

Challenges in genetic screening for inherited endocrinopathy affecting the thyroid, parathyroid and adrenal glands in Singapore

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ABSTRACT

Significant progress has been made in the understanding of many human diseases, especially cancers, which has contributed to improved and increased survival. The Human Genome Project and The Cancer Genome Atlas project brought about a new era, with an understanding of inherited diseases at a molecular level, which subsequently facilitated the option of precision medicine. Precision medicine has helped tailor treatment decisions at an individual level, for instance in terms of surgical treatments or targeted therapies in advanced diseases. Despite the increasing advances in genetic-lead precision medicine, this has not translated into increasing uptake among patients. Reasons for this may be potential knowledge gaps among clinicians; on reasons for poor uptake of genetic testing such as for cultural, religious or personal beliefs; and on financial implications such as lack of support from insurance companies. In this review, we look at the current scenario of genetic screening for common inherited endocrine conditions affecting the thyroid, parathyroid and adrenal glands in Singapore, and the implications associated with it.

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CLINICAL IMPACT

What is New

- Inherited endocrinopathies are usually suspected with the presentation of classic phenotypes and should be confirmed with genetic testing where feasible.
- Genetic screening has made precision medicine possible in most common endocrinopathies affecting the thyroid, parathyroid and adrenal glands.
- Outcomes of management of syndromic conditions affecting the thyroid, parathyroid and adrenal glands are not well reported in Singapore.

Clinical Implications

- Genetic screening uptake in the management of various endocrinopathies is poor in Singapore for reasons including lack of centralised care, poor patient uptake for cultural and religious reasons, and lack of insurance coverage despite subsidies in care.
- Improved effort is needed by all stakeholders including policymakers, clinicians, geneticists and patients themselves to improve outcomes in treating these rare conditions.

INTRODUCTION

In the current landscape of medicine, it is well known that most diseases incorporate a genetic component to some degree. Genetic testing of human diseases originated in the 1950s, and screening for genetic disorders followed a decade after.¹ It is worthwhile noting that the Human Genome Project (1990–2003), which sequenced the whole human genome, revolutionised the field of medicine, and thereby opened a wide array of novel avenues for screening, diagnosis and treatment of syndromic conditions.² Another landmark project in genetics, The Cancer Genome

Atlas (TCGA, since 2005) has fuelled research across the globe, and provided valuable insight into the molecular biology of about 33 human cancers.³

Genetic testing and screening encompass finding a pathogenic or likely pathogenic variant in gene(s) involved in a specific disorder in an individual. This could be in the index patient or a relative (when inheritance is involved), where findings would guide clinicians on targeted care and provide a whole new outlook on many avenues of a patient's or relative's life. Genetic testing and screening have become an integral part of patient care, with an array of tests currently available,

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ranging from presymptomatic diagnosis to genetic predisposition tests, pharmacogenomics, detection of carriers, and prenatal and new-born screening for congenital metabolic disorders.⁴ In an ever-expanding field where “genomic medicine” may become the primary modality of evaluating and managing a disease, integrating genomic medicine into clinical practice is important.

Inherited syndromic conditions are usually suspected with the presentation of classic phenotypes and should be confirmed with genetic testing where feasible. A significant proportion of endocrine syndromes seen in clinical practice has an associated genetic component, mainly affecting the thyroid, parathyroid, pituitary and adrenal glands. Currently, the clinical diagnosis is based on the anatomy of the gland involved, which helps us understand the pathophysiological mechanisms but which has significant limitations with errors in diagnosis and treatment.⁵ A clear understanding of the genotype-phenotype correlation associated with molecular phenotyping is therefore essential for the optimal diagnosis, treatment, and prognosis.⁵ Furthermore, appropriate screening may also provide an opportunity to offer prophylactic surgery in high-risk disease such as in multiple endocrine neoplasia (MEN) type 2.⁶

Despite improved availability of genetic screening, there appear to be lacunae on many fronts, which prevent an optimal management strategy for patients with inherited endocrinopathy affecting the thyroid, parathyroid and adrenal glands. In this review, we aim to investigate several of the potential issues that may have prevented uptake of genetic screening in Singapore thus far.

Endocrinopathies affecting the thyroid, parathyroid and adrenal glands

Most of the endocrine syndromes affecting the thyroid, parathyroid and adrenal glands inherited in an autosomal dominant fashion, which means that nearly 50% of first-degree relatives (FDRs) are at risk of carrying the familial pathogenic variant and would require further investigations and surveillance if found to harbour the familial pathogenic variant. In selected instances, this value is lower as some of the same syndromes present as *de novo* germline mutations (i.e. 10% of multiple endocrine neoplasia type 1 [MEN1] are *de novo* mutations⁷). The endocrinopathies affecting the thyroid, parathyroid and adrenal glands are shown in Table 1. The age of occurrence of the clinical syndrome has a wide distribution, with certain conditions occurring at an earlier age, some as young as in the first year of life, while others in later years of life. Moreover,

in these conditions, certain organs are affected earlier than others, such as the parathyroid glands in MEN1 or the thyroid gland in multiple endocrine neoplasia type 2 (MEN2) conditions.^{6,8}

It is important to note that both benign as well as malignant tumours can be seen in the thyroid, parathyroid and adrenal glands in these conditions, based on the mutational profile as highlighted in Table 1.⁹ Moreover, in syndromes such as Cowden syndrome, some malignant tumours can occur in non-endocrine organs, such as the breast and the colon.¹⁰ The importance of screening and detecting these tumours early in these inherited conditions, lies in the potential of offering prophylactic surgery, such that patients may have reduced cancer risk and enhanced quality of life.^{10,11} Index patient screening and confirmation, would also help inform family members or FDRs of any potential risks and facilitate genetic screening for them as well.

How does genetic testing help in the management of endocrine tumours?

Genetic testing helps in the appropriate management of patients with inherited endocrinopathies in terms of optimising investigations, treatment and surveillance post-intervention. In this section, we will focus on MEN1, MEN2 and familial pheochromocytoma (PCC) and paraganglioma (PGL) to illustrate how genetics play a role in some conditions affecting the thyroid, parathyroid and adrenal glands.

Pheochromocytomas and paragangliomas (PPGLs)

PPGLs were initially characterised by the now abandoned, axiom of following the 10% rule, which was used to describe PCCs/PGLs as follows: 10% are extra-adrenal, and of those, 10% are extra-abdominal; 10% are malignant; 10% are found in children; 10% of patients are normotensive; and 10% are hereditary.¹² However, we currently know that the underlying genetic cause for the condition is much higher.¹³ It is now evident that the genotype defines the phenotype of the disease, and that it thus helps us understand the pathophysiology of the disease and the biological behaviour of these tumours.¹⁴ Genetics help predict the biochemical profile as to whether the tumours are likely or unlikely to be, for instance, adrenaline or noradrenaline-secreting. In tumours that secrete predominantly noradrenaline and its products, one can conclude that the tumours are of extra-adrenal location involving the cluster 1 genes and pseudohypoxia pathway associated with Von Hippel-Lindau (VHL) and succinate dehydrogenase (SDH) mutations.¹⁵ Tumours associated with genetic alterations

Table 1. Syndromic conditions affecting the thyroid, parathyroid and adrenal glands.

Syndrome and incidence	Affected endocrine organ/s	Presentation	Earliest age of onset/mean	Inheritance	Mutated gene/s
Neurofibromatosis type 1 (NF1) 1:3,000	Adrenal	Pheochromocytoma	Adult onset/ 4th decade	AD	NF1
Multiple endocrine neoplasia type 1 (MEN1) 1:30,000	Parathyroid	1° hyperparathyroidism	Adult onset/ 95% biochemical evidence by the 5th decade	AD	MEN1
	Pancreas	Cancer	Adult onset/ middle age		
Multiple endocrine neoplasia type 2A (MEN2A) 1:35,000	Thyroid	Medullary thyroid carcinoma	Paediatric onset/ 2nd year onward	AD	RET
	Parathyroid	1° hyperparathyroidism	Adult onset/ 80% by 7th decade		
	Adrenal	Pheochromocytoma	Adult onset/ Codon 634: 70% by 6th decade		
Multiple endocrine neoplasia type 2B (MEN2B) 1:35,000	Thyroid	Medullary thyroid carcinoma	Paediatric onset/ Codon 918: infancy	AD	RET
	Adrenal	Pheochromocytoma	Adult onset/ risk from 2nd decade		
Von Hippel-Lindau (VHL) syndrome 1:36,000	Adrenal	Pheochromocytoma	Adult onset/ 4th decade	AD	VHL
Hereditary paraganglioma syndrome Unknown incidence	Chromaffin cells	Paraganglioma	Adult onset	AD	SDH complex (SDHA, SDHB, SDHC, SDHD)
Familial adenomatous polyposis 1:8,000–18,000	Thyroid	Papillary thyroid carcinoma	Adult onset/ 3rd decade: mostly in females	AD	APC
Cowden syndrome 1:200,000	Thyroid	Papillary/follicular thyroid carcinoma	Adult onset/ 2nd to 3rd decade	AD	PTEN
Carney complex Unknown incidence	Thyroid	Papillary/follicular thyroid carcinoma	Adult onset/ as early as 2nd decade	AD	PRKAR1A
Werner (WRN) syndrome 1:200,000	Thyroid	Follicular thyroid carcinoma	Adult onset/ 3rd decade	AR	WRN

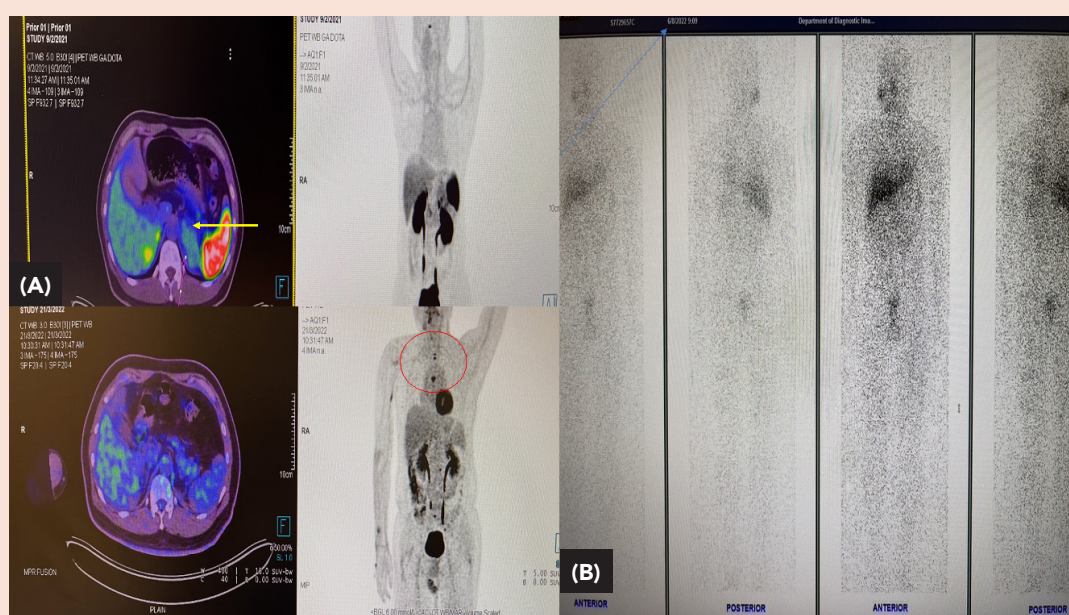
AD: autosomal dominant; AR: autosomal recessive; PRKAR1A: protein kinase cAMP-dependent type I regulatory subunit alpha; PTEN: phosphatase and tensin homologue; RET: rearranged during transfection; SDH: succinate dehydrogenase; SDHA/B/C/D: SDH complex, subunit A/B/C/D

involving the pseudohypoxia pathways tend to be more aggressive, with increased risk of malignant behaviour;¹⁶ therefore, one could argue that these tumours may be best treated by an open approach rather than with laparoscopic surgery.¹⁷ (Fig. 1)

A clinical scenario commonly encountered involves the question of whether a patient should undergo total or cortical-sparing adrenalectomy for patients with bilateral adrenal tumours (Fig. 2). There is some evidence now to suggest that patients with mutations associated with low risk

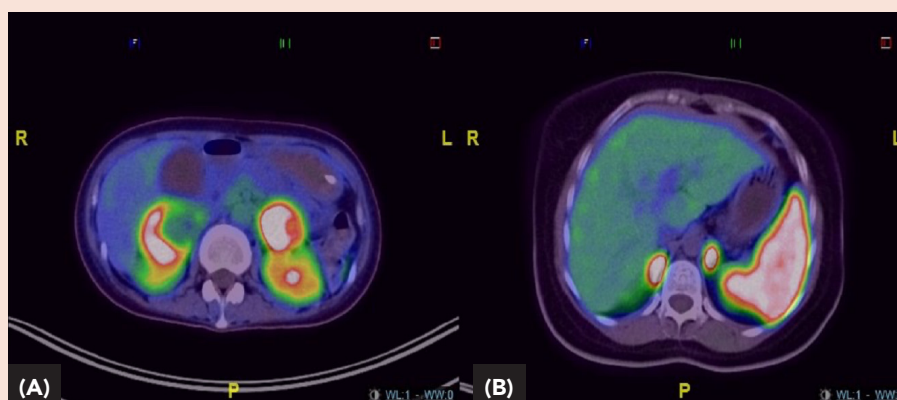
of malignancy, such as of neurofibromatosis type 1 (*NF1*), rearranged during transfection (*RET*) and *VHL* genes, should undergo a minimally invasive surgical approach and cortical-sparing adrenalectomy to prevent an Addisonian crisis and to avoid lifelong steroid replacement.¹⁸ Therefore, it is recommended that all patients with PCC/PGL should undergo genetic testing irrespective of age and family history, to help manage not only this patient but also allow for screening of the affected members.¹⁹

Fig. 1. (A) Upper panel: A patient with SDHB mutation with a large left paraganglioma with lack of avidity on Ga-DOTA PET (indicated by yellow arrow). Lower panel: Repeat DOTA PET showing multiple bony metastasis 6-months post-surgery (highlighted in red-circle). (B) MIBG scan showing no uptake due to lack of SSTR expression.



DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; Ga: gallium; MIBG: meta-iodobenzylguanidine; PET: positron emission tomography; SSTR: somatostatin receptor

Fig. 2. (A) A patient with multiple endocrine neoplasia type 2B (MEN2B) codon mutation 918 with bilateral pheochromocytomas in whom cortical sparing was not possible because of the large size of the tumours. (B) Patient with multiple endocrine neoplasia type 2A (MEN2A) with codon 634 mutation with bilateral small pheochromocytomas where cortical-sparing surgery was attempted via a retroperitoneal approach.



Multiple endocrine neoplasia type 1 (MEN1)

MEN1 is an autosomal dominant syndromic condition caused by inactivating mutations of the *MEN1* gene, a tumour suppressor gene.²⁰ Though classically described to affect the 3-P's (parathyroid, pituitary and pancreas) glands, we now know that the condition predisposes to form both endocrine and non-endocrine tumours⁸ (Fig. 3). The condition affects a range of age groups, but in nearly a fifth, the onset of disease is before the age of 21.⁸ Primary hyperparathyroidism (PHPT) is the most common manifestation, with no gender differences and characterised by elevated receptor, parathyroid hormone levels, earlier onset of osteopaenia, and asymmetrical hyperplasia of all the parathyroid glands compared to patients with sporadic PHPT.²¹ The surgical management of parathyroid disease in MEN1 is controversial in terms of what the best approach is (subtotal parathyroidectomy with bilateral thymectomy versus total parathyroidectomy and autotransplantation).^{22,23} Even more controversial is the performance of a routine prophylactic thymectomy in MEN1 to prevent thymic carcinoids.²⁴

One of the challenges that clinicians face in practice, is that in MEN1, there may be a delay in the diagnosis due to later appearance of symptoms, as shown in studies from Japan and France.^{25,26} The delay in diagnosis can have significant consequences for the patients, as the

condition is associated with high morbidity.²¹ In a Dutch study including 74 patients with MEN1, patients with a genetic diagnosis had better outcome than in those where the diagnosis was based on clinical parameters only, with fewer incidences of malignancy and death.²⁷ The mortality risk is higher in MEN1 patients compared to normal individuals or unaffected family members.²⁵ Most deaths in MEN1 were due to advanced duodenopancreatic neuroendocrine tumours and thymic carcinoids.²¹ Therefore, it is not only important to diagnose MEN1 as per the recommended guidelines, but once the disease manifests, screening should also be according to the recommendations to allow for appropriate and early interventions.²⁸

Multiple endocrine neoplasia type 2A/2B (MEN2A/2B)

This condition is characterised by the presence of medullary thyroid carcinoma, PCC and PHPT. The PCC can be unilateral or bilateral, and PHPT can be a single gland or multiglandular disease, based on the specific codon mutation. For example, in patients with codon 634 mutation in MEN2A, PHPT may present with single adenomas or hyperplastic glands, unlike in a patient with codon 918 mutation wherein no adenomas are usually seen. Therein lies in the opportunity to treat both the PHPT and medullary thyroid cancer

Fig. 3. (A) Multiple endocrine neoplasia type 1 (MEN1) patient with thymic neuroendocrine carcinoma (recurrent), (B) hyperplastic parathyroid glands, (C) non-functioning adrenal carcinoma and (D) intraoperative image showing the right adrenocortical carcinoma.

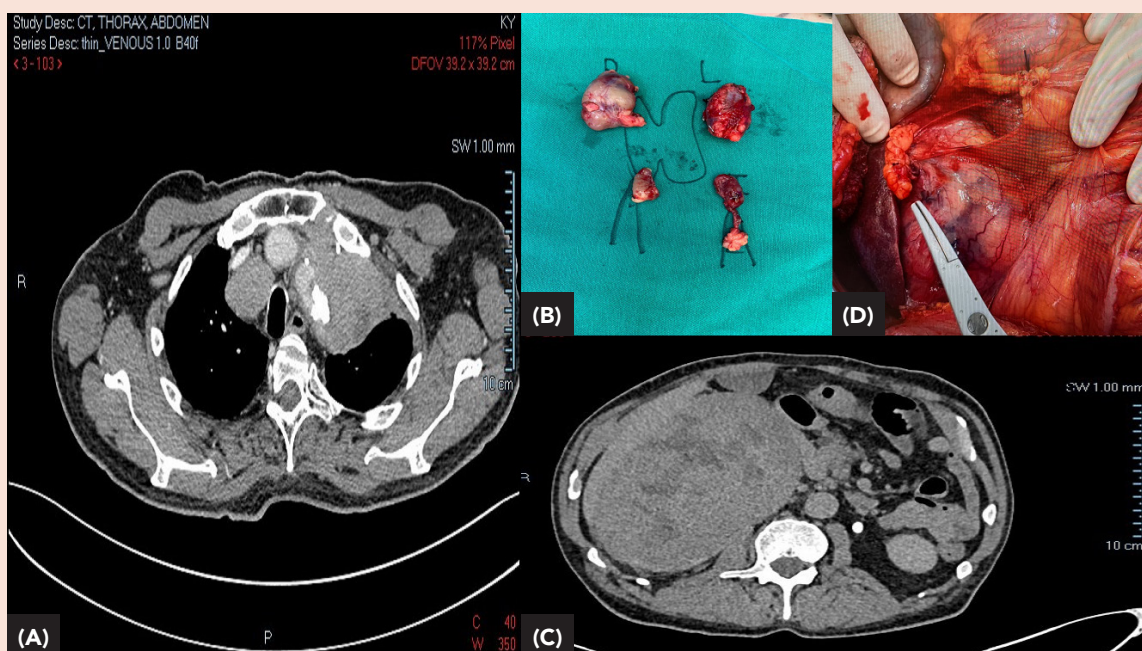


Table 2. RET gene, codon mutations and risks in inherited medullary thyroid cancer (modified from Wells et al.).³⁰

RET gene	Codon mutations	Syndrome	ATA risk	ATA recommendations for thyroidectomy
10	609 611 618 620	FMTC/MEN2A	Moderate	More than 5 years of age if basal and stimulated calcitonin levels are normal
11	630 631 666	FMTC	Moderate	More than 5 years of age if basal and stimulated calcitonin levels are normal
	634	FMTC/MEN2A	High	Less than 5 years of age
13	768 790	FMTC	Low	More than 10 years of age if basal and stimulated calcitonin levels are normal
14	804 826 840	FMTC	Low	More than 10 years of age if basal and stimulated calcitonin levels are normal
15	883	MEN2B	High	Less than 5 years of age
	891	FMTC/MEN2A	Moderate	More than 5 years of age if basal and stimulated calcitonin levels are normal
16	912		Moderate	
	918	MEN2B	Highest	Less than 1 year of age

ATA: American Thyroid Association; FMTC: familial medullary thyroid cancer; MEN2A/2B: multiple endocrine neoplasia type 2A/2B; RET: rearranged during transfection

Colours denote different levels of risk. Green: highest; yellow: high; red: moderate; blue: low

(MTC) in a patient with codon 634 mutation at the same setting. By not doing genetic testing, the patients may have suboptimal surgery and may require repeat surgical interventions, which poses significant morbidity.²⁹ Today we can risk stratify patients based on the codon mutations, and this helps the clinician to accurately predict the nature and severity of the condition in the index patient (Table 2).

What is nowadays evident from the wealth of genomic information is that there appears to be an age-related progression from C-cell hyperplasia to cancer and that this correlates with mutation risks. In clinical terms, this means that surgical cure is possible in the form of prophylactic thyroidectomy if a child has the surgery before 1 year of age for the highest risk (i.e. M918T mutation)^{29,30} and by 10 years of age in moderate high-risk mutations.²⁹ Basal calcitonin also has the potential to predict the stage of the disease in patients with MTC. In carriers of the mutation, it has been shown that if the basal calcitonin is within the normal range, MTC has usually not yet developed.³¹ When the level of calcitonin starts rising, it generally means malignant transformation is taking place, with higher levels correlating with nodal and distant metastasis, and when metastases develop, the chances of cure become slim.³¹

Current studies and data on genetic screening in Singapore

Singapore is a developed nation with an estimated population of about 5.9 million people. It has a well-established healthcare system, which is catered by both public and private hospitals. However, comprehensive genetic services are mainly provided by 2 tertiary institutions (National University Hospital and Singapore General Hospital). Genetic services, especially in cancer-related diseases, were introduced to Singapore in 2001.³² Even though healthcare is expensive in Singapore, the government provides subsidies to increase affordability for all its citizens,³² but these subsidies do not extend to genetic testing. There are some data to suggest that providing subsidies may increase uptake for genetic testing and potentially reduce the overall burden of cancer care.³³²

In terms of the incidence of cancers in Singapore, the most common cancers reported in males were colorectal, prostate and lung cancers, whereas in females, breast cancer was most common, followed by colorectal and lung cancers.³⁴ Moreover, thyroid cancers were the seventh most common cancer in women, while cancers involving the rest of the endocrine glands were uncommon. While there are some data available on breast and colorectal cancer genetics from Singapore, there seems

to be a paucity of data when it comes to familial endocrine tumours.³⁵⁻³⁹ The incidence of various endocrinopathies in Singapore is not well reported, apart from a few sporadic case reports of MTC in MEN2A and 2B.⁴⁰⁻⁴² Out of the limited published data, 2 series on PCC and PGLs nationally showed only a small proportion of patients underwent genetic testing.^{43,44}

In a series of 124 patients diagnosed with PPGLs over a period of 11 years at a tertiary institution, Chew et al. showed that while only 27/124 (21.8%) were referred for genetic testing, only 12/27 (44.4%) actually underwent testing following counselling.⁴⁴ Moreover, this study showed that only 3.7% of sporadic tumours were referred, compared to those with a known family history of syndromic conditions. In a similar fashion, results from another tertiary institution in Singapore reported that only 13/38 (34%) patients with PPGLs were referred for genetic screening over a period of 19 years.⁴³ Of those referred, 10/13 (76.9%) patients underwent multigene sequencing following counselling, of whom 7 were found to have pathogenic mutations. The authors reported that in the 25 (66%) patients who did not undergo genetic testing, the reasons for this were varied, including patient choice, cost of testing and non-referral by physicians. Overall, it is evident from both studies that there was an increased likelihood of referral to genetic services for younger patients (with 50% among them being under than 20 years old). A dramatic decrease in genetic referral was seen thereafter (14.3% among those aged ≥ 20 to < 40 years, 4.3% in those ≥ 40 to < 60 years and 2.6% in those ≥ 60 years).⁴⁴

The shortage of data on genetic screening for endocrine syndromes in Singapore could be due to several causes. An important reason is the lack of centralised care in the management of these rare conditions and therefore, not all clinicians may evaluate the patient as recommended by the various guidelines. This echoes the findings of a recent unpublished survey by the author on clinicians' attitude to genetic screening of inherited endocrinopathies across various hospitals in Europe, where a significant proportion of clinicians were not aware of any pathways or local guidelines to help them refer to a clinical geneticist. Another reason would then be insufficient genetic screening done, as highlighted in the abovementioned studies, where nearly 60% of patients were not referred for genetic screening. For most of the mentioned endocrine syndromes (Table 1), only genetic testing of index patients would confirm the diagnosis. In addition, cascade testing of FDRs is also essential. All published guidelines on the

management of most endocrine conditions, such as PCC, PGL and parathyroid cancer, advocate genetic testing for all patients with these conditions.

Challenges for genetic screening in Singapore and the way forward

In Singapore, one of the reasons for poor uptake of genetic screening and testing could be the associated costs, as reported by several studies.^{32,45} Courtney et al. in 2019, demonstrated that cascade testing (an efficient and cost-effective method of identifying high-risk patients) in FDRs was taken up more when this was offered as subsidised care, and the uptake tripled when it was offered for free.^{33,45} An additional notable observation was that the uptake of genetic screening was higher in syndromic symptomatic patients and in the young.⁴⁵ Despite variable subsidised plans being offered for certain tests, especially for breast and colon cancers, most patients must still pay out-of-pocket for testing, thus reducing the likelihood of undergoing testing. This is despite the cost of genetic testing already being significantly lower now than in the past. There is not much data on genetics in endocrine conditions in Singapore, or on uptake among index patients and FDRs.

Another important aspect which potentially obstructs genetic screening among FDRs with syndromic endocrine conditions is the role that family plays. In the Western world, patient autonomy is paramount and it is generally the patient's own choice to share their health matters with rest of the family. In syndromic conditions, this is particularly important, as not sharing could deny FDRs the opportunity to be screened for the condition to enable targeted interventions and improve survival. Conversely, in some South Asian countries, it is still practice to withhold crucial information from the patients themselves, as this is considered being more humane.⁴⁶ The treatment decisions are made by the family as a whole, in order to provide support, strength and hope to the ailing patient.^{47,48} In this light, genetic testing of index patients or FDRs could be difficult. In Singapore, there appeared to be a family-oriented approach, when cascade testing was done in clusters with inherited conditions.⁴⁵ Specifically, in our practice where patients with MEN-syndromes or PCC/PGL-syndromes were encountered, many patients declined to undergo genetic testing themselves, and in cases when they were found to be gene-positive generally, patients refused to share the information with FDRs, thus preventing appropriate treatment for them.

Furthermore, clinicians themselves probably also play a significant role in the lack of genetic

screening. Specifically, there are significant developments in genetic knowledge, and clinicians could thus find it difficult to keep up to date. This rapid pace could make clinicians feel uncomfortable, in terms of knowing which test exactly to order, or how to interpret the findings of a specific genetics test, especially for outcomes reporting on variants of unknown significance, as shown in a survey of oncologists and cardiologists.^{49,50} Moreover, to understand and explain implications to patients, solid knowledge on the inheritance and penetrance pattern is of utmost importance, which could be something that some clinicians fail to understand.⁵¹ Barriers to the uptake of genomic medicine in clinical practice by clinicians include lack of engagement and participation towards research in genomics and its implementation, and low integration of genomic data into electronic health records such as that advocated by the Implementing Genomics in Practice network.⁵²

If genetics are ignored, the diagnosis of these syndromes falls solely on obtaining a 3-generation pedigree of familial conditions during consultation. However, a detailed family history is difficult to obtain in most patients, as forgetfulness and unawareness are common. Improving awareness of these syndromes and of the available services (genetic counselling, available tests and costs) through seminars and continuous medical education platforms, could be beneficial in alleviating this issue. Moreover, grant-based research could help fill the gaps in the knowledge of the population. As discussed earlier, centralised care of patients with inherited endocrinopathies, ensures uniformity of care and better outcomes for patients.

Any decision of a patient following genetic counselling, depends on a multitude of personal factors. In this regard, understanding of genetics, and a person's background and their belief system are all major players. In a recent study on genetic literacy in Singapore, it was shown that younger participants (21–40 years), with higher level of education and above-average income had more genetic literacy.⁵³ Importantly, genetic testing was seen as an act against “the will of God” by 38.7% in this cohort. Shaw et al. assessed factors influencing screening for breast cancer among Malay women in Singapore.⁵⁴ Participants' religious beliefs, e.g. believing a disease is caused by black magic and avoiding becoming a burden to family following a positive result, were cited as reasons not to undergo screening, by non-participants of the offered screening programmes.⁵⁴ We have encountered similar patients in our clinical practice who refused genetic screening for religious beliefs, due to worries about the impact on other siblings, or the impact on marriage.

Legal and ethical aspects of genetic testing in endocrine surgical patients

It is well-known that any results of genetic testing can impose severe changes in a person's psycho-socio-economic well-being. Because of these ramifications, the ethical and legal aspects of genetic testing have been well studied and documented. Genetic counselling and testing are thus dependent on the fundamental pillars of medical ethics, i.e. patient autonomy, non-maleficence and beneficence.⁵⁵ Genetic discrimination in one's own family, in society and in the workplace are actual issues patients could face following a positive test; thus, utmost care must be applied for confidentiality. Western medical practice has developed on from “paternalism” in the clinician-patient relationship. Despite this, dilemmas could occur when a positive diagnosis of an inherited syndrome is made. In MEN2 syndrome, where germline mutations of autosomal dominant pattern would lead to MTC in 90–100%, which is the leading cause of death, clinicians could feel a duty to inform the index patient, and the FDRs as well. As mentioned above, this feeling could potentially conflict with the index patient's autonomy and the genetic counselling of FDRs could lead to discrimination in their social circles. On the other hand, people who are found to have a MEN2 mutation are offered tailored screening with serial calcitonin measurements and prophylactic total thyroidectomy, both beneficial towards their survival. In MEN2B mutations, particular consideration of ethics should be undertaken, as affected individuals may develop MTC as early as infancy, and therefore for FDRs, prophylactic surgery is advised as early as during the first year of life.^{56,57}

Two separate lawsuits in the US regarding similar inherited conditions can be applied to explain the legal issues surrounding these situations. In one of these cases, there was a failure to offer risk-reducing prophylactic surgery for a multicancer syndrome. In the other case, involving a case of familial adenomatous polyposis, it was highlighted that relaying the results to the index patient only, should be regarded as an inadequate “duty to warn”. These cases fell under medical malpractice and resulted in financial settlements.⁵⁸ How straightforward the clinician should be when discussing these results should be guided by the individual patient's concerns and this should be determined at the pre-test counselling stage.⁵⁸ Informed consent should be obtained after genetic counselling prior to testing. If the suspected index patient or FDR is mentally incapacitated and/or a minor, they can be tested with the consent of a parent or a guardian (specifically important in case

of a potential MEN2 mutation). Not only is pre-genetic test counselling important, post-genetic test counselling is as essential, and this may require the disclosure of the test's implications on family members. Unfortunately, the clinician's exact duty to inform FDRs on these implications remains unclear in guidelines.⁵⁹

An even more sensitive topic entails the reproductive considerations of adults when an inherited mutation, such as succinate dehydrogenase subunit B (SDHB) or MEN2B (codon 918), is found. Both have such high penetration, that up to 50% of offspring will be born with this mutation. Specifically, this means that MEN2B children would be exposed to surgery during infancy. Being silent yet aggressive, SDHB is in a sense even more sinister, as it is exposing individuals to lifelong surveillance at least. Raygada et al. reported a cohort of patients with an SDH-mutation, where several patients did not alter their initial intents of having children, even after a detailed discussion of the course of the disease.⁶⁰ Interestingly, one patient successfully conceived through in-vitro fertilisation with pre-natal genetic screening for SDH mutation.⁶⁰

Genetic discrimination and insurance

In 2018, the Singapore's Ministry of Health released a code of practice in genetic testing, though this has been rescinded. These guidelines categorise genetic testing for inherited syndromes as so-called "Level 3" testing (germline mutation testing).⁵⁹ As discussed, testing positive for an inherited syndrome can result in genetic discrimination. From a financial standpoint, an individual's employability may change in light of this type of diagnosis,⁶¹ in turn leading to unemployment, reassignments and resignations, all potentially culminating in economic constraints. Conversely, in the case of FDRs, a negative test could result in "survivor's guilt". Additionally, life, health and disability insurance companies consider not only an individual's current health risks, but also their potential future health risks, before offering coverage. Therefore, any personal genetic data predictive of such diseases (e.g. FDRs of MEN2A individuals) could diminish the chances of securing a substantial insurance policy. With the current standpoints of "genetic exceptionalism" (i.e. where genetic information is not shared), genetic data are incorporated into one's medical records, allowing them to be examined before insurance contracts.⁶¹ Genetic discrimination in health insurance could result in an individual's policy request rejected, surcharged or restricted.⁶² Some countries, such

as the Netherlands, have blocked insurance companies from obtaining an individual's genetic data.⁶³

CONCLUSION

Significant progress in genetics has made precision medicine possible in a wide range of inherited endocrinopathies affecting the thyroid, parathyroid and adrenal glands. Limited studies from Singapore show poor uptake of genetic screening in this country, for a wide range of reasons, which can be personal, religious or related to funding care, not only affecting the optimal management of index patient but also FDRs, who are denied the benefit of prophylactic interventions. Moreover, it seems the progress in genetics has outpaced clinicians' understanding of the complexities involved in the management of patients with inherited conditions. There needs to a concerted and coordinated effort by all the stakeholders (i.e. the Ministry of Health of Singapore, health systems, clinicians and patients) to ameliorate genetic screening, to improve outcomes for all patients with these rare conditions.

Disclosure

No conflict of interests to declare.

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