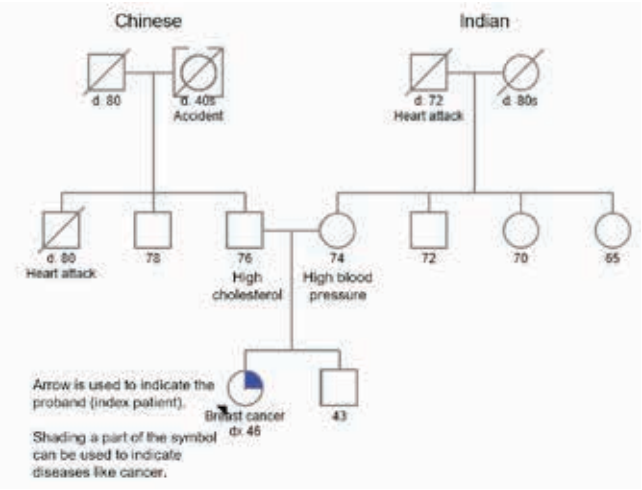


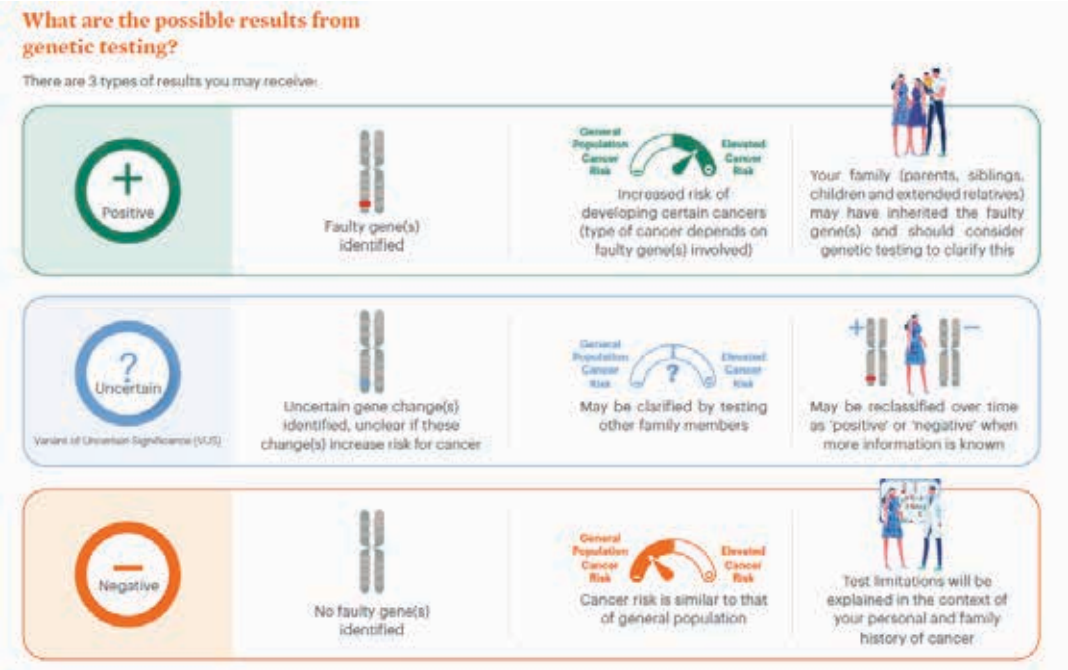
Figure 3. An example of a pedigree



POSSIBLE RESULTS FROM GENETIC TESTING

There are three possible genetic test results that patients may receive following genetic testing: positive, negative, and VUS (refer to **Figure 4**).

Figure 4. Explanation of possible genetic test results and its implications in hereditary cancer syndromes.



Positive Result

A positive result either refers to the identification of a pathogenic gene variant associated with a genetic condition or it can indicate an increased risk of a disease (like cancer). It can usually provide a diagnosis of monogenic conditions like Huntington's disease, neurofibromatosis, familial hypercholesterolaemia, and hereditary breast and ovarian cancer syndrome. Following the communication of a positive result, patients are usually counselled on their options for disease/risk management. At-risk blood relatives are also strongly encouraged to undergo cascade (single-site/family-directed) testing to determine their carrier status, allowing them to make informed decisions regarding their own health and/or risk management. A positive test result also allows clinicians to offer targeted therapies for certain hereditary forms of cancer.[12] For example, *PARP* inhibitors such as Olaparib are highly effective in patients with germline or sporadic *BRCA1/2* mutated breast, ovarian, prostate, and pancreatic cancer.[13-15] First-degree relatives (parents, siblings, children) of an individual who tested positive have a 50 percent chance of inheriting the same familial pathogenic variant within autosomal dominant conditions.

Negative Result

This indicates that no pathogenic variants were identified in the sample for the genes analysed. This usually means that the individual does not have the genetic condition in question. For people with cancer, it means their cancer is less likely to be caused by a monogenic hereditary cancer predisposition syndrome and may not respond well to targeted therapies. However, there are still limitations to such a result as there may be genes not yet discovered and therefore not included in the test. Family members of individuals with a negative test result are usually not offered further genetic testing.

Variant of Uncertain Significance (VUS) Result

These represent genetic variants that have not been sufficiently studied and characterised, and the implication of it is currently unclear.[16] Over time, as more data is collected, they may be reclassified as a negative (benign) or pathogenic positive result. VUS results should not result in any changes in clinical care. Family members of individuals with a VUS result are usually not offered further genetic testing, unless they themselves have personal histories of disease/cancer that are suspicious for a hereditary cause, of which further testing can help with resolution of the VUS classification.

THE PRACTICE OF GENETIC COUNSELLING

A big component of clinical genetics includes the practice of pre- and post-test genetic counselling. Genetic counselling is the communication process that aims to help individuals, couples, and families understand and adapt to the medical, psychological, familial, and reproductive implications of their genetic test results.[17] It is usually provided by a genetic counsellor or a clinician trained in genetics. They play a crucial role in facilitating informed decision-making, addressing psychosocial concerns, and offering support to those at risk of or affected by genetic conditions.

Genetic counselling can be provided for the following settings:

1. Genetic testing to provide a diagnosis of a genetic condition (e.g., diagnosis of a rare genetic syndrome in a child with multiple congenital anomalies; diagnosis of a hereditary cancer syndrome in an individual with a personal or family history of cancer).

2. Cascade testing for asymptomatic individuals or family members where a genetic condition has been identified (e.g., family members of individuals with cystic fibrosis

or Duchenne muscular dystrophy or hereditary breast and ovarian cancer syndrome).

3. Prenatal or preconception genetic counselling:
    - where an individual/couple is found to be (a) carrier(s) of autosomal or X-linked conditions like cystic fibrosis or fragile X syndrome, respectively.
    - where there is a personal or family history of a known genetic condition, such as spinal muscular atrophy that can affect pregnancies and offspring.

    Techniques such as chorionic villus sampling (CVS) and amniocentesis allow for the detection of chromosomal abnormalities, while carrier screening aids in assessing the risk of passing on specific genetic disorders.

4. Education and provision of risk advice where a family member has a condition that is rarely due to single gene, i.e., it is related to a polygenic condition like autism, dementia, and mental illness.

Genetic counselling is generally offered as pre- and post-test manner. Before genetic testing is conducted, pre-test genetic counselling will be arranged with a genetic counsellor and/or a genetics specialist to discuss the following:

- Personal and family history of cancer and/or disease to construct a pedigree
- Assessment of how likely a genetic condition is running in the family and whether genetic testing is recommended
- Benefits and limitations of genetic testing personalised for you and your family
- Implications of the genetic test result on insurance, legal, and privacy issues

If the patient proceeds with genetic testing, a post-test genetic counselling will be scheduled to discuss the following aspects of the genetic test result:

- What this result means for the patient and their family members
- Whether anyone else in the family should consider genetic testing
- Personalised recommendations on how to manage the genetic condition (if any) based on the result received
- Referrals to other specialities for management of the genetic condition (if needed)
- Support for patients and their family members

ETHICAL, LEGAL, AND SOCIAL ISSUES ASSOCIATED WITH CLINICAL GENETICS

Many ethical, legal, and social implications (ELSI) associated with genetic testing have been raised; these issues should be discussed with patients and families so that they are aware of the implications of genetic testing. This section provides a brief overview of some of the major ELSI concerns.

Informed Consent

A very crucial aspect of genetic counselling is to ensure that patients are informed on the pros, cons, and the process of genetic testing personalised to their circumstances, allowing them to make an educated and informed decision regarding genetic testing. These include several key points that should be explained and discussed to facilitate informed consent: i) genetic testing is voluntary; ii) risk, benefits, and limitations of testing; iii) types of genetic testing available to them; iii) details of the genetic testing process; iv) potential results and implications of genetic testing; v) impact of genetic testing results on clinical management; vi) possible emotional and psychological reactions; and lastly vii) implications of the result for family members. Patients should only decide whether or not to do genetic testing once these topics have been sufficiently explained.

Communication of Test Results

It is critical that genetic test results are discussed with patients in an understandable manner. As many genetic tests will not provide simple positive/negative results, but potentially inconclusive results like VUS results, it is important that patients are informed of all the possible test results. Notably, Asians encounter a higher VUS detection rate at 13-42 percent vs 6-27 percent in Europeans,[18-21] as Asians are, for now, under-represented in genomic sequencing databases. A local study revealed around 50 percent of patients will receive VUS test results.[16] Most VUS were eventually downgraded (94.1 percent), with a small percentage (5.9 percent) being upgraded (16). The uncertainty associated with VUS results may be challenging for both patients and clinicians.[22-25] A recent study that explored the psychosocial impact of receiving VUS results in Asians[26] revealed that VUS results may leave patients feeling confused and anxious, but this can be mitigated with pre-test and post-test counselling addressing the possibility and implications of a VUS result.[26] This highlights the need to effectively manage these patients through adequate genetic counselling, to ensure optimal patient care and prevent potential misinterpretation and confusion over test results.

Privacy of Genetic Information

The privacy of genetic information remains a major concern for patients: in particular, the question of who should have or who needs access to that information. Whilst global collaboration and data sharing is essential to extending the benefits of genomic medicine at a population level, it introduces significant concerns regarding data privacy. Specifically, it raises questions regarding how and with whom data should be stored and shared. Despite efforts to

"deidentify" or "anonymise" data by removing protected health information, such as an individual's name or date of birth, genomic sequencing in combination with other forms of demographic or clinical information are able to reveal (or have the potential to reveal) participant identifiers.[27-30]

The general public's willingness to donate their genetic material or health information to other groups (e.g., doctors, researchers, government) was found to be low.[31] Increasing trust amongst the public on how their sensitive information is managed is fundamental to increasing the willingness of people to undergo genomic sequencing in both clinical and research settings. The "*Your DNA, Your Say*" study, a global survey to gather and explore public attitudes towards genomic research, found that transparency was fundamental to public trust. A list of ranked measures that researchers can adopt to increase trust in genomic and health data sharing was compiled.[32] The following three measures were ranked as the most crucial factors to increase trust in data sharing:

1. Transparent information about who will benefit from the data access
2. The option to withdraw your information in the future
3. Knowing exactly who is using your information, and for what purpose. These reflect the public's need for transparency and autonomy in the management of their genetic information.

GENETIC DISCRIMINATION AND INSURANCE

Furthermore, concerns about privacy and genetic discrimination in areas like insurance and employment can discourage individuals from proceeding with genetic testing. There has been legislation enacted to counter genetic discrimination such as the Genetic Information Non-discrimination Act (GINA) in the USA and The EU Charter on Fundamental Rights, Article 21.1 prohibiting discrimination on "genetic features". These laws come with significant limitations though as they do not prohibit all forms of genetic discrimination.[33] For example, in the USA, companies with fewer than 15 employees are not subject to GINA regulations, and at least 10 percent of private sector employees are not covered by GINA's protections against employment discrimination.[34] On the insurance side, GINA does not prohibit life insurance companies, disability insurance companies, or long-term care insurers from using genetic information to deny coverage or raise premiums.[35] None of the countries in Asia, with the exception of South Korea and Singapore, have imposed certain guidelines to prevent genetic discrimination[36] – highlighting the fact that insurance and employment discrimination is a reality for most carriers.

Singapore introduced the "Moratorium on genetic testing and insurance" in October 2021 with the aim of preventing individuals from being deterred to undergo clinical genetic tests for any medical indications and/or participating in precision medicine research due to concerns about insurability. Under the moratorium, insurers are not allowed to ask applicants to undergo a genetic test as part of their insurance applications or request the disclosure of genetic test results that were conducted as part of research or as a result of family-directed (cascade) testing.[37]

DUTY TO DISCLOSE

As genes are shared within the family, genetic testing results have implications for family members as well. For example, when a pathogenic variant is identified in an individual with an autosomal dominant genetic condition, minimally all first-degree relatives are recommended to undergo cascade testing to determine their carrier status to guide decisions about health and risk management. However, therein lies the challenge to communicate the test result to at-risk family members. Healthcare providers like genetic counsellors and genetics professionals have an obligation to the patient who underwent testing, but not to their family members. In general, patients/probands are opposed to doctors/healthcare professionals informing at-risk members without their consent, even in cases where the disease is easily preventable for the at-risk family member. The duty to inform varies by country and state, and courts have ruled on differing sides in different cases.[38]

The American Society of Human Genetics suggests that disclosure to at-risk individuals can be considered when the following criteria are met[39]:

- Attempts to encourage result disclosure by patient have failed
- Harm to third parties is highly likely, serious, imminent, and foreseeable
- At-risk relatives are identifiable
- Disease is preventable, or medically accepted standards for treatment or screening are available
- The harm from failing to disclose outweighs the harm from disclosure

In Singapore, no such guidelines currently exist. Instead, the service actively encourages patients to disclose their results to at-risk family members, facilitating family consultations for genetic counselling. There are also efforts invested into creating a hereditary cancer registry database, where with the consent of patients, genetic counsellors reach out to at-risk family members to facilitate cascade testing.

DIRECT-TO-CONSUMER GENETIC TESTS

Direct-to-Consumer genetic testing is a recent trend where companies market genetic tests directly to consumers without requiring physician involvement. This usually does not include pre- or post-test genetic counselling and are generally discouraged as patients may not understand the type of genetic testing they are signing up for. The general

public might be drawn to DTC genetic testing in the hope it will provide information that can promote better decisions regarding their health management. This hope might be due to inaccurate advertising. A review of DTC advertising noted that the test was marketed as empowering, and genetic tests were presented as one's responsibility to take an active role in managing their health.[40]

However, there are several limitations to DTC testing. First, the predictive value of the test is low when there is no family history of disease.[41] This might lead to asymptomatic individuals overestimating their risk to certain conditions, generating unnecessary worry or anxiety. Furthermore, false positives and false negative results are common, especially where third-party variant curation services are used. Individuals may choose to act on these false positive results, which may result in unnecessary screening and/or surgeries.[42] Those with false negative results might misunderstand their risk, potentially missing opportunities for early screening and detection especially in the case of hereditary cancer syndromes. Inaccurate results can arise for a number of reasons: poor quality control for DTC genetic tests and/or the reference databases used for variation curation are outdated, with variants classified incorrectly.[42]

In Singapore, the Ministry of Health (MOH) outlines that clinical genetic testing services cannot be offered or provided by suppliers directly to consumers.[43] Therefore, clinical genetic tests for hereditary cancer syndromes like HBOC cannot be offered as DTC tests in Singapore. However, non-clinical genetic tests used for other purposes like general wellness and ancestry are considered as "low risk" and may be offered directly to consumers. Nonetheless, a guidance document was by issued by MOH in May 2021 outlining the recommended practices for providers offering non-clinical genetic testing. It also aims to educate consumers on the dangers and limitations of such testing, which may include exaggerated claims, the possible sharing and commercial use of genetic data by third parties, and the lack of proper medical interpretation of test results.[44]

DISPARITIES IN GENETIC TESTING ACCESS

Despite the advancements in genomic medicine and genetic testing, access to genetic testing can be limited due to cost, insurance coverage, and geographic disparities. Not everyone who could benefit from testing has access to it. The potential for high out-of-pocket costs to patients have frequently been cited as a barrier to genetic testing.[45] The disparity of access to genetic testing remains, with individuals in minority populations, the uninsured, non-citizens, and individuals with less education being among the most affected.[46] Economic disparities between high-, middle-, and low-income countries pose a major hurdle, particularly when there are limited healthcare resources or substantial variations in insurance coverage between populations. Furthermore, significant geographical disparities exist, with many people isolated in rural and remote communities. Increasing the genomic literacy of both the general population and the healthcare workforce and raising awareness of the ethical, legal, and social issues surrounding genetic testing is of critical importance. Addressing these challenges will require innovative and novel approaches, such as the use of technologies (e.g., telehealth, electronic consent approaches, AI-assisted chat-bots for genetic education and counselling), as well as considering the local cultural and social norms.

PSYCHOSOCIAL CONCERNS AND IMPLICATIONS

A genetic test result can identify carriers, predict diseases like cancer in presymptomatic individuals, or confirm a genetic diagnosis, which may lead to notable psychological effects, associated with increased anxiety and depression.[47] Additionally, understanding one's carrier status often marks the start of navigating challenging decisions, which includes considering one's options for screening, risk-reducing surgery, and sometimes drug-related therapies. One is also faced with the task of communicating one's genetic test result to at-risk relatives, with challenges that differ by age, sex, and life stage.[48-50] The responsibility for informing relatives of genetic test results falls on the proband, who already faces several challenges including incomplete understanding of test results, emotional distance among family members, familial conflicts, and poor communication skills.[51]

CONCLUSION

The principles of clinical genetics form the foundation of genomic and precision medicine. As the demand for genetic testing continues to grow, physicians with knowledge of key genetic concepts can help identify and manage individuals and families with genetic conditions. Their understanding and explanation of the role of genetic counselling to at-risk patients will be vital in bridging the gap for the unaware public who may benefit from genetic testing. Staying cognisant of current ethical, social, and legal issues related to genetic testing can help better integrate the practice of clinical genetics into primary care by ensuring informed consent to genetic testing, increasing access to genetic services and advocating against genetic discrimination.

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LEARNING POINTS

- **Genetic conditions can affect any body system and any age group. To date, there are over 10,000 human genetic conditions caused by faulty genetic variation, also known as pathogenic variants or mutations.**
- **The practice of clinical genetics and genetic counselling aims to help patients and their family members affected by, or at-risk of, a genetic condition to manage their condition as best as possible, empowering them with the information and resources to acclimatise and adapt to their genetic diagnosis.**
- **Ethical issues surrounding the use of genetic testing include: ensuring informed consent, privacy concerns regarding genetic information, and the issue of disclosing results to at-risk family members.**
- **Legal issues include the use of genetic testing results to affect insurability or employment and the need for more protective legislation.**
- **Social concerns include the responsibility of the patient to share a positive result with their family members and the challenges associated with a genetic diagnosis.**