Missed diagnosis or misdiagnosis: common pitfalls in genetic testing

Tarryn Shaw[1], MSc, Rose Fok[1], MBBS, FCFP, Eliza Courtney[1], MGC, Shao-Tzu Li[1], MS, Jianbang Chiang[1,2], MBBS, MRCP, Joanne Ngeow[1,2,3], MBBS, MPH

[1]Cancer Genetics Service, Division of Medical Oncology, National Cancer Centre Singapore, [2]Oncology Academic Clinical Program, Duke-NUS Medical School, [3]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Abstract

Genetic testing has the power to identify individuals with increased predisposition to disease, allowing individuals the opportunity to make informed management, treatment and reproductive decisions. As genomic medicine continues to be integrated into aspects of everyday patient care and the indications for genetic testing continue to expand, genetic services are increasingly being offered by non-genetic clinicians. The current complexities of genetic testing highlight the need to support and ensure non-genetic professionals are adequately equipped with the knowledge and skills to provide services. We describe a series of misdiagnosed/mismanaged cases, highlighting the common pitfalls in genetic testing to identify the knowledge gaps and where education and support is needed. We highlight that education focusing on differential diagnoses, test selection and result interpretation is needed. Collaboration and communication between genetic and non-genetic clinicians and integration of genetic counsellors into different medical settings are important. This will minimise the risks and maximise the benefits of genetic testing, ensuring adverse outcomes are mitigated.

Keywords: Adverse outcomes, cancer, genetic services, misdiagnosis, mismanagement

INTRODUCTION

Clinical genetics is continuing to emerge as a significant discipline, with genetic testing increasingly being integrated into everyday patient care.[1-3] Appropriate genetic testing can confirm a suspected diagnosis or determine susceptibility to disease long before symptom onset occurs.[1] This offers individuals the opportunity to make informed preventative, risk-reducing, early detection, treatment and reproductive decisions.[4,5]

Pre- and post-test genetic counselling is the required standard. During a pre-test consultation, a formal risk assessment is conducted and the purpose, process, benefits and limitations of genetic testing are explained. Informed consent is obtained for individuals who are recommended to proceed with testing. The result is explained during a post-test consultation, and risk management for the patient and family is discussed.

For those who proceed with genetic testing, selection of the appropriate test and accurate interpretation of the corresponding result by the healthcare provider is fundamental and has continued to grow in complexity.[6] For example, the traditional model of genetic testing involved testing a single or finite number of genes for a particular hereditary condition, such as *BRCA1/BRCA2* in the case of Hereditary Breast and Ovarian Cancer syndrome (HBOC).[7] While this was relatively straightforward to interpret, advancements in next-generation sequencing technologies and expansion in knowledge on cancer predisposition genes have led to a transition in the genetic testing landscape to more comprehensive multi-gene panel testing. This offers the possibility to test numerous genes in a reasonably affordable manner with a relatively rapid turnaround time.[7]

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Correspondence: A/Prof Joanne Ngeow, Lee Kong Chian School of Medicine, Nanyang Technological University, Novena Campus, Headquarters & Clinical Sciences Building, 11 Mandalay Road, 308232, Singapore.
E-mail: joanne.ngeow@ntu.edu.sg

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During the analysis, genes are sequenced to determine if any heritable disease-causing DNA sequence changes, termed 'likely pathogenic/pathogenic variants', are present.[8] A likely pathogenic/pathogenic variant disrupts the gene function and causes a hereditary predisposition to cancer, and risk-management recommendations for the corresponding cancer predisposition syndrome, together with predictive testing for the family, should be offered. Other variants, such as uncertain likely benign and benign variants, can also be detected.[8] Likely benign/benign variants are non-disease causing, while variants of uncertain significance (VUSs) have unknown clinical significance for which a hereditary cause cannot be confirmed at that time. The classification of VUSs may change as further evidence evolves and should be followed up over time. Interpretation of the result from multi-gene panel testing can be complex and challenging. For instance, likely pathogenic/pathogenic variants can be reported in low to moderate risk or limited evidence genes, whereby cancer risks or management options have yet to be fully characterised.[6,7] Additionally, the relatively frequent occurrence of VUS makes both result interpretation and patient management challenging.[6,7] Family histories may also be misleading, inconclusive or absent,[1] leading to challenges in ordering the correct test and interpreting the result.

Traditionally, genetic services have been largely provided by specialised genetic clinicians, such as clinical geneticists and/or trained genetic counsellors with a Master's degree.[2] More recently, the demand for genetic testing has significantly increased, largely due to technological advances leading to reduction in costs and relatively rapid turnaround times.[7] Furthermore, there has been an expansion of indicators in which genetic testing is used to guide management and treatment decisions.[9,10] This, together with the direct marketing of genetic tests to healthcare providers/the public, has increased awareness of the availability of these tests, leading to further demand.[2] With the introduction of mainstream genetic testing, defined as the implementation of genetic testing into other medical specialties, *BRCA1*/*BRCA2* genetic testing has been routinely offered to ovarian cancer patients by oncologists to assist with treatment-based decisions.[11] Evidence shows that mainstreaming of *BRCA1*/*BRCA2* testing in gynaecological-oncology clinics has been successfully implemented in some countries. However, the ability of non-genetic professionals to expand this to a more complex multi-gene approach, together with their views about offering this, is unknown.[11,12]

With the increased demand for genetic testing, non-genetic healthcare providers are increasingly providing genetic services. Previous studies have reported that a significant number of non-genetic clinicians find it challenging ordering the appropriate genetic test,[6] have limited experience[1] and often lack the required knowledge to provide genetic services.[13,14] An incorrect test ordered or a misinterpreted genetic test result introduces risks of misdiagnosis and mismanagement, leading to negative/unfavourable consequences known as adverse outcomes. These include irreversible and unnecessary medical interventions such as prophylactic surgeries, incorrect screening recommendations, inappropriate therapies, inaccurate risk assessments and missed opportunities to reduce risks or prevent a disease.[1,2] If errors in diagnosis are not identified, potentially preventable disease could progress undetected.[1] Such errors could potentially lead to iatrogenic harm, resulting in wide-ranging and long-lasting consequences[1,6] and could place clinicians at professional, legal and financial risk.[1]

Given the complexity of providing genetic counselling and testing and the increased need for non-genetic professionals to provide these services, it is fundamental to support and ensure they are adequately equipped with knowledge/skills to do so. We describe three cases as teachable examples where patient adverse outcomes had occurred following a misdiagnosis or missed diagnosis [Table 1]. We highlight the common pitfalls in the genetic testing process and provide recommendations to support and equip non-genetic professionals, to ensure adverse outcomes are mitigated.

CASE 1

A 42-year-old man was clinically diagnosed with Familial Adenomatous Polyposis (FAP) by his colorectal surgeon, based on the identification of 100 small adenomatous, hamartomatous and hyperplastic polyps throughout his gastrointestinal tract following upper endoscopy and colonoscopy. In view of his implicit diagnosis of FAP and its high associated risk for colorectal cancer, a restorative proctocolectomy was performed. Following the surgery, his colorectal surgeon ordered genetic testing, which failed to report an *APC* pathogenic variant associated with FAP. The patient was subsequently referred to a genetic service after his clinical diagnosis of FAP became questionable. In addition to his finding of hamartomatous polyps, a feature not associated with FAP, he had a multinodular thyroid goitre, cutaneous haemangiomas and a meningioma. On evaluation, he was found to have macrocephaly, keratosis, short stature, trichilemmomas and dysmorphic features indicative of Cowden syndrome, together with a family history of breast, gynaecological and possibly gastrointestinal cancer and intellectual disability suggestive of this condition [Figure 1]. As the patient met the clinical diagnostic criteria for Cowden syndrome,[15] genetic testing was conducted through an accredited laboratory, which reported a pathogenic variant in the *PTEN* gene, namely c.802-2A > G (splice acceptor), confirming a diagnosis of *PTEN* Hamartoma Tumour syndrome (PHTS)/Cowden syndrome. As the lifetime risk for colorectal cancer in Cowden syndrome is low (9%),[16] prophylactic colectomy is not the standard of care.[17] The patient's late age of onset and family history made a differential of FAP less likely. Genetic testing

Table 1. Summary of cases with a missed diagnosis or misdiagnosis.

Case	Clinical presentations	Misdiagnosis/missed diagnosis	Actual diagnosis	Adverse outcome	Common pitfalls
1	Multiple polyps, multinodular thyroid goitre, cutaneous haemangiomas, meningioma, macrocephaly, keratosis, short stature, trichilemmoma and dysmorphic features	Familial Adenomatous Polyposis (no genetic testing done to confirm clinical diagnosis)	*PTEN* Hamartoma Tumour syndrome (*PTEN* pathogenic variant reported after retesting)	Prophylactic proctocolectomy	• No genetic testing done at the time of clinical diagnosis • Misdiagnosis resulting in mismanagement • Increased cost from unnecessary surgery and retesting
2	Recurrent bilateral phaeochromocytomas	Multiple Endocrine Neoplasia Type 2 (based on *RET* benign variant)	Hereditary Paraganglioma–Phaeochromocytomas syndrome (*SDHD* pathogenic variant reported after retesting)	Prophylactic total thyroidectomy	• Inadequate testing ordered • Result misinterpretation resulting in mismanagement • Increased cost from unnecessary surgery and retesting
3	Breast cancer (age 32)	Hereditary Breast and Ovarian Cancer syndrome (based on *BRCA2* uncertain variant reported through research study)	Clinical significance of the variant is unknown, and the variant is not segregating with disease in the family	Risk-reducing bilateral salpingo-oophorectomy	• Result misinterpretation resulting in mismanagement • Increased cost from unnecessary surgery and retesting

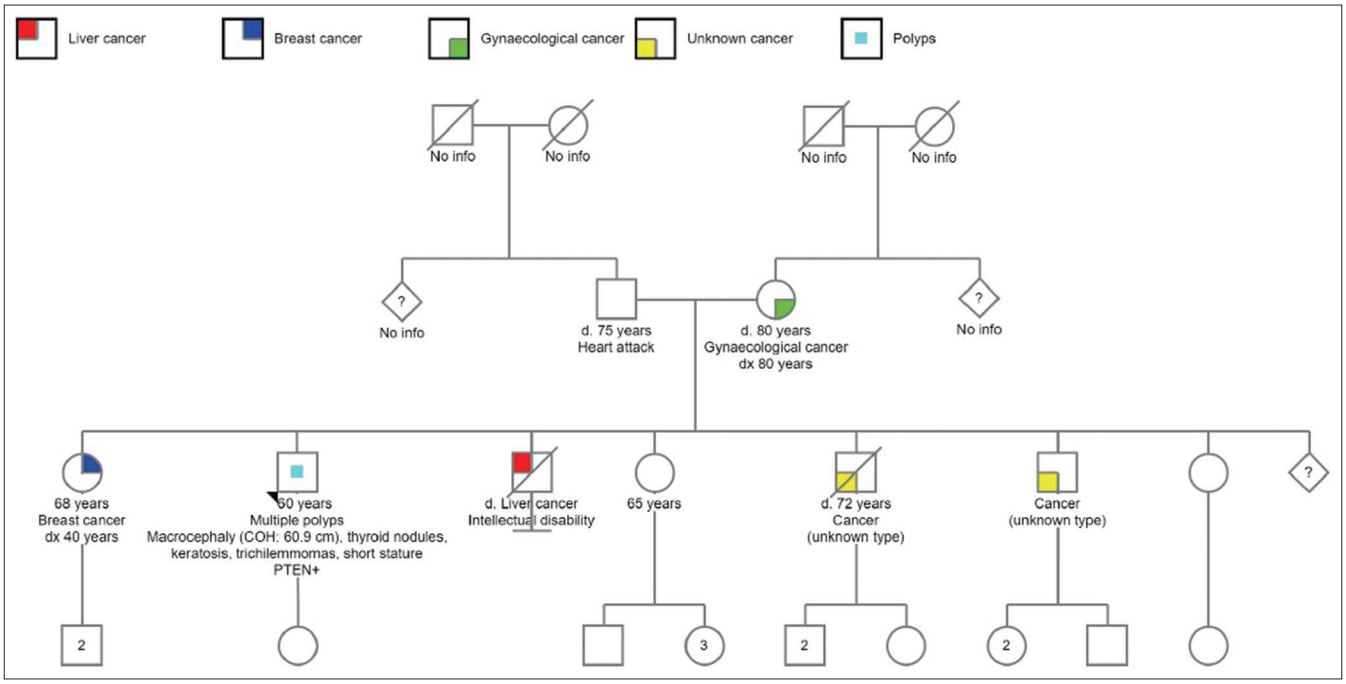

Figure 1: Case 1 family history. Clues suggestive of Cowden syndrome include: 1) the unusual clinical features the patient presented with (macrocephaly, keratosis, short stature, trichilemmomas); 2) the patient's tumour histology of hamartomatous polyps; and 3) family history of breast cancer, gynaecological cancer and intellectual disability. Clues against Familial Adenomatous Polyposis (FAP) include: 1) the later age of disease onset in affected family members; 2) family history of breast and gynaecological cancer not associated with FAP; and 3) and the patient's tumour histology of hamartomatous polyps.

would have been helpful to confirm the diagnosis first before prophylactic surgery recommendations were given.

CASE 2

A 32-year-old man had a clinical history of bilateral adrenal phaeochromocytomas diagnosed at age 12 and 19, for which he underwent bilateral adrenalectomies [Figure 2]. At the time, his endocrinologist ordered genetic testing for Multiple Endocrine Neoplasia Type 2 (MEN2), and the result reported a benign variant in the *RET* proto-oncogene, namely c.2307T> G (silent).

As early-onset predisposition to phaeochromocytomas is a hallmark of MEN2 caused by pathogenic variants in the *RET* gene, the patient's endocrinologist misinterpreted the benign variant as disease causing and misdiagnosed the patient with Multiple Endocrine Neoplasia Type 2A (MEN2A). Given that MEN2A is associated with a high risk for medullary thyroid cancer (MTC), the patient was recommended to have a prophylactic total thyroidectomy in the absence of clinical disease, which he underwent at age 28. Following recurrence of phaeochromocytoma-related symptoms at age 31, the patient sought a second opinion from a different endocrinologist, who referred him to a genetic service on suspicion of misdiagnosis. The original genetic result was reviewed and in view of the *RET* benign variant, together with the fact that he did not meet the clinical diagnostic criteria for MEN2 (≥2 specific endocrine tumours, namely MTC, phaeochromocytoma or parathyroid adenoma/hyperplasia[18]), testing for other causes of hereditary phaeochromocytoma was recommended. Panel-based genetic testing ordered through an accredited laboratory reported a pathogenic variant in the *SDHD* gene, namely c.3G>C (initiator codon), confirming a diagnosis of Hereditary Paraganglioma–Phaeochromocytoma syndrome. The previously identified *RET* variant was reported as benign, highlighting that his previous diagnosis of MEN2A was incorrect. The result eliminated the justification for this patient's previous prophylactic total thyroidectomy, as MTC is not a known risk factor associated with heritable *SDHD* pathogenic variants.[19]

CASE 3

A 30-year-old woman was referred to a genetic service on account of her personal history of breast cancer at age 30 and family history of HBOC. This condition had reportedly been diagnosed in her sister who had a history of breast cancer diagnosed at age 32. There was no family history of ovarian cancer [Figure 3]. During the consultation, a copy of her sister's genetic result was requested to confirm the diagnosis of HBOC and establish the familial pathogenic variant needed to facilitate predictive testing. Upon evaluation of the sister's genetic result, it was established that this diagnosis had not been confirmed clinically, as testing had been conducted through a genetic research study. The research result reported a *BRCA2* VUS, namely c.371T>G (p.Met124Arg), which, to our knowledge, has not been reported before or reclassified from VUS since. The sister was recommended by her gynaecologist to have a risk-reducing bilateral salpingo-oophorectomy in view of the result. Risk-reducing surgery may, in some cases, be recommended in view of clinical presentations or a significant family history; however, a VUS result should not be the basis for this decision. The sister was recommended to confirm the research result through clinical testing, which reported the same *BRCA2* VUS by an accredited laboratory. Our patient was offered multi-gene panel testing and her result was negative and did not report the *BRCA2* VUS identified in her sister. This made it less likely for the *BRCA2* VUS to be an explanation for the family history of breast cancer, as we would expect both sisters to carry the variant

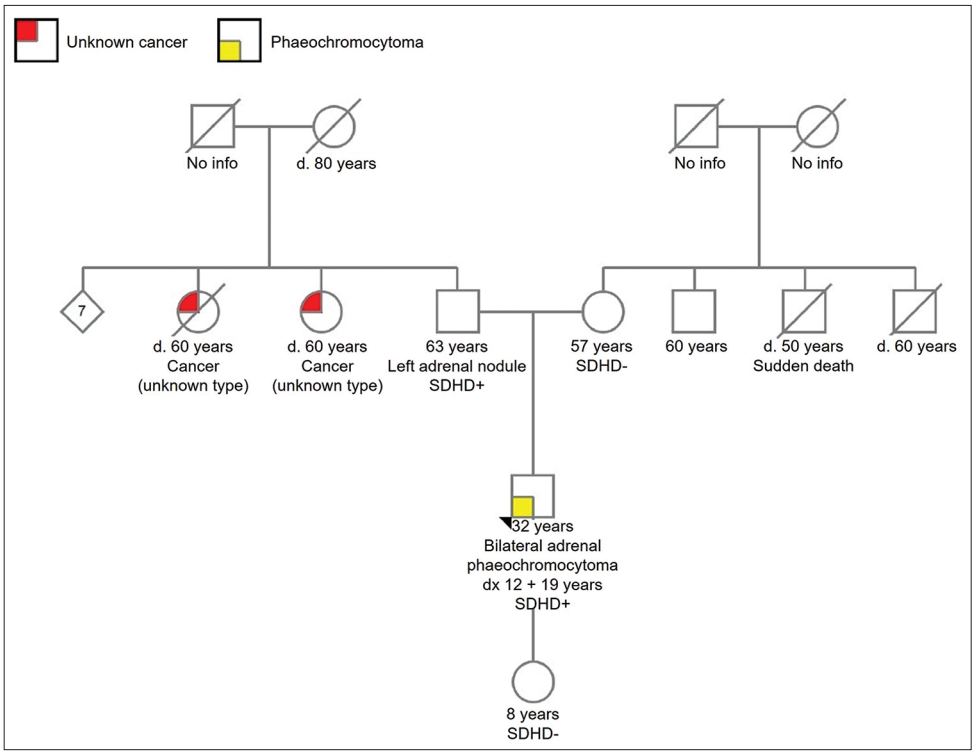

Figure 2: Case 2 family history. Clues suggesting MEN2A may not be an explanation for the patient's disease include the fact that he did not meet the clinical diagnostic criteria for MEN2A and a *RET* pathogenic/likely pathogenic variant was absent.

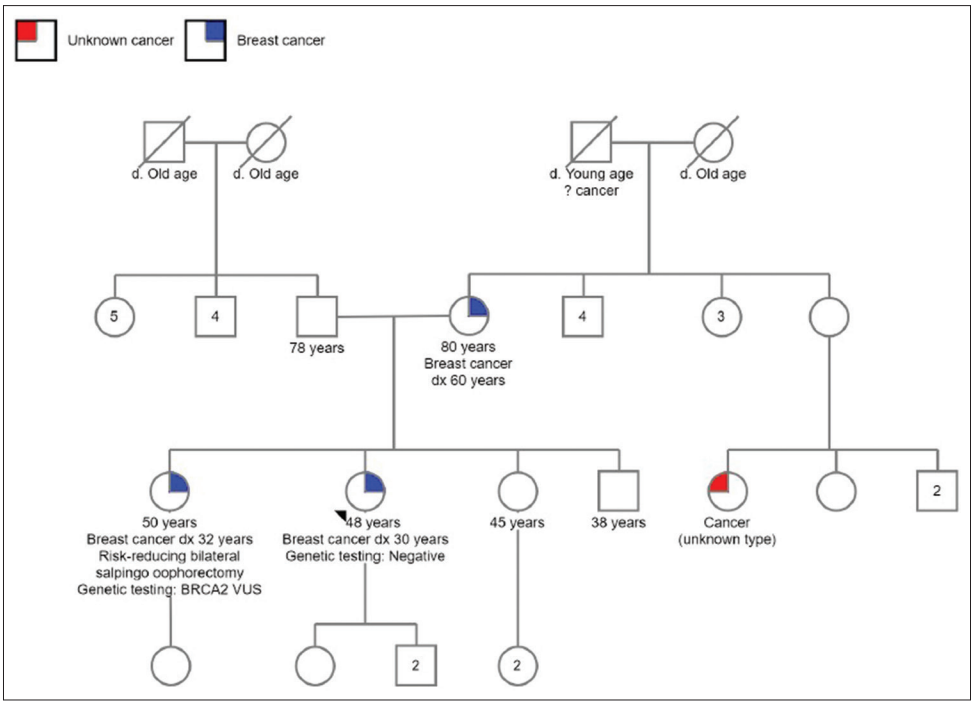

Figure 3: Case 3 family history. Clues suggesting that the *BRCA2* variant may not be an explanation for disease in this family include the fact that the variant has not been proven to be disease causing and is not carried by all family members with breast cancer. VUS: variant of uncertain significance

if this was the case. Management should have been based on the family history of breast cancer, including the recommendation for close female relatives to commence breast surveillance from a younger age than that recommended for the general population.

DISCUSSION

We report a series of misdiagnosed and/or mismanaged cases, emphasising the potential for harm when errors in the genetic testing process, or lack thereof, prompt incorrect clinical decisions [Table 1]. The cases highlight common pitfalls in genetic testing, which are as follows: 1) absent/inadequate genetic testing ordered to confirm a suspected diagnosis; 2) inappropriate patient management following misdiagnosis and/or result misinterpretation, including unnecessary prophylactic surgeries; and 3) increased liability/costs to the patient/healthcare system. Other case-specific issues include adverse psychosocial effects, subsequent distrust in the healthcare system and missed opportunities to correctly manage and/or potentially reduce cancer risks.

Case 1 demonstrates the importance of offering genetic testing to confirm a clinical diagnosis before major interventions. Clues suggestive of Cowden syndrome in this case include the unusual clinical features the patient presented with, such as macrocephaly, keratosis, short stature and trichilemmomas, the histology findings of hamartomatous polyps, and the patient's family history of breast and gynaecological cancer and intellectual disability, commonly associated with Cowden syndrome. The later age of disease onset, together with the family history, made a differential of FAP unlikely. The correct diagnosis of Cowden syndrome would have avoided a prophylactic proctocolectomy, and correct management for his family would have been recommended.

For case 2, a misdiagnosis of MEN2A and unnecessary prophylactic total thyroidectomy would have been avoided if the appropriate test was performed and the *RET* benign variant was correctly interpreted as non-disease causing. The clue to making the correct diagnosis in this case is to determine if the patient met the clinical diagnostic criteria for MEN2A and to offer multi-gene panel testing where all differentials for hereditary forms of paraganglioma/phaeochromocytoma are included. In this case, the patient did not meet the clinical diagnostic criteria for MEN2A, as he did not present with two or more specific endocrine tumours (MTC, phaeochromocytoma or parathyroid adenoma/hyperplasia), nor was a heterozygous germline *RET* pathogenic/likely pathogenic variant identified following testing.[18] Prophylactic surgery should only be offered if a pathogenic/likely pathogenic variant is reported.

Similarly, for case 3, a misdiagnosis of HBOC could have been avoided, together with unnecessary risk-reducing bilateral salpingo-oophorectomy. This misdiagnosis likely resulted from a lack of understanding that VUSs are not confirmed to be disease causing. A VUS result can be reclassified as further evidence evolves and should be followed up over time. Prophylactic surgery and predictive testing for family members should only be offered if the VUS is reclassified as pathogenic/likely pathogenic in the future.

Table 2. Approaches to inform best practice.

Pre-test
Establish a three-generation pedigree, detailing medical histories and ages of disease onset.
Review and confirm patient and family medical information, including histology.
Conduct a clinical examination to check for unusual features/presentations.
Determine if medical history, family history and/or clinical presentations are consistent with a hereditary condition and if the clinical diagnostic criteria are met.
Take note that absence of a family history does not exclude a hereditary cause.
Discuss potential differentials and inheritance pattern with the patient/family.
Discuss implications for family members if a hereditary cause is identified.
Understand and incorporate ethical considerations (e.g. patient autonomy).
Obtain informed consent.
Ordering the correct test
Ensure genetic testing laboratory is accredited.
Review reporting standards of laboratory and methodology used.
Understand testing limitations (e.g. VUSs, incidental findings, technology limitations).
Ensure all clinically relevant genes are tested.
Post-test
Correctly interpret/explain genetic result as follows:
Pathogenic/likely pathogenic variants confirm a hereditary condition. Offer risk management to the patient and predictive testing to the family.
A VUS has unknown clinical significance. Management should not be based on this result, and the classification of the variant should be followed up over time.
Benign/likely benign variants are non-disease causing.
Explain the limited value of a negative result (i.e. personal/family history could be explained by a pathogenic variant in an untested/unknown gene, polygenic or multifactorial cause, etc.).
Prophylactic surgery should only be offered following genetic testing and if a pathogenic/likely pathogenic variant is reported.
If no hereditary cause is identified/confirmed, provide recommended management based on family history.

VUS: variant of uncertain significance

These cases are described as teachable examples to highlight common mistakes in the genetic testing process and to emphasise the importance of upskilling knowledge pertaining to genomic medicine for those offering genetic services. Firstly, knowledge about genetic conditions and appropriate test selection is imperative. Multi-gene panel testing, including all possible differentials and clinically relevant genes, should be offered before risk management. Secondly, genetic result interpretation is crucial. Prophylactic surgery should only be offered in the case of pathogenic/likely pathogenic variants and should not be offered when VUSs or benign/likely benign variants are reported, unless clinically warranted. Management should be tailored according to the family history when a hereditary cause has yet to be identified. Uncertain variants should be followed up over time, as classifications may change as further evidence evolves.

Training in these key areas needs to be addressed urgently, given the current need to include non-genetic healthcare providers in the genetic testing process.[20] This urgent need stems from the current gap in the number of trained genetic professionals to meet the exponential increase in demand for services[14,20] and the continuous expansion in clinical utility of genetic testing in medicine.[3] This demand will only continue to increase as the cost of genetic testing decreases and the appeal for cost-effective multi-gene panel testing,[7] particularly for treatment-based decisions, increases. Furthermore, with the advent of mainstreaming genetic testing, it is likely that all healthcare professionals will engage in genomic medicine and be required to communicate genetic results at some point.[21]

Suggested strategies to equip non-genetic professionals with adequate knowledge/skills include educational and awareness programmes, mandatory integration of genetic knowledge into formal medical training programmes/syllabuses, requirement to conduct informal learning through clinical genetic placements and provision of comprehensive guidelines and educational support.[2,3,22,23] A minimal training/educational requirement for provision of genetic services is required.[24] We outline a number of best practice approaches in Table 2 to assist non-genetic clinicians in providing genetic services. Healthcare professionals also need to be informed when and how to refer patients to genetic services when they encounter knowledge limitations.[3] The establishment of formal collaborative relationships between genetic and non-genetic clinicians where skills can be shared,[20] as well as effective communication channels between specialists, is imperative.[23] Furthermore, as genetic counsellors have been proven to be cost effective and increase the clinical capacity,[25] integrating them into different medical settings would be beneficial and could help to better support non-genetic clinicians through the process of providing genetic services.

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Ethics approval and consent to participate

Research consent was obtained for the cases described. The study was approved by the Singhealth Centralized Institutional Review Board (CIRB number 2011/826/B).

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Conflicts of interest

There are no conflicts of interest.

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