Review Article

# Pitfalls in clinical genetics

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## Abstract

With the increasing availability of genetic tests, more doctors are offering and ordering such tests for their patients. Ordering a genetic test appears to be a simple process of filling in paperwork, drawing 3 mL of blood in an ethylenediaminetetraacetic acid tube and receiving a test report. This is identical to sending off a full blood count. However, it is far more complex than that. There are many potential pitfalls, as shown by the increasing number of complaints and lawsuits filed against doctors and allied health staff. Furthermore, clinical genetics involves more than just ordering tests; in fact, focusing on genetic tests alone is a potential pitfall. In this review, we discuss the common pitfalls in clinical genetics and how doctors can avoid these pitfalls to ensure patient safety and to safeguard their practice.

**Keywords:** Doctors, genetic test, informed consent, negative results, variant of uncertain significance

## INTRODUCTION

Genetic testing is increasingly being offered to patients as genetic tests become more readily available. Although the process of ordering a genetic test is simple and identical to that of a full blood count, genetic testing is far more complex than that. With the number of complaints and lawsuits filed against doctors and allied health workers on the rise, it is clear that many potential pitfalls exist in genetic testing. Clinical genetics involves more than ordering tests; in fact, a focus on genetic tests in itself is a potential pitfall. In this review, we discuss what clinical genetics involves, the types of genetic tests that are available, and the common pitfalls that doctors should avoid in order to safeguard their patients and their practice.

## WHAT IS CLINICAL GENETICS?

Clinical genetics is a medical practice that provides diagnostic, management, risk assessment, education and counselling services to individuals and/or their family members who have or are at risk of conditions with a genetic basis. While clinical genetics is usually practiced by a clinical geneticist, the Ministry of Health's (MOH) code of practice (COP) on the standards for the provision of clinical genetic/genomic testing services allows doctors with adequate experience to also provide such services (see COP section 4.3, 9.3 and 14.4).[1]

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## WHAT IS A GENETIC TEST?

The COP defines genetic tests as tests done to detect a germline or somatic variant(s), genotype(s), phenotype(s) or karyotype(s). Genetic tests can be performed on various samples such as blood, skin, saliva, buccal swab and other tissues (e.g. muscle, liver and tumours).

Genetic tests offered in Singapore are governed by laws and regulations enforced by agencies such as Health Sciences Authority and MOH. Genetic tests can be clinical or non-clinical. Box 1 shows the definition of clinical genetic testing of the MOH. Clinical genetic tests are classified as Level 1, 2 or 3, based on their risks to the individual test taker (see the COP). While this categorisation may seem novel, it is really not. For example, in the case of a patient with palpitations, all doctors can order an electrocardiogram (similar to a Level 1 test), cardiologists or trained technicians can perform an echocardiogram (similar to a Level 2 test), but only

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subspecialised cardiologists can perform electrophysiological studies (similar to a Level 3 test).

## ACCESS TO GENETIC TESTS

Depending on the nature of the genetic tests and the location of the provider, an individual can access genetic tests via a healthcare provider and/or the direct-to-consumer (DTC) retail model.

In Singapore, there are healthcare providers who provide patient access to appropriate clinical testing. These healthcare providers can be clinical geneticists (e.g. from National University Hospital and KK Women's and Children's Hospital, Singapore), or specialists who are well versed in disease-specific genetics (e.g. an oncologist who is familiar with the genetics of a particular cancer or a cardiologist who understands the genetics of cardiomyopathy). Genetic counsellors also help in these processes.

In addition, there are also thousands of clinical genetic tests offered by local- and overseas-accredited laboratories [Figure 1]. Individuals can access local or overseas DTC tests. The scope of DTC tests vary depending on consumer needs and the company's business plans. DTC tests tend to be about biometric or life-related concerns (e.g. should you drink coffee or tea?), but some overseas DTC tests provide clinically relevant tests (e.g. carrier screening, diagnostic and treatment-related testing). Hence, DTC tests are not always 'non-diagnostic' or 'non-clinical' and could be risky to the individual's safety, welfare and privacy. MOH has issued a guide on how a clinician should respond to DTC genetic testing.[2] DTC tests offered by local laboratories or local distributors must be non-clinical and are subject to Singapore's law and regulations. However, DTC tests offered by overseas laboratories are beyond the jurisdiction of Singapore's laws and regulations.

## POTENTIAL BENEFITS OF CLINICAL GENETICS

When done correctly, clinical genetics and clinical genetic testing have potential benefits for patients, including providing closure, ending the diagnostic odyssey, prognostication, guiding treatment, allowing for more accurate risk-of-recurrence counselling and risk stratification of relatives. We will not discuss these benefits in details, as they are beyond the scope of this review.

## POTENTIAL PITFALLS IN CLINICAL GENETICS

There are, however, many potential pitfalls when one is dealing with patients or family members who have or are at risk of a genetic condition. These pitfalls are summarised in Box 2. Further elaboration of these pitfalls and their possible solutions are provided in the subsequent sections.

### Failure to recognise that the patient is at risk

The average genetic patient wanders through the healthcare service on a diagnostic odyssey that lasts an average of 3–5 years. One of the contributing causes is the failure to recognise that a patient is at risk of a genetic condition. This tends to be the consequence of making certain erroneous assumptions.

1. Not taking into account family history

   Adults can be at risk of late-onset genetic conditions, and their family history can be informative. For example, the family history of an adult male who presented with acute altered mental status showed that his brother had experienced multiple episodes of drowsiness related to hyperammonaemia. This raised the suspicion of an undiagnosed urea cycle defect, and appropriate testing and treatment were immediately instituted. Failure to obtain family history in such cases may lead to increased morbidity and mortality due to delay in diagnosis.

**Box 1. Ministry of Health definition of clinical genetic testing.[2]**

If it is used for either of the following purposes:
- To confirm or exclude the presence of a genetic disease in a symptomatic person (diagnostic genetic testing)
- To predict the risk of having affected children (carrier testing)
- To predict a genetic condition in an asymptomatic person for a disease that will occur later in life (predictive screening/testing)
- To predict a person's drug response (pharmacogenetic testing)
- To predict a person's risk of developing a disease or condition (whether inherited or not inherited)
- Any purposes that purport to assess, diagnose, prevent, alleviate or a medical condition or disorder

OR

If the test reports conditions and terms, which connote meanings similar to medical conditions or induce consumers to seek further medical solutions

**Box 2. Potential pitfalls when dealing with a patient or family member who has or is at risk of a genetic condition.**

- Failure to recognise that the patient is at risk
- Failure to refer the patient to a relevant specialist
- Inappropriate tests
- Inadequate provision of information to patient
- Lack of informed consent
- Inadequate information provided to the laboratory
- Wrong test specimen sent
- Laboratory-related issues
- Variant calling-related issues
- Incorrect interpretation of test results
- Variant of uncertain significance
- Negative test reports
- Inappropriate use of data
- Inadequate risk-of-recurrence counselling
- Inadequate 'risk mitigation' strategies
- Provision of appropriate or wrong treatment
- Disclosure to next of kin
- Disclosure to minors
- Disclosure after death
- Failure to communicate results and share information with other clinicians involved in the care of the patient
- Insufficient time to deliver complex care

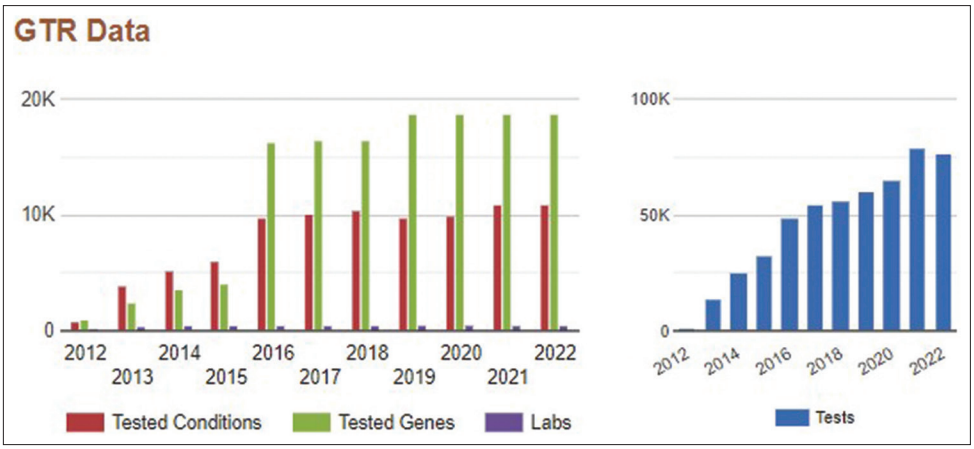


**Figure 1:** Graphs from Genetics Testing Registry (GTR®). The GTR® provides a central location for voluntary submission of genetic test information by test providers (labs). The graphs show that the number of "Tested conditions", "Tested Genes", "Labs" and "Tests" listed in the registry have been increasing over the years and that there are about 75,000 different clinical genetic tests listed in the registry in 2022. [Reproduced from: National Library of Medicine. Available from: https://www.ncbi.nlm.nih.gov/gtr/. Last accessed on 18 Aug 2021]

2. Assuming that a negative family history rules out a genetic condition
   A person with a genetic condition can be the first affected in the family. Such individuals could have a recessive genetic disease or a *de novo* disease, or be symptomatic of an incompletely penetrant condition in the family (and hence have no positive family history).
3. Not completing a comprehensive assessment of the patient
   To detect relevant signs and symptoms that could indicate a genetic condition, a doctor needs to take a comprehensive medical history (including family history) and perform a full body examination of the patient. Clinical acumen does matter. If one looks only at a single body system, one may miss important clues. Nonetheless, some signs of genetic conditions may be subtle, rare or non-specific.

## Failure to refer the patient to a relevant specialist

Failure to refer the patient to a relevant specialist stems from several possible reasons. A doctor may be convinced that there is no benefit in referring the patient to a specialist who knows genetics. The doctor may want to keep an interesting patient so that he or she can 'solve' the issue the patient is going through. The doctor may want to complete all the non-genetic tests first before referral, even though the evidence suggests that the genetic test should be done first. In some cases, the doctor does not know who to refer to.

## Inappropriate tests

Inappropriate tests recommended or ordered is one of the most common pitfalls, usually resulting from insufficient knowledge and lack of due diligence. For instance, a doctor who does not know enough about the range of genetic tests available for a particular clinical problem may offer only the test he or she is aware of, or may not offer any at all. There may be instances where the doctor does not know enough about the test ordered and assumes that the test will cover what is needed. For example, a doctor with a patient who has iron overload considers ordering a haemochromatosis gene (*HFE*) variant detection test. Some questions that may surface include: What does this test do? Should I look it up in the test catalogue? What if the test catalogue indicates that it is 'for detection of disease-causing variants, p.Cys282Tyr(C282Y) and p.His63Asp(H63D) associated with hereditary haemochromatosis'? Would this be the correct test for my patient? If my patient has Asian ancestry, would this test be appropriate, as these variants are not the common cause of iron overload in a person of Asian ethnicity? Should I order sequence analysis of the *HFE* genes (and perhaps some other related genes)?

It is thus important to look at the details of the tests. Not all gene tests are created equally, especially when it comes to gene panels. The genes included on a gene panel can vary between laboratories, as each laboratory has different criteria for gene inclusion. Some gene panels may also be outdated and may not include recently identified relevant genes. How each laboratory analyses the included genes may also differ; some will only sequence, and some will sequence and conduct deletion/duplication analysis. Additionally, disease related to some forms of genetic variation like trinucleotide repeats, methylation or mitochondrial genome may not be covered in a panel. For example, for a patient with ataxia, it would be appropriate to check if the panel includes sizing the repeats in the relevant *SCA* genes.

Sometimes, the wrong test is ordered because the doctor wrongly assumes that the disease and its causative gene have the same name. For example, if one has a patient with familial adenomatous polyposis (FAP), it would be inappropriate to order a test for the *FAP* gene, as FAP is caused by the *APC* gene.

Patients are often price conscious because many genetic tests are not covered by insurance schemes. Therefore, it would be prudent to recommend a cost-effective test to minimise expenditure. The prices of genetic tests vary even if one is testing the same genes. Furthermore, certain institutions may have access to preferential pricing. For example, to test for the

six genes known to cause recurrent pancreatitis, doing so via Sanger sequencing would cost about SGD 10,000. Conversely, a gene panel using next generation sequencing would cost about SGD 600.

## Inadequate provision of information to patient and lack of informed consent

We illustrate this pitfall with the following scenerio: If a patient has a vague mass, would it be more appropriate to say, "I think surgery may be needed. Let me know if you want surgery. If you do, I will make the referral to the surgeon." or "I think surgery may be needed. Let me refer you to a surgeon for further evaluation and discussion on the appropriate treatment."? Evidently, the latter would be the more appropriate approach, as the former approach would not have provided the patient with sufficient information to make an informed decision.

The same applies to genetic testing. It is not appropriate to say, "I think genetic testing may be needed. Let me know if you want to be tested. If you do, I will refer you to a geneticist." or "There is a genetic test available. It is a blood test and will cost SGD 500. The test results will be available within 4 weeks." Is that adequate information for informed consent? If this were a Level 3 test, the two examples would be insufficient as per COP Sections 20 and 21.

The following areas are some common deficiencies in pre-test genetic counselling: potential benefits of genetic testing; what the test can and cannot do; alternatives to genetic tests; option of not testing and its implications; cost of genetic tests; potential outcome of the results and its implications; potential adverse effects on insurance, psychological state and family; and risk of incidental findings.

In addition, one ought to be cognizant that, regardless of the type of tissue being tested, the proper procedure for a Level 3 test must be followed. For instance, a pathologist, concerned about the possibility of FAP after a review of a patient's colonic polyp specimens, will need to get the patient's consent before the specimen is sent for an *APC* gene test (as this is a Level 3 test looking for a hereditary cancer syndrome).

## Wrong specimen and/or inadequate information provided to the laboratory

Sometimes, there are issues with the specimen sent (e.g. wrong tissue sent, inadequate quantity, wrong tube used, wrong transport medium used, specimen sent at the wrong temperature). This is usually due to inadequate knowledge or failure to follow the test requirements stipulated by the laboratory.

As many diagnostic genetic tests look for changes in many genes simultaneously, the laboratory's ability to identify the causative genetic variant depends in part on the phenotype provided. Inadequate information provided to the laboratories reduces their ability to find the cause. Inadequate provision of information can be due to insufficient phenotyping and/or incomplete phenotypic detail mentioned on the order form.

## Laboratory-related issues

The choice of the laboratory makes a difference to the quality of the report. Laboratories may differ in quality assurance, ability to do good variant curation and the quality of their interpretation, despite being similarly accredited. Such information is usually unpublished, but seasoned practitioners are more likely to know which laboratories are trustworthy.

## Variant calling-related issues

Prior to 2015, there were no widely used guidelines on how to classify variants. Thus, there was discordance in variant calling (i.e. inconsistency between laboratories), as well as inaccurate variant calling. In 2015, the American College of Medical Genetics and Genomics (ACMG)-Association for Molecular Pathology (AMP) introduced guidelines on variant calling to help standardise the process. These guidelines, however, were not described for copy number variants or for somatic/cancer variant calling. Subsequently, other guidelines were introduced to cover or clarify the areas of contention. While the guidelines exist, they are imperfect. There may be differences in interpretation, which can result in discordant classification among laboratories/clinicians.

Currently, we do not know everything about genomic variation. Over time, as we learn more, some genetic variants will be reclassified. This has happened to the *MTHFR* gene. Initial studies had identified two variants as disease causing, sparking much testing and treatment for patients with these variants. Today, we know that these two variants are benign and contribute very little to the disease, and patients carrying them do not need treatment. Unfortunately, information about these 'disease variants' remains widespread on the Internet and continues to result in unnecessary treatment. There are many genes with such changes in variant classification, including genes such as the *BRCA1* gene.

Variant calling-related issues and re-classification have potential implications for doctors. If there is a test report, is it the doctor's duty to re-evaluate the patient's genomic information in the future? If there is re-classification and the patient no longer sees the doctor, does the doctor have a duty to re-contact/inform the patient? Many of these questions have no clear-cut answers.

## Incorrect interpretation of test results

Interpretation of test results is potentially very complicated. Most laboratory reports come with interpretations of the results. Some are well written and complete, while others are not as well written and may leave out important information. All laboratory reports require a clinical correlation. Additionally, knowing what a test can or cannot do has several implications on how one interprets a negative result.

Some common reasons for mistakes include:

- Not understanding the differences between heterozygote, compound heterozygote, homozygote, hemizygote, homoplasmic and heteroplasmic

- Not understanding what it means when the laboratory indicates that two variants are detected and the laboratory does not know whether the variants are in cis or in trans
- Not understanding the difference between a silent carrier and a pre-symptomatic affected individual
- Misinterpretation of a variant of uncertain significance
- Assuming that a negative report is a true negative without considering the possibility of false-negative results or residual risk
- Assuming that all tests can detect mosaicism, alternative transcript analysis, imprinting and trinucleotide repeats
- Assuming that a polymorphism is always benign
- Assuming that when a variant is rare, it must be disease causing
- Attributing disease causality based on old publications without realising that the variant has been reclassified as benign.

## Variant of uncertain significance

Variant of uncertain significance (VUS) is a classification derived from guidelines such as the ACMG-AMP. VUS means that there are insufficient criteria for the variant to be classified as likely pathogenic/pathogenic or likely benign/benign; in other words, we are not sure if this variant is disease causing. This creates difficulty in deciding whether this information should or should not be used to manage a patient. It is important for doctors to know what they can and cannot do based on a VUS result, as it has implications on patients and their families.

How do we resolve a VUS? This can be done in several ways: re-evaluate the patient very carefully (reverse deep phenotyping); conduct parental testing and familial segregation analysis; look for functional tests that can assess the impact of the variant on gene function; or await the test of time, as on average, 25% of VUS will be upgraded to likely pathogenic and 75% will be downgraded to likely benign over time.

Whose job is it to re-evaluate the VUS? Some laboratories have taken on this responsibility, periodically evaluating their reports with VUS and issuing updated reports when there is a reclassification. The onus is then left to the ordering doctor to inform the patient, although it remains a question whether it is the duty of the ordering doctor to provide this update to the patient. If the laboratory does not take on the responsibility of re-evaluation, we are then left with the question on whether the ordering doctor or the current doctor has the responsibility to re-evaluate the VUS. Re-evaluation of a VUS requires skills and knowledge in genomics, use of databases, and use of bioinformatics tools. These are highly complex areas where the novice is likely to make mistakes. What if the doctor does not have that expertise? Is the doctor still responsible?

## Negative test report

A negative test report could mean:

- The patient truly does not have a genetic cause (true negative).
- The cause has not yet been identified (false negative).
- The causative gene was not in the test (false negative).
- The causative gene was included but the part with the disease-causing variant was excluded in the test (e.g. promotor, intron, another exon and another transcript) (false negative).
- The test cannot identify certain kinds of variants (e.g. if a person tested negative on the *SMN1* carrier test and that person still has a residual risk of 1/700 of being a carrier) (small risk of being a false negative).

Hence, when there is a negative result, the doctor should consider whether there is the possibility of a false-negative result and the possibility of residual risk.

## Inappropriate use of data

Doctors have the responsibility to ensure that patients are evaluated using credible tests. If a patient has a DTC test result that is potentially actionable, the doctor has the duty to recommend that this finding be verified in a clinical laboratory before acting on it. It would be inappropriate to act on such DTC results. Sometimes, a patient who has taken a DTC genetic test may ask a doctor to conduct the data/variant analysis. It would be unwise to take on this task as the reliability of the data cannot be ascertained (e.g. one may not be able to evaluate the sequence reads or differentiate between a true sequence change and a noise that the software has flagged as a sequence change).

## Inadequate risk-of-recurrence counselling

Doctors tend to make mistakes in risk-of-recurrence counselling when it involves the first affected case in a family. For example, if a male child is the only person in the family to have haemophilia A, what is the risk of his mother having another child with haemophilia A? If one had answered '25%' to this question, about 30% of mothers would have been wrongfully deemed to be carriers of haemophilia A. This is because about 30% of new cases of haemophilia A are due to *de novo* mutations and the mothers are not carriers (and hence would not have a 25% risk of transmission in the next pregnancy).

It is important to remember that the first affected case in a family can be due to inheritance from parent(s) or a spontaneous mutation. There are also other factors that can cause a first case in the family, such as incomplete penetrance, gender-based penetrance, variable expression, mosaicism and imprinting. All these can affect the risk of recurrence.

## Inadequate 'risk mitigation' strategies and provision of inappropriate or wrong treatment

Many diverse genetic conditions exist, and their advancement in treatment can sometimes be less well known. Hence, there is a risk of inadequate 'risk mitigation' strategies and provision of inappropriate or wrong treatment. It is thus important to keep current and check for recent updates in management. While there are practice guidelines, these can lag temporally compared to the advancement of knowledge and practice. Is adhering

to practice guidelines a defensible position? Or are doctors expected to keep up to date and go beyond the guidelines when evidence suggests that the guidelines are outdated?

### Disclosure to next of kin and minors and/or disclosure after death

The COP prioritises the patient's autonomy and confidentiality over the next of kin's beneficence and non-maleficence. The clinician must guard against disclosing the patient's results to relatives if no prior authorisation was given. For example, a doctor who had previously tested and found a disease-associated variant in a patient (Ms A) is approached by the patient's sister (Ms B) requesting to be tested for the variant identified in her sister. Can the doctor oblige Ms B? In this case, if Ms A did not authorise the use of her results for Ms B, the doctor cannot order a test specifically only for Ms A's variant.

Disclosure to minors is challenging. If a minor is tested to have a genetic disease, how much does one disclose to him/her? If one chooses to delay disclosure to a minor, one should remember to disclose the information when the minor becomes an adult. One should also consider how to guard against accidental disclosure. What if the minor accidentally saw the diagnosis, did his/her own research, misunderstood the disease implications or came to harm (e.g., psychological harm, self-harm)?

What happens to genetic information after a person's death? Which next of kin has the right to the information? The current regulation suggests that genetic information should be handled as if it is a part of the deceased's estate.

### Failure to communicate results and share information

For some patients who require multi-disciplinary care, the genetic diagnosis/results must be shared and explained to the rest of the team involved in the patient's care. This will reduce the risk of morbidity, mortality, unnecessary testing and unnecessary cost to the patient.

### Insufficient time to deliver complex care

Many of the above-mentioned pitfalls can be avoided if doctors have and correctly apply the right knowledge, skills and attitudes. Even then, one must have sufficient time to do things correctly. For many healthcare workers, this is a problem, for example, clinic time allocation is insufficient to deliver such complex care.

## SOLUTIONS

To avoid the pitfalls mentioned, doctors should practice within their competencies. To do this, doctors need to be trained and kept up to date. This can be challenging as advancements in genetics and genetic testing occur rapidly, often faster than the rate of release of new handphone models. Many medical school curriculums now incorporate elements of clinical genetics. There are also postgraduate training programmes, conferences, journal articles and podcasts that can help to keep doctors up to date.

Alternatively, doctors can consider referral to the appropriate specialists. Generally, geneticists will help the doctor diagnose the patient. Geneticists usually do not want to take over the patient, as they may not be the best person to manage the patient. As such, after the diagnosis, the patient is usually sent back to the primary doctor, the domain expert in management, or co-managed by both the geneticist and the primary doctor.

We acknowledge that resources and access to appropriate specialists may be challenging at times. There is work to be done to make available referral guidelines, referral pathways and additional manpower such as genetic counsellors.

## CONCLUSION

In today's world, clinical genetics and genetic testing are becoming more complex and more common. It is essential that doctors remain aware of not only their potential benefits, but also their potential pitfalls. This will ensure safety for the patients and the healthcare worker. This review is referenced to the COP in Singapore. It is anticipated that in late 2023, the Health Care Services Act (HCSA) of Singapore will replace the COP. More information about HCSA can be found here: https://www.moh.gov.sg/hcsa/home

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### Conflicts of interest

There are no conflicts of interest.

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