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Improving Outcomes with Genetic Testing

Diagnosing Rare Diseases with Genetic Testing

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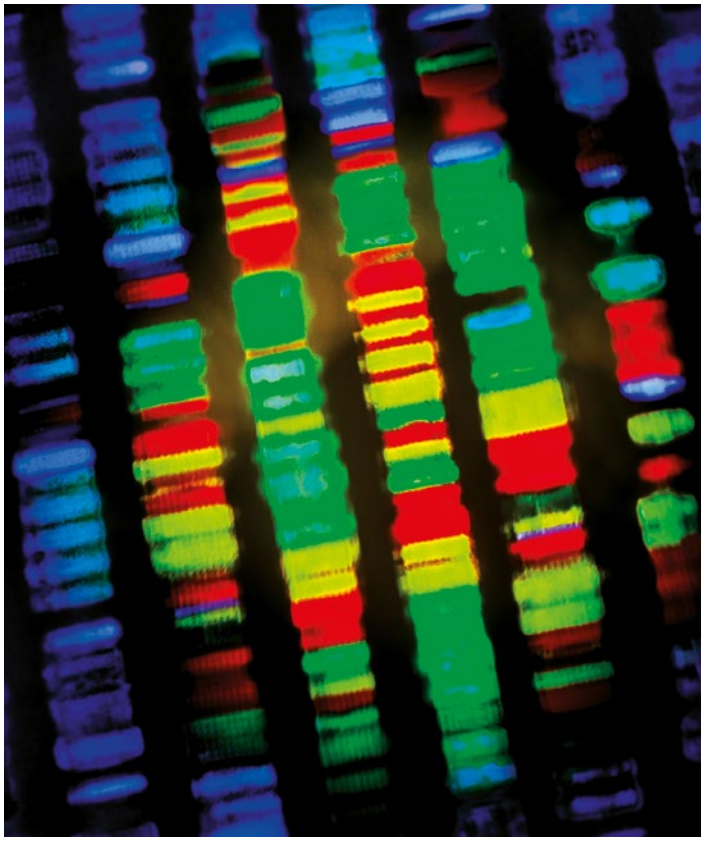
Improving Outcomes with Genetic Testing

Understanding Hereditary Cancer Predisposition Syndromes for Better Patient Outcomes

Jeanette Yuen
Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre;
Division of Medical Oncology, National Cancer Centre Singapore

Dr Chiang Jianbang
Associate Consultant, SingHealth Duke-NUS Genomic Medicine Centre;
Division of Medical Oncology, National Cancer Centre Singapore

Associate Professor Joanne Ngeow
Senior Consultant, SingHealth Duke-NUS Genomic Medicine Centre;
Division of Medical Oncology, National Cancer Centre Singapore



As the use of genetic testing increasingly impacts patient outcomes, the role of general practitioners (GPs) in the identification and care of patients at high risk for hereditary cancer becomes even more important. A GP-led model of surveillance provides a convenient and accessible platform to support adherence to screening strategies.

INTRODUCTION

The past decade has seen great strides in our understanding of the genetic basis of human disease. Arguably, the most profound impact has been in the area of cancer genetics, where cancer genes with high-penetrance familial pathogenic variants are increasingly identified. These insights have paved the way for the integration of genetics into mainstream cancer care.

Understanding the hereditary cancer predisposition syndrome that underlies one's personal and/or family history realises the potential of gene-directed cancer prevention, management and treatment.

HEREDITARY CANCER PREDISPOSITION SYNDROMES

Currently, over 400 hereditary cancer predisposition syndromes have been identified, most of which have an autosomal dominant inheritance pattern. Although many of these are rare syndromes, they account for at least 5–10% of all cancer incidence ***(Figure 1)***.

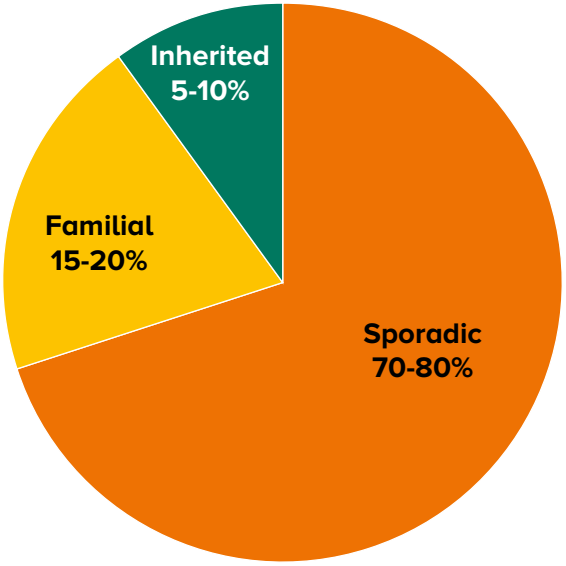


Figure 1 Inherited cancers account for about 10% of all cancers

A hereditary cancer predisposition syndrome is usually suspected in families with the following characteristics ***(Figure 2):***

- **A strong family history of cancer:** Multiple individuals diagnosed with similar types or patterns of cancer on either side (paternal or maternal) of the family
- **Young age of cancer diagnosis:** Individuals who are diagnosed with cancer (generally under the age of 50)
- **Multiple cancers:** Individuals who are diagnosed with more than one primary cancer
- **Rare tumours or cancers:** Unusual types of tumours (e.g., neuroendocrine tumours) or cancers (e.g., sarcoma)

However, due to phenotypic variability, incomplete penetrance, and gender-specific cancer risks, some families with a hereditary cancer predisposition syndrome may not meet these criteria. A negative family history of cancer does not rule out the possibility of a hereditary cancer syndrome.

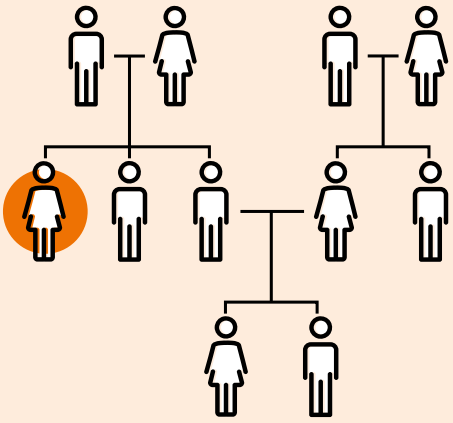
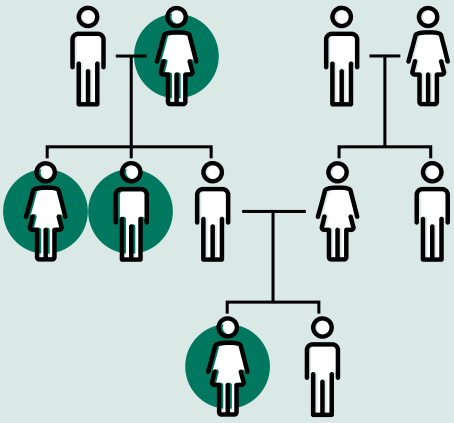
Sporadic	Inherited
	
• Later ages of onset (60-70s) • Little or no family history of cancer • Single of unilateral cancers	• Early ages of onset (under 50s) • Multiple generations with cancer • Multiple or bilateral cancers • Clustering of certain cancers (e.g., breast and ovarian)

Figure 2 Red flags for hereditary cancers

INDICATIONS FOR HEREDITARY CANCER SYNDROMES

1. **Breast cancer**
   - Hereditary breast and ovarian cancer syndrome
   - Cowden syndrome
   - Li-Fraumeni syndrome
   - Fanconi anaemia
   - Neurofibromatosis type 1
   - Hereditary diffuse gastric cancer syndrome (lobular histology)
   - Peutz-Jeghers syndrome

2. **Ovary/fallopian tube cancer**
   - Hereditary breast and ovarian cancer syndrome
   - Lynch syndrome

3. **Prostate cancer**
   - Hereditary breast and ovarian cancer syndrome

4. **Pancreatic cancer**
   - Peutz-Jeghers syndrome
   - Hereditary breast and ovarian cancer syndrome
   - Hereditary melanoma and pancreatic cancer

5. **Colorectal cancer**
   - Familial adenomatous polyposis syndrome
   - Lynch syndrome
   - Cowden syndrome
   - *MUTYH*-associated polyposis
   - Polymerase proof-reading associated polyposis
   - Juvenile polyposis syndrome

6. **Endometrial / uterine cancer**
   - Lynch syndrome
   - Cowden syndrome
   - Polymerase proof-reading associated polyposis

7. **Gastric cancer**
   - Hereditary diffuse gastric cancer syndrome
   - Lynch syndrome
   - Juvenile polyposis syndrome
   - Peutz-Jeghers syndrome

8. **Renal cancer**
   - Von Hippel-Lindau syndrome
   - Hereditary leiomyoma renal cell carcinoma
   - Birt-Hogg-Dube syndrome
   - Cowden syndrome
   - Paraganglioma-phaeochromocytoma predisposition syndromes

9. **Thyroid cancer**
   - Multiple endocrine neoplasia type 2
   - Cowden syndrome

10. **Phaechromocytoma / Paraganglioma**
    - Von Hippel-Lindau syndrome
    - Paraganglioma-phaeochromocytoma predisposition syndromes
    - Neurofibromatosis type 1

11. **Leukaemia**
    - Fanconi anaemia
    - Lynch syndrome

12. **Neuroendocrine tumour**
    - Multiple endocrine neoplasia type 1
    - Von Hippel-Lindau syndrome

13. **Adrenocortical tumour**
    - Multiple endocrine neoplasia type 1
    - Li Fraumeni syndrome

14. **Basal cell carcinoma**
    - Gorlin syndrome / nevoid basal cell carcinoma syndrome

At the Cancer Genetics Service (CGS) in the National Cancer Centre Singapore (NCCS), we have helped over 400 families identify pathogenic variants associated with a hereditary risk of cancer.

1 Hereditary Breast Cancer

Breast cancer is the most common cancer that afflicts women in Singapore. Almost 25% of breast cancer patients have an underlying breast cancer predisposition syndrome.

Breast cancer genetic testing minimally includes over 20 breast cancer susceptibility genes. Clinically, the most important of these are the *BRCA1* and *BRCA2* genes. These are high-risk breast cancer genes, where carriers of pathogenic *BRCA1/2* variants are predisposed to an increased risk of breast cancer (49–57% vs. general population risk of 12%) and ovarian cancer (18–40% vs. general population risk of 1%).

How to manage individuals at risk of hereditary breast cancer?
Female carriers of a breast cancer susceptibility gene are recommended the following screening and surveillance measures to detect signs of cancer at the earliest and most treatable stage:

- Annual mammograms and/or breast magnetic resonance imaging (MRIs)
- 6-monthly clinical breast examination
- Consider chemo-prevention drugs (e.g., Tamoxifen) on a case-by-case basis to reduce breast cancer risk
- Consider risk-reducing bilateral mastectomy and/or bilateral salpingo-oophorectomy to reduce breast and ovarian cancer incidence

Treatment implications
Cancers that arise as a result of a germline predisposition are typically managed differently from those that arise sporadically. Patients may undergo more extensive local therapy if they are at an increased risk for metachronous malignancy.

Studies have also identified *BRCA1/2* status as clinically relevant in the selection of therapy for patients already diagnosed with breast cancer. Emerging breast and ovarian cancer research indicates that *BRCA1/2* status predicts responsiveness to platinum-based chemotherapy, as well as to inhibitors of poly (ADP-ribose) polymerase (PARP), owing to the ability of these interventions to inhibit DNA repair pathways.

BRCA1/2 germline testing thus has important and expanding roles in treatment planning for subsets of patients with breast cancer.

2 Hereditary Colorectal Cancer

Colorectal cancer is the most common cancer observed in Singaporean men. Approximately 5–10% of cases are caused by a hereditary cancer predisposition syndrome.

Colorectal cancer genetic testing minimally includes over 19 colorectal cancer susceptibility genes. Clinically, the most important of these are the genes that cause **familial adenomatous polyposis** *(APC)* **and Lynch syndrome** *(MLH1, MSH2, MSH6, PMS2, and EPCAM).* Patients with familial adenomatous polyposis have a lifetime risk of colorectal cancer above 90%, while patients with Lynch syndrome are predisposed to an increased risk of colorectal cancer (20–47% vs. general population risk of 13–17%) and endometrial cancer (10–36% vs. general population risk of 6.9%).

How to manage individuals at risk of hereditary colorectal cancer?
Carriers of a colorectal cancer susceptibility gene are recommended the following measures to detect signs of cancer early:

- Annual colonoscopy from age 25
- Aspirin may decrease colorectal cancer risk, as indicated by preliminary studies
- Consider risk-reducing colectomy to reduce colorectal cancer incidence

PERSONALISED RISK MANAGEMENT

Perhaps the most important application of genetic testing is in individual cancer risk assessment. For the at-risk individual, identification of pathogenic variants in cancer predisposition genes enables risk reduction via enhanced surveillance or risk-reducing surgery.

Knowing who is at high risk allows us to intensify screening, resulting in early cancer detection and overall cost savings ***(Figure 3)***. Correspondingly, unaffected family members can avoid the inconveniences and costs of unnecessary surveillance.

GP-LED MODEL FOR SCREENING AND SURVEILLANCE

We believe that a GP-led model of surveillance for high-risk individuals poses a convenient and accessible platform for the strategies outlined above, increasing patient adherence. We support initiatives to promote multidisciplinary coordinated care, potentially through academic-community partnerships, as these are valuable opportunities to enhance care for our patients.

We welcome any interested GP partners to contact us at **cgsgroup@nccs.com.sg** or **6436 8000**.

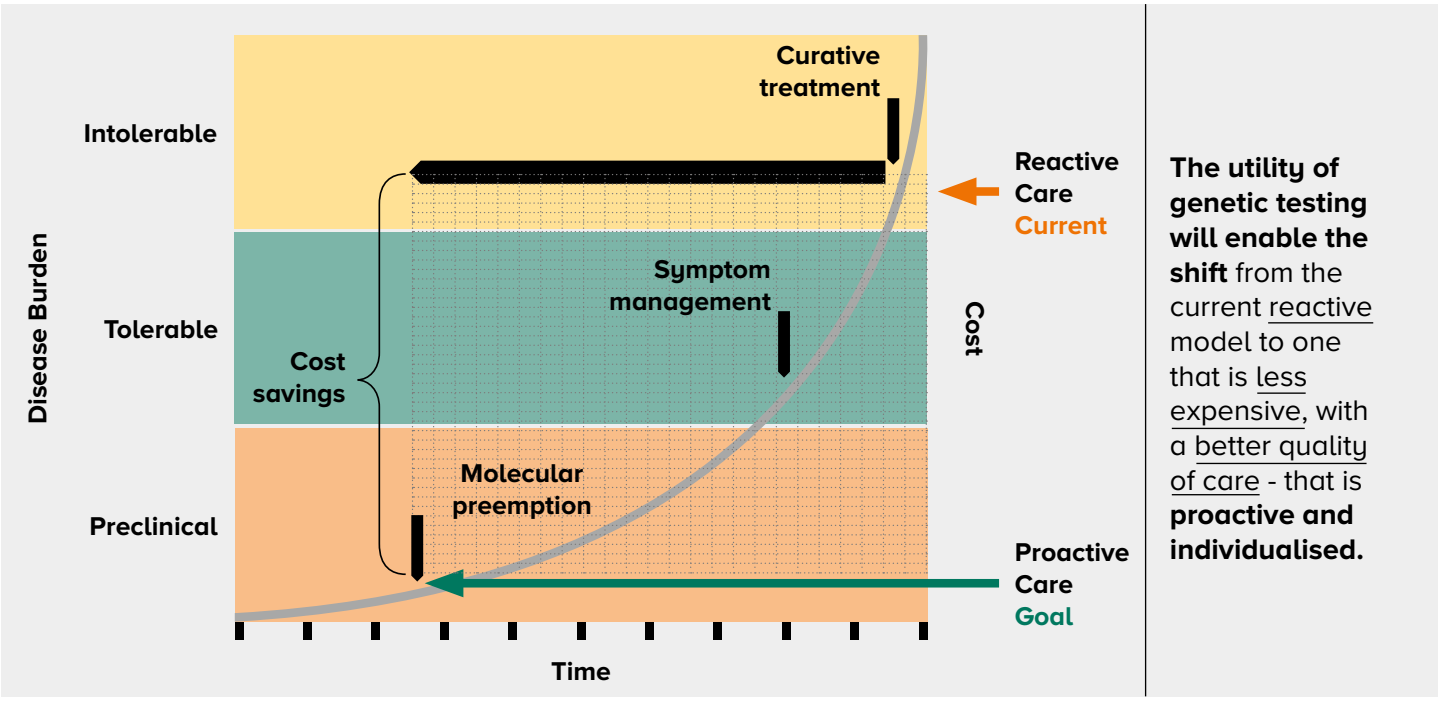


Figure 3 Genomics allow us to identify high-risk patients early

THE CANCER GENETIC SERVICE (CGS) AT NCCS

CLINICAL RESEARCH

The CGS actively contributes to research on a national and international scale. We have multiple ongoing research studies to identify novel pathogenic gene variants that predispose individuals to cancer. We are also involved in health services research to understand the psychosocial impact of hereditary cancer syndromes and are exploring the use of outreach methods to improve accessibility for cancer genetics testing. Lastly, we are also interested in the design of novel drugs tailored for gene-directed targeted treatment of patients with metastatic cancer.

EDUCATION

The team at CGS are strong advocates in raising awareness and providing education to both the public and healthcare professionals. We regularly conduct public outreach programmes to educate the public on hereditary cancers. This is often done in conjunction with our annual 'Jeans for Genes' campaign in April to raise awareness on hereditary cancers.

We contribute knowledge through various channels which include GP education forums, multidisciplinary tumour board meetings, clinical rotation training, as well as local and international workshops, conferences and lectures.

In addition to training international aspiring genetics professionals, we are actively involved in the training of medical students, doctors and nurses – where CGS is regarded as a regional and international centre for cancer genetics training.

Medical professionals are welcome to contact us at cgsgroup@nccs.com.sg or 6436 8000 if they are interested to partner with us, find out more about our educational and training opportunities, or refer a patient or family with a cancer predisposition syndrome to any of our research programmes.

National Cancer Centre Singapore
SingHealth

Jeanette Yuen

Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre;
Division of Medical Oncology, National Cancer Centre Singapore

Jeanette Yuen is a Genetic Counsellor at the National Cancer Centre Singapore. She received her Masters of Genetic Counselling from the University of Sydney, where she studied the use of internet-based platforms to facilitate population screening.

She has a keen interest in hereditary cancer syndromes and related health services research to improve patient outcomes through genetic counselling and testing.

GPs who would like more information on this topic, please contact Ms Yuen at **jeanette.yuen.x.y.@nccs.com.sg.**

National Cancer Centre Singapore
SingHealth

Dr Chiang Jianbang

Associate Consultant, SingHealth Duke-NUS Genomic Medicine Centre;
Division of Medical Oncology, National Cancer Centre Singapore

Dr Chiang Jianbang is an Associate Consultant in Medical Oncology, National Cancer Centre Singapore (NCCS). He completed his internal medicine residency at Singapore General Hospital and senior residency in medical oncology at NCCS.

He works with a dedicated team of geneticists and genetic counsellors in the Cancer Genetics Service at NCCS. He hopes to empower patients, family members and healthcare professionals with cancer genetics knowledge to improve personal and public health. His interests are in cancer genetics and lymphoproliferative disorders.

GPs who would like more information on this topic, please contact Dr Chiang at **chiang.jianbang@singhealth.com.sg.**

National Cancer Centre Singapore
SingHealth

Associate Professor Joanne Ngeow

Senior Consultant, SingHealth Duke-NUS Genomic Medicine Centre;
Division of Medical Oncology, National Cancer Centre Singapore

Associate Professor Joanne Ngeow is a Senior Consultant in Medical Oncology, National Cancer Centre Singapore (NCCS) and Associate Professor at Lee Kong Chian School of Medicine, Nanyang Technological University.

She heads the NCCS Cancer Genetics Service with an academic interest in hereditary cancer syndromes and translational cancer genetics. Her current clinical and research focus revolves around understanding cancer predisposition by studying cancers clustered in families, young adults with cancers and patients with multiple or rare cancers.

GPs who would like more information on this topic, please contact Prof Ngeow at **joanne.ngeow.y.y@singhealth.com.sg.**

GPs can call the **SingHealth Duke-NUS Genomic Medicine Centre** for appointments at the following hotlines, or scan the QR code for more information:

KK Women's and Children's Hospital
6692 2984

National Cancer Centre Singapore
6436 8288

Hope Should Not Be Rare for Patients with Rare Diseases

Sylvia Kam
Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre;
Genetics Service, Department of Paediatrics, KK Women's and Children's Hospital

Dr Koh Ai Ling
Associate Consultant, SingHealth Duke-NUS Genomic Medicine Centre;
Genetics Service, Department of Paediatrics, KK Women's and Children's Hospital

Lim Jiin Ying
Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre;
Genetics Service, Department of Paediatrics, KK Women's and Children's Hospital

Patients affected by a rare genetic disease often face a diagnostic odyssey of misdiagnosis and multiple visits across specialties. Next generation sequencing technology coupled with a multidisciplinary approach has now shortened the diagnostic journey for such patients.

INTRODUCTION

There are more than 7,000 rare diseases in the world, 80% of which are genetic in origin. Many patients embark on a diagnostic odyssey, involving numerous misdiagnoses and visits to multiple medical specialists; it takes an average of 5 years to end the odyssey and achieve a diagnosis of a rare disease. 50% of patients with rare diseases are children, of whom 30% do not live beyond their fifth birthday.

Benefits of a genetic diagnosis

Rare diseases are not always immediately identifiable to all medical specialists. A clinical diagnosis of a rare genetic condition may be established based on the presence of physical features and/or biochemical findings.

Further benefits of a genetic diagnosis include enabling patients and their families to receive advice about the familial and reproductive risks. Genetic testing is a powerful tool in establishing a genetic diagnosis for patients. However, not all patients can afford the high costs of genetic testing. With developments in technology, the costs of genetic testing have been rapidly declining.

NEXT GENERATION SEQUENCING

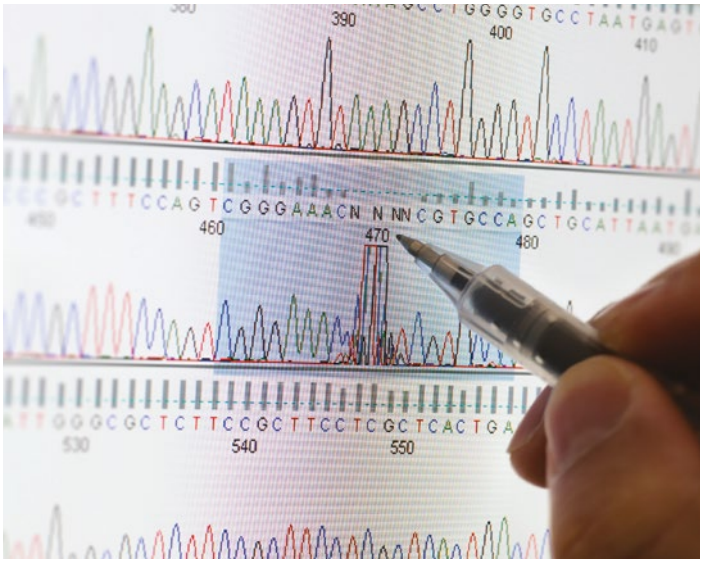
From the ability to sequence a single gene at a time, technology has advanced to be able to sequence multiple genes in parallel; this is also known as **next generation sequencing (NGS).** Instead of eliminating one gene at a time, NGS allows multiple genes, with overlapping features, to be analysed at a time. It is particularly helpful in conditions with great heterogeneity and a wide phenotypic spectrum.

NGS is available in the form of *targeted panels, exome sequencing,* or *genome sequencing*. ***Exome sequencing*** is a method of identifying possible disease-causing variants by sequencing protein-coding exons in the genome, while ***genome sequencing*** includes areas outside of the protein-coding regions. However, a key limitation is the analysis of the identified variants; the greater the area sequenced, the more variants identified for analysis, interpretation, and correlation with the patient's presentation.

Targeted panels using NGS technology have been especially beneficial for genetically heterogeneous conditions with multiple overlapping phenotypes.

In Singapore, rare diseases are defined as conditions that affect fewer than one in 2,000 people. 6–8% of the population are affected by a rare disease, many of whom have faced, or are currently on, a diagnostic odyssey. In addition, serial genetic testing in a stepwise manner may incur higher costs with no definitive diagnosis for the patient and their families. As the cost of testing decreases, more patients can access genetic testing and shorten their diagnostic odyssey.

A genetic diagnosis can impact medical management, such as directing the patient to relevant surveillance of other organ systems, if necessary, prior to the development of symptoms.

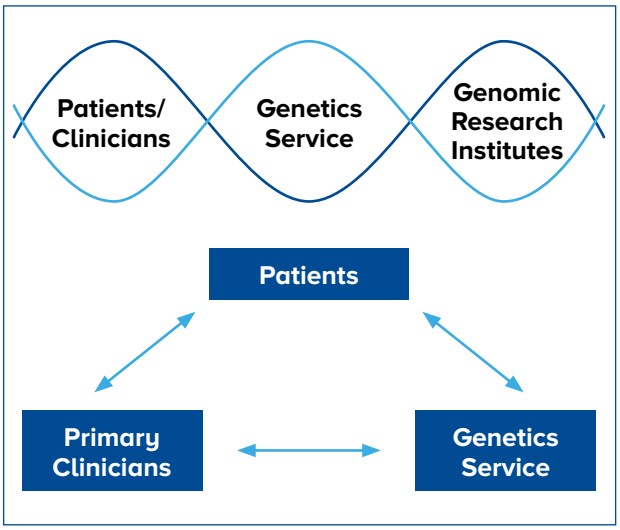


In attempts to shorten the diagnostic journey for patients with rare diseases, new initiatives utilising NGS technology together with a multidisciplinary approach have been established.

1 BRIDGES

Improving access to genetic testing

The research programme **BRIDGES (Bringing Research Innovations for the Diagnosis of GEnetic diseases in Singapore)** was established in 2014 with the primary aim of utilising genomic technologies in collaboration with genomic research institutes (Duke-NUS and A*STAR) to benefit patients and improve their health outcomes.



Over 400 patients and their family members were recruited to have their genome sequenced. It involved the collection of clinical information and family history, review and prioritisation of identified variants as well as clinical correlation. Functional validation of the findings was conducted where applicable, to support the pathogenicity of the variants in some families.

For patients who had either exome or genome sequencing, there was an overall diagnostic yield of 38.4%. In addition, cases with trio (proband and biological parents) or quad (proband, biological parents and biological sibling) sequencing yielded a better diagnostic rate than proband only or duo sequencing (proband and one first-degree relative).

Over the years, BRIDGES has allowed patients with previously undiagnosed diseases to access genetic testing and receive a genetic diagnosis, some of which have impacted their medical management. With genetic results, families can also be counselled about the recurrence risk and some have gone on to have unaffected children.

2 RAPIDSEQ

Targeting critically ill patients in NICU and CICU

A genetic diagnosis is particularly critical for the 35% of patients who will not survive their first year of life due to a rare disease. With the aim of bringing research capabilities to clinical services, a translational program, **Rapid Next Generation Sequencing (RapidSeq),** was launched in April 2018 at the KK Women's and Children's Hospital (KKH).

It is targeted at critically ill patients in the neonatal or paediatric intensive care units (NICU or CICU) with suspected underlying genetic conditions, with or without multiple congenital anomalies (defined by the involvement of two or more major organ systems *or* foetal malformations detected on foetal imaging) related to the suspected diagnosis.

RapidSeq is a multidisciplinary effort that involves sequencing and analysing targeted exonic regions of approximately 4,800 genes associated with human diseases, also known as a clinical exome. It hinges on the expertise of the clinical team, including physicians, genetic counsellors, laboratory staff and bioinformaticians, to meet the turnaround time of 10 to 14 working days ***(Figure 1).***

The clinical team first needs to assess and phenotype the patient, establishing a list of differential diagnoses, before obtaining consent for RapidSeq. The samples are processed and sequenced by the laboratory, and a list of variants generated will be filtered and prioritised using in-house computational algorithms by the bioinformatics team.

If a result is obtained, it will be disclosed to the primary care team and parents, and a preliminary report will be issued. Confirmation via Sanger sequencing will be done before a final report is issued. If no preliminary results are obtained, other tests as per the clinical indication may be considered, including exome sequencing.

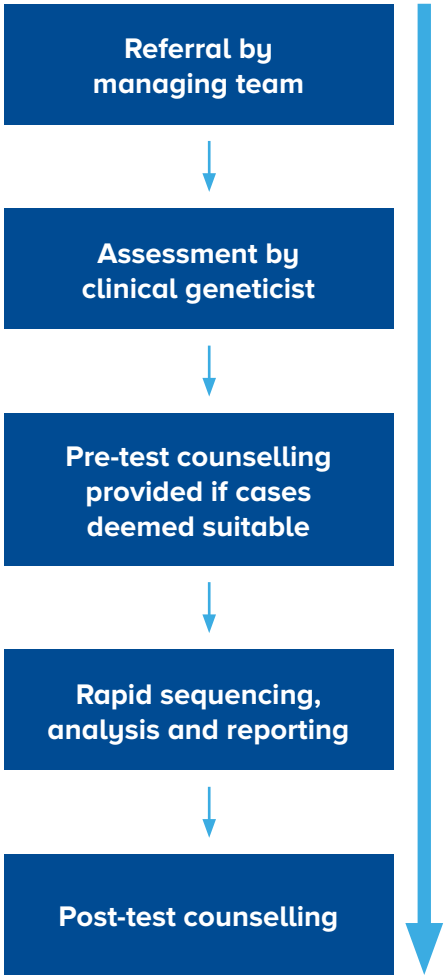


Figure 1 The RapidSeq process

In the pilot phase, the first 10 cases saw a high diagnostic yield of 40% within a short turnaround time.

The provision of a genetic diagnosis in critically ill patients can be beneficial through the modification of existing treatments, as well as the reduction of unnecessary investigations, some of which may be invasive.

Should the diagnosis be one of poor prognosis, it can also help the clinical team support the family through decisions such as treatment limitation and palliative care. Apart from that, the family can also benefit from information about the recurrence risk.

SINGHEALTH DUKE-NUS GENOMIC MEDICINE CENTRE

Bringing genomic expertise across SingHealth for more accessible care

Establishing a genetic diagnosis may end the diagnostic odyssey, but that is merely the tip of the iceberg. Patients with rare genetic syndromes often require care from multiple specialties. At present, care tends to be fragmented and not standardised due to differing practices and management between healthcare institutions.

The SingHealth Duke-NUS Genomic Medicine Centre (SDGMC) brings together genomic expertise across SingHealth institutions to enable more accessible care for patients with rare genetic diseases.

Standardised care across SingHealth institutions

The SDGMC endeavours to enhance the patient experience and provide standardised care for patients with genetic conditions across SingHealth. The establishment of specialty genetics clinics would enable patients to receive appropriate genetics support at the institution where they are receiving care.

Coordinating care across specialties

There would also be more coordinated care and support plans, for patients and families, as communication between various specialities are improved. In addition, opportunities for closer collaborations are created, and research findings are accelerated by breaking down disease boundaries and investigating clinical challenges in a holistic and efficient manner.

RARE DISEASES ARE ACTUALLY NOT THAT RARE

As more rare diseases continue to be discovered each year, they are collectively not that rare. Leveraging on current technology and genomic advances will allow us to provide better medical care support for patients and families with rare genetic diseases.

Primary care doctors play an important role in screening during a patient's regular visit. Patients with suspected undiagnosed genetic conditions, or individuals with family history of specific genetic conditions, should be referred to a specialty genetics clinic or genetics service for evaluation and genetic counselling.

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KK Women's and Children's Hospital SingHealth

Sylvia Kam
Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre;
Genetics Service, Department of Paediatrics, KK Women's and Children's Hospital

Sylvia Kam is a Genetic Counsellor at the SingHealth-Duke NUS Genomic Medicine Centre. She is part of the teams at the KK Women's and Children's Hospital Genetics Service as well as the SingHealth Duke-NUS Institute of Precision Medicine. She received her Master of Genetic Counselling from the University of Melbourne, Australia, and is a Member of the Human Genetics Society of Australasia (MHGSA). Apart from her clinical interests in paediatric and inherited conditions, she also has an interest in the curation of genetic variants. She is currently a member of the ClinGen Syndromic Disorders Working Group as a biocurator.

GPs who would like more information on this topic, please contact Ms Kam at **sylvia.kam.p.r@kkh.com.sg.**

KK Women's and Children's Hospital SingHealth

Dr Koh Ai Ling
Associate Consultant, SingHealth Duke-NUS Genomic Medicine Centre;
Genetics Service, Department of Paediatrics, KK Women's and Children's Hospital

Dr Koh Ai Ling is an Associate Consultant Paediatrician in the Genetics Service, Department of Paediatrics at KK Women's and Children's Hospital. Her clinical and research areas include rare genetic disorders and inherited metabolic disorders. She has a strong interest in medical education and provides regular genetics and metabolic teaching for paediatric residents. She currently serves as a trainer in the Genetics Education for Healthcare Professionals workshop at SingHealth Academy which focuses on the application of a wide range of genetic tests, and the understanding of roles in genetic counselling and the legal framework regulating genetic testing.

GPs who would like more information on this topic, please contact Dr Koh at **koh.ai.ling@singhealth.com.sg.**

KK Women's and Children's Hospital SingHealth

Lim Jiin Ying
Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre;
Genetics Service, Department of Paediatrics, KK Women's and Children's Hospital

Lim Jiin Ying received a Bachelor of Science (double degrees in Genetics and Biochemistry and Molecular Biology), and a Master's in Genetic Counselling from the University of Melbourne. She joined the Genetics Service at KK Women's and Children's Hospital as a Genetic Counsellor in 2013. She works closely with families to provide genetic counselling and support. Her clinical interests include prenatal, paediatric, metabolic and genodermatoses. In addition to her clinical role, she has also taken an active interest in research including the genetic basis of rare disorders and genetic counselling processes in next generation sequencing technology.

GPs who would like more information on this topic, please contact Ms Lim at **lim.jiin.ying@kkh.com.sg.**

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KK Women's and Children's Hospital
6692 2984

National Cancer Centre Singapore
6436 8288

Integrating Genomics into Cardiovascular Disease Management

Yasmin Bylstra
Principal Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre;
SingHealth Duke-NUS Institute of Precision Medicine (PRISM)

Genetic testing can establish a definitive, etiologically-based diagnosis for inherited cardiovascular diseases. Playing a vital role in early identification and treatment, it can save the lives of the patient and at-risk family members. Two studies at the National Heart Centre Singapore have led to a better understanding of inherited cardiovascular diseases in the local population.

Cardiovascular disease (CVD) has accounted for almost one out of three deaths in Singapore over the past few years, which equates to 17 people dying from either heart disease or stroke per day. It is currently ranked as one of the top three causes of hospitalisation and death.[1]

OVERVIEW OF INHERITED CARDIOVASCULAR DISEASE

Progress over the past three decades has led to the discovery of an underlying genetic basis for many CVDs, resulting in the routine use of genetic testing in clinical practice. Some of these conditions are caused by disruption to a single gene that has a deleterious effect, known as monogenic conditions.

These inherited conditions can be divided into: [2]

- Hypertrophic and dilated cardiomyopathy (associated with pathogenic variants in sarcomere and structural genes)
- Arrhythmogenic cardiomyopathy (associated with pathogenic variants in desmosomal genes)
- Inherited arrhythmias (associated with pathogenic variants in transmembrane ion channels genes)
- Marfan and related syndromes and thoracic aortic aneurysms (associated with pathogenic variants in genes encoding connective tissue elements)
- Other conditions such as familial hypercholesterolemia

Many inherited CVDs exhibit phenotypic overlay and genetic heterogeneity, with pathogenic variants in multiple genes causing the same condition.

Analysis can require sequencing the entire region of many genes to identify a genetic cause. Traditional genetic testing methods were time-consuming and expensive as single genes were tested sequentially.

Next generation sequencing (NGS) technologies have enabled large gene sequencing panels containing hundreds of genes of interest to be tested simultaneously at a much lower cost and with reduction in turnaround time. This has vastly increased the accessibility of genetic testing in clinical practice.

More recently, **genome-wide association studies (GWAS)** have identified a multitude of common genetic variants that underlie risk for the development of common CVDs such as coronary heart disease and atrial fibrillation. Individually these variants have a subtle effect, however collectively they can cause disease, referred to as polygenic risk.

A recent study found that more than 30% of coronary artery disease cases were attributed to genetic factors.[3] The utility of genetic testing for polygenic CVD is progressing although not yet widely available for clinical integration.

WHY CONSIDER GENETIC TESTING?

The main utility of genetic testing is to establish a definitive, etiologically-based diagnosis.

1 It is particularly beneficial when the clinical phenotype can be shared by multiple conditions (known as phenocopies) which could each have different underlying genetic causes, prognoses, treatments and implications for family members.

For example, left ventricular hypertrophy in hypertrophic cardiomyopathy could have an overlapping diagnosis with athlete's heart, hypertensive heart disease, lysosomal storage cardiomyopathy (e.g., Fabry disease), metabolic storage cardiomyopathy (e.g., Danon disease), infiltrative process (e.g., cardiac amyloidosis), or be part of a phenotypic spectrum of Noonan syndrome and Friedreich ataxia.[4]

2 Likewise, genetic testing could distinguish long QT syndrome from rare multisystemic syndromic disorders with prolonged QTs including Timothy syndrome, Andersen-Tawil syndrome and recessive disorders Jervell and Lange-Nielson syndrome, as well as non-syndromic versus syndromic aortopathy.[5]

Understanding the genetic etiology guides management and treatment for both cardiac and noncardiac manifestations.

3 Once the underlying genetic cause for an inherited CVD in the family is established by diagnostic genetic testing, then testing for the same pathogenic variant(s) can be offered to asymptomatic family members for preclinical diagnosis and prevention, which is referred to as cascade testing.

Family members found to carry the familial pathogenic variant can be referred for ongoing specialist care. Relatives found not to carry the familial pathogenic variant do not require ongoing cardiac screening if the genetic etiology of CVD in the family has been well established.

WHEN TO CONSIDER INHERITED CVD

Familial inheritance

Indications of familial inheritance are documented through the collection of over three generations of family medical history information, noting all affected and unaffected family members, and the age of onset and death of any cardiac-related events. The family history information can then be interpreted to assess the likelihood of a genetic condition being present and its inheritance pattern ***(Table 1)***.

Age of onset

Adult onset conditions are more often autosomal dominant, whereas childhood conditions can be autosomal dominant, autosomal recessive, X-linked or mitochondrial.[6] Prior to genetic testing, screening advice for family members can be recommended according to the family history information.

Who should be tested

Patients who clearly meet diagnostic criteria for disease, have a younger age of onset and a family history of CVD have an increased chance of identifying a genetic cause. Therefore, it is recommended to commence testing with the youngest diagnosis in the family or a definitive phenotype.

If genetic testing is performed on individuals with an undefined or borderline diagnosis, the interpretation of the genetic variants and their implications in clinical practice can be inconclusive.

Testing with no family history

Genetic testing is also recommended for patients who do not present with a family history of CVD or sudden death to account for inaccuracies in the collection, incomplete penetrance or variable expression of disease, or the presence of a de novo pathogenic variant.

INDICATIONS FOR INHERITED CARDIOVASCULAR DISEASE	
Cardiomyopathy	• Hypertrophic, dilated (non-ischaemic), peripartum, restrictive cardiomyopathy • Arrhythmogenic (right) ventricular cardiomyopathy • Left ventricular non-compaction cardiomyopathy
Arrhythmia	• Long QT syndrome • Brugada syndrome • Catecholaminergic polymorphic ventricular tachycardia • Unexplained cardiac arrest or sudden death • Sudden infant death syndrome • Atrial fibrillation (<45 years)
Connective tissue disease	• Marfan, Vascular Ehlers-Danlos or Loeys-Dietz syndrome • Aortic aneurysm or dissection (<50 years)
Other inherited conditions	• Familial hypercholesterolemia • Familial or unexplained pulmonary hypertension • Heart attack or coronary heart disease • Heart defects • Familial amyloidosis
Heart procedures	• Implantable cardioverter defibrillator or pacemaker implant (<50 years) • Left ventricular assist device or heart transplant (<60 years) • Coronary artery bypass or stent surgery (females <65 years and males <60 years)

Table 1 *Adapted from Moscarello, Tia, Chloe Reuter, and Euan A. Ashley. "Is Genetic Testing for Heart Disease Right for Me?." JAMA Cardiol. 4.9 (2019): 956-956.*

DIAGNOSING INHERITED CVD IN SINGAPORE

Until recently, the recognition of genetic factors predisposing to inherited CVDs has been derived largely from Western cohort studies, with a paucity of data from non-European populations. As genetic variation can be ethnic-specific, this renders challenges in interpreting genomic data from under-represented populations and has previously led to the misdiagnosis and mismanagement of cardiac disease.[7] As such, genomic data from diverse populations is required for accurate genetic diagnoses.

Since 2013, the National Heart Centre Singapore (NHCS) has initiated two prospective interlinked cohort studies called Biobank and SingHeart, led by Professor Stuart Cook and Associate Professor Yeo Khung Keong, which collect and store biological samples, health information and imaging data from Singaporeans with CVD (cases) and healthy volunteers (controls).

These studies are contributing to understanding of:

1. The genetic etiology of inherited CVD amongst Singaporeans

2. The prevalence of inherited CVD by identifying pathogenic genomic variants

3. Genotype-phenotype correlations

The genomic analysis involves screening a panel of 174 genes with known associations to 17 inherited cardiac conditions which was developed by NHCS.[8] The Biobank study has partnered with the **SingHealth Duke-NUS Institute of Precision Medicine (PRISM)** to perform the genomic analysis and return clinically actionable findings to consenting participants involved.

ANALYSIS OF CARDIAC GENOMIC VARIANTS

Establishing a local control group

The identification of pathogenic variants is complex due to causative variants being rare and often unique to each family, and rare variants occur in individuals with and without disease.

With the creation of a Singaporean genomic control population database (the Singapore Exome Consortium) which comprises aggregated genomic data from over 3,000 "healthy individuals" to date of South East Asian ancestry,[9] this enables the frequency of the variants amongst affected individuals to be compared. This local control genomic database aids in distinguishing rare pathogenic variants from benign variants that may be enriched amongst Singaporeans.

Classifying genomic variants

To classify each genomic variant, PRISM uses the American College of Medical Genetics and Genomics (ACMG) guidelines[10] to characterise variants into five tiers of classification: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign and benign.

These classifications draw on evidence to include population prevalence data, the effect of the variant to the protein function, segregation of the variant amongst affected family members and presence of the same variant in other patients with the same phenotype.

The data for each possible causative genetic variant is presented at a monthly multidisciplinary team meeting comprising cardiologists, clinical geneticists, genetic counsellors, scientists and bioinformatics experts from SingHealth, and is critically reviewed until consensus regarding pathogenicity is reached. A research report is then generated which documents each monogenic disease and/or carrier risk variant identified, and contains brief information about the associated genetic condition, inheritance and health risks.

DISCUSSING GENETIC RESULTS WITH PATIENTS

A **monthly inherited cardiac clinic** is held at NHCS where research participants who have consented to receive genetic findings can meet with the clinical genetics team from PRISM (a clinical geneticist and genetic counsellor) and a cardiologist. They are provided information regarding the outcome of genetic testing, genetic variants detected, associated health risk information, and the inheritance, penetrance and implications for family members.

Pathogenic variant detected

If a pathogenic variant associated with their clinical diagnosis is detected, research patients are given the opportunity to have the variant clinically validated at a certified laboratory to avoid false positives detected through sequencing, and this requires re-consent for a clinical test. In addition, a new blood sample is collected for variant analysis to avoid the possibility of any sample mix-up at recruitment.

During the consent process, the psychosocial impact of receiving such results, any possible genetic discrimination such as insurance, intention of sharing this information with family members and their possible responses are explored. Patients are then invited back to the clinic to receive the clinical validation results with further discussion regarding medical screening specific to their age and health history.

No pathogenic variant reported

If no pathogenic variants are reported, this could suggest that there is a variant which was either not detected with current technology, or that the presenting phenotype is caused by a combination of polygenic and environmental factors.

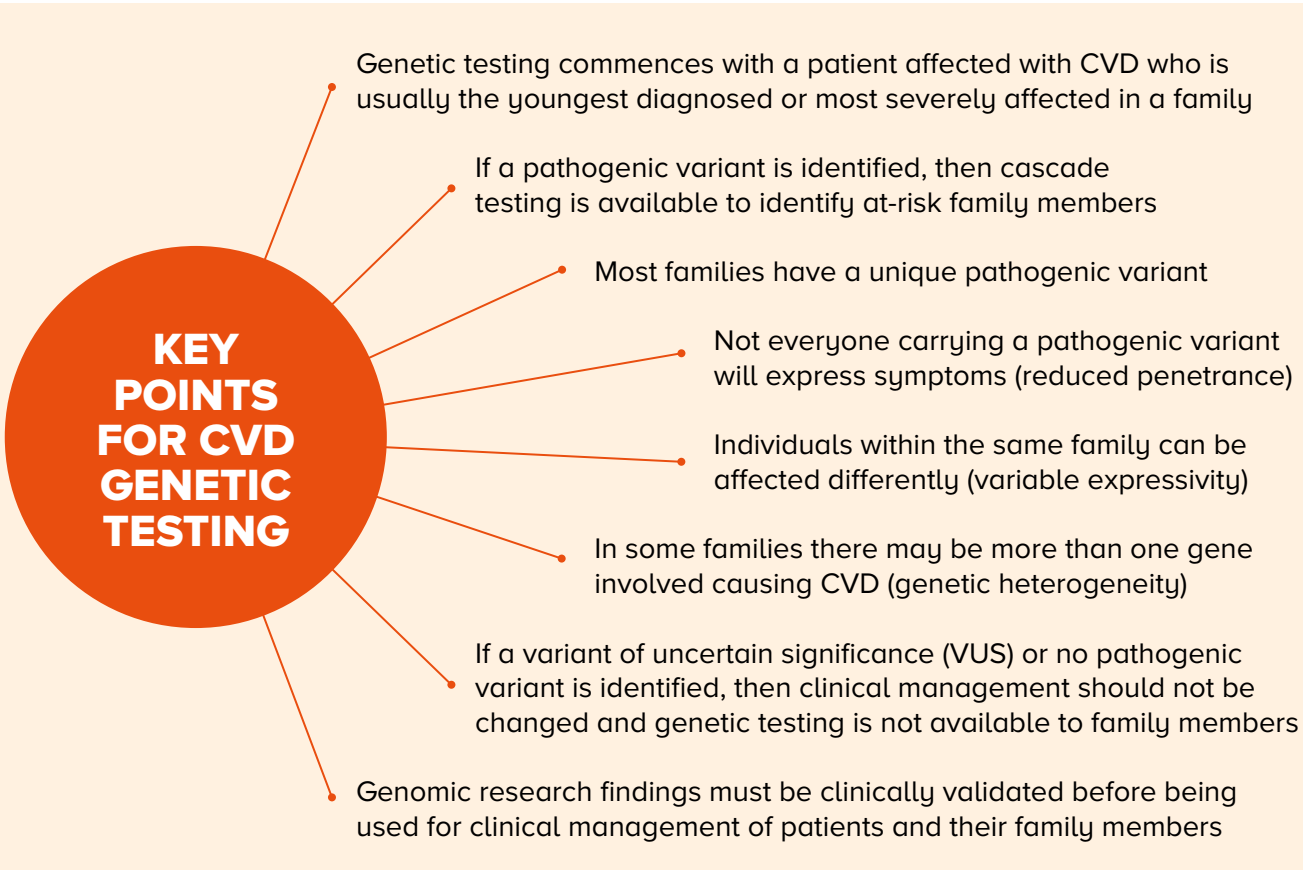
In this scenario, cardiac screening advice for family members is assessed according to family history information. When screening multiple genes, the detection of variants of uncertain significance is frequent. As the familial cause of CVD is uncertain, cascade testing is not available to family members. Information regarding variant interpretation does change over time as more knowledge becomes available and test results may be updated with new classifications.

IMPLICATIONS FOR CLINICAL MANAGEMENT

The detection of a pathogenic variant could have implications for lifestyle recommendations, such as exercise; medical therapies; risk to pregnancy; and surgical interventions such as an implantable cardioverter defibrillator, aortic root surgery or heart transplant[6] (see ***Table 2*** for examples experienced at the PRISM clinic).

Pregnancy planning, if relevant, is also discussed. Frequently, patients ask how the pathogenic variant will affect their family members, and in particular, their children.

Unfortunately, genetic testing for inherited CVD cannot predict age of onset or severity of disease. However, not everyone carrying a pathogenic variant expresses symptoms (known as reduced penetrance), and individuals within the same family or carrying the same pathogenic variant can be affected differently (known as variable expressivity). Clinical management for family members is advised with disease progression.



EXPERIENCES IN THE INHERITED CARDIAC CLINIC

Changing clinical management	• A female aged 53 years had developed an aneurysm at 43 years and was subsequently diagnosed with dilated cardiomyopathy (DCM) • She was discharged when heart check readings were normal, as DCM was attributed to aneurysm • A pathogenic *TTN* genetic variant associated with DCM was detected through the NHCS Biobank screening programme, and she was advised to reinitiate heart screening • Cascade testing was available to identify at-risk family members
Understanding triggers for disease onset	• A male aged 42 years was a competitive hockey player and had been diagnosed with DCM at 37 years • He attributed diagnosis to growth hormone use • A pathogenic *TTN* pathogenic variant was detected which explained his diagnosis • He ceased hormone use and adopted a healthy lifestyle which helped manage symptoms • Cascade testing was available to identify at-risk family members

Table 2

CONCLUSION

Through the NHCS Biobank study, the aggregation of genomic data from CVD patients and the control group of healthy individuals is facilitating the differentiation between pathogenic and benign variants present in our local population. This analysis is leading to a further understanding of genomic variants and their association with CVD.

The identification of pathogenic variants has enabled the clinical management of CVD patients to be refined and their at-risk family members to be identified through cascade testing. Genetic investigations for CVD are rapidly evolving world-wide and will continue to play a vital role in guiding optimal treatment and risk stratification for patients and their families.

REFER A PATIENT

If you have a patient with a suspected inherited CVD you may refer them to the NHCS Cardiogenetics Clinic by contacting:

Tel: +65 6704 2222
Fax: +65 6222 9258
Email: central.appt@nhcs.com.sg

ENROL AS A VOLUNTEER

For Biobank study enquiries or those interested in enrolling as a healthy volunteer, please contact:

NHCS Biobank Coordinators
Tel: 9159 7029 (office hours 8.30am – 5.30pm)
Email: biobanking_enqueries@nhcs.com.sg

Publications derived from the NHCS Biobank genomic data:

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Yasmin Bylstra
Principal Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre; SingHealth Duke-NUS Institute of Precision Medicine (PRISM)

Yasmin Bylstra is a Principal Genetic Counsellor at the SingHealth Duke-NUS Institute of Precision Medicine (PRISM). She has a key role in the provision of genetic counselling to individuals with or at risk of developing genetic conditions, genomic variant interpretation and population genomics research. She is board-certified with the Human Genetics Society of Australasia (HGSA).

GPs can call the **SingHealth Duke-NUS Genomic Medicine Centre** for appointments at the following hotlines, or scan the QR code for more information:

KK Women's and Children's Hospital
6692 2984

National Cancer Centre Singapore
6436 8288

Non-Invasive Prenatal Testing:
Paradigm Shift in Aneuploidy Screening During Pregnancy

Christina Choi
Senior Principal Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre;
Antenatal Diagnostic Centre, KK Women's and Children's Hospital

Non-invasive prenatal testing (NIPS) has emerged as a high-accuracy screening test for chromosomal abnormalities in pregnancy. NIPS can be ordered as early as 10 weeks in the pregnancy and offers a higher sensitivity and a lower false positive rate than the traditional combined first trimester screening test.

INTRODUCTION

Approximately one in 150 live births are affected by a chromosomal abnormality. Although it is well understood that the risks of chromosome problems in pregnancy increase with maternal age, all pregnancies, regardless of maternal age, could be affected.[1] Hence, screening or diagnostic testing for chromosomal abnormalities should be discussed and offered to all pregnant women.

The most common chromosomal abnormality is Down syndrome, which occurs at a prevalence of approximately one in 800 live births.[1] In the last few decades, clinicians in Singapore have seen prenatal screening for Down syndrome transition from being part of the second trimester triple test to the combined first trimester screening test.

The combined first trimester screening test has been routinely offered to patients at KK Women's and Children's Hospital (KKH) for the past 15 years. It takes into account maternal age, maternal serum markers (free β-hCG and PAPP-A) and ultrasound markers of the fetal nuchal translucency measurement and assessment of the fetal nasal bone, to reach a 90% detection rate for Down syndrome at a false positive rate of 5%.

More recently in 2011, Down syndrome screening experienced a paradigm shift through the introduction of the analysis of cell-free DNA (cfDNA), which is derived from the placenta that circulates in the maternal blood.

This method of testing is also known as **non-invasive prenatal screening (NIPS)** and is often referred to by the general public by the various test names of different commercial companies (e.g., *Harmony, Panorama*).

Compared to the combined first trimester screening test, NIPS has a higher accuracy and is able to achieve an over 99% detection rate for Down syndrome at a 0.04% false positive rate.

WHAT IS NIPS

NIPS is an optional blood test that can be performed during pregnancy. Conditions primarily tested for through NIPS include **Down syndrome, trisomy 18, trisomy 13 and chromosomes X and Y.** Expanded screening for other chromosome defects may also be included.

NIPS involves the assessment of cfDNA that is derived from the placenta that circulates in the maternal blood. The cfDNA is quantified through whole genome sequencing, targeted sequencing or targeted microarray. The sample is then identified as *"high risk"* or *"screen positive"* if the proportion of DNA sequences from a particular chromosome is found to be elevated.

WHEN CAN IT BE DONE?

The amount of cfDNA in the peripheral blood of a pregnant woman is usually sufficient for analysis from **as early as 10 weeks of gestation until term.** This cfDNA accumulates with gestation and is cleared from the maternal circulation within hours after childbirth.

Hence, the result of NIPS for the current pregnancy would not be affected by cfDNA from any previous pregnancies.

BENEFITS OF NIPS

NIPS provides a very accurate assessment of the risks of Down syndrome, trisomy 18 and trisomy 13 in the pregnancy through the analysis of the blood of a pregnant woman, drawn via venepuncture.

Based on a recent meta-analysis of 35 relevant studies, the weighted pooled sensitivities of NIPS were 99.7% for Down syndrome, 97.9% for trisomy 18 and 99.0% for trisomy 13. The pooled false positive rate was 0.04%.[2]

NIPS is clearly a more accurate test with a higher sensitivity and a lower false positive rate compared to traditional methods of screening such as the combined first trimester screening test.

LIMITATIONS OF NIPS

- Despite its high accuracy for Down syndrome, trisomy 18 and trisomy 13, **NIPS is still considered a screening test and false positive and negative results can still occur.** There could be several reasons for false positive and false negative results including discordance between placental and fetal chromosomes, fetal mosaicism, maternal chromosomal abnormality or variation, low fetal fraction and a vanishing twin.

  A *"low risk" or "screen negative"* result through NIPS indicates a decreased risk for the condition but does not rule out the possibility of the condition in the pregnancy, while a *"high risk" or "screen positive"* result indicates an increased risk for the condition but is not confirmatory either. Hence, follow-up diagnostic testing through invasive testing (chorionic villus sampling or amniocentesis) may be subsequently offered for confirmatory results.

- Although NIPS tests for the common chromosomal aneuploidies, **the list of chromosome problems is not exhaustive and varies between commercial companies.** Furthermore, the accuracy of the conditions screened for through NIPS depends on the condition that is assessed and the platform that is used.

- Since NIPS is a blood test, it does not involve an ultrasound of the pregnancy and is thus **unable to screen for structural defects or markers** that may or may not be related to chromosome defects in the fetus. Hence, it is still important to offer prenatal ultrasound scans to all pregnant women to help screen for structural defects or markers, which may suggest testing beyond the few conditions that are covered through NIPS.

- Furthermore, **testing of some samples through NIPS may not produce any results and be marked as "inconclusive".** This occurs in 0.03–11% of samples[2] and may be due to technical or biological reasons. A subsequent redraw of the pregnant woman's blood, in hopes of producing a result, may or may not be possible.

- Testing through NIPS has also been extended to twin pregnancies, but its performance is less extensively validated compared to that of singleton pregnancies. NIPS is also not suitable for pregnancies with a co-twin demise, a vanishing twin or an empty second sac.

HOW CAN GPs ORDER NIPS?

If a patient expresses interest in NIPS, she may be referred to KKH for an appointment with an obstetrician. This will involve:

Ultrasound

Besides taking a detailed pregnancy history, the obstetrician will also arrange for an ultrasound scan to be done to determine important details of the pregnancy before NIPS is performed.

NIPS is performed in-house at KKH, using the *Harmony* prenatal test. By being run locally, *Harmony* allows more efficient reporting of results and better communication between the laboratory and the ordering physician.

Prenatal genetic counselling

Besides laboratory services, KKH also provides patients with prenatal genetic counselling services to help them better understand the details of NIPS as well as other test options that may be available. Prenatal genetic counselling is an integral part of obstetric care.

- **Pre-test counselling** aims to help facilitate informed decisions about testing by providing patients with information about the tests, helping patients understand the similarities and differences with alternative methods of testing, and helping them anticipate the consequences of various decisions that might be made.

- **Post-test counselling** involves the communication of results, discussion about the predictive value of NIPS as a screening test in relation to other information that might be known about the pregnancy, offering of diagnostic testing though chorionic villus sampling or amniocentesis, and discussion about follow-up management of the pregnancy. The choice to pursue or decline testing should be made by the pregnant woman herself as each individual has different goals and values that may influence their decisions.

Although NIPS is a highly accurate test for the common chromosomal aneuploidies, it must be offered and considered carefully in order for pregnant women to exercise their reproductive autonomy and make informed decisions about their pregnancies.

THE FUTURE OF NIPS

The feasibility of extending NIPS beyond the common aneuploidies has been demonstrated. The use of NIPS for monogenic disorders such as thalassemia is widely anticipated, especially by patients with family histories of certain monogenic disorders and who are reluctant to pursue invasive diagnostic testing.

The many technical and analytical challenges associated with NIPS for monogenic disorders are currently being worked out, and hopefully with thorough validation and cautious implementation, NIPS for monogenic disorders will be an option that is clinically available to pregnant women in the future.

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KK Women's and Children's Hospital
SingHealth

Christina Choi
Senior Principal Genetic Counsellor, SingHealth Duke-NUS Genomic Medicine Centre; Antenatal Diagnostic Centre, KK Women's and Children's Hospital

Christina Choi, MS, CGC is the Senior Principal Genetic Counsellor at the Antenatal Diagnostic Centre at KK Women's and Children's Hospital (KKH). She joined KKH in 2012, and as a prenatal genetic counsellor with the Fetal Medicine team, uses her knowledge in medical genetics and understanding of the psychosocial impact of communication to provide genetic counselling to high-risk pregnancies. She also leads a team of nurse counsellors and oversees the execution of prenatal chromosomal/genetic testing at the Antenatal Diagnostic Centre at KKH.

Ms Choi received her B.A. in Biology and M.S. in Biotechnology from Johns Hopkins University and went on to obtain her M.S. in Genetic Counselling from Boston University School of Medicine. She continued to work in the San Francisco Bay Area as a prenatal genetic counsellor at a private obstetrics practice and was also involved in early startup days of technology company Counsyl Inc. She is board certified with the American Board of Genetic Counselling.

GPs can call the **SingHealth Duke-NUS Genomic Medicine Centre** for appointments at the following hotlines, or scan the QR code for more information:

KK Women's and Children's Hospital
6692 2984

National Cancer Centre Singapore
6436 8288

Eight Joint Clinics in One Centre for High-Risk Pregnancy

Providing Integrated, One-Stop Multidisciplinary Care for Mothers-to-Be

CHiRP is a one-stop multidisciplinary tertiary integrated care centre for high-risk pregnancies. By optimising pre-pregnancy care and counselling for prospective mothers with risk factors, it aims to ensure the best possible outcomes for both mothers and babies.

CHiRP: CENTRE FOR HIGH-RISK PREGNANCY

The Department of Obstetrics & Gynaecology (O&G) at Singapore General Hospital has built a strong reputation for managing high-risk pregnancies, in particular mothers with medical disorders and complications.

Drawing on the strengths and depth of expertise available in a tertiary teaching hospital and an academic medical centre, the department has now established a one-stop centre for joint multidisciplinary clinics and services between obstetrics and a growing pool of medical specialties. A close working relationship with the departments of Neonatology and Anaesthesia has also been forged to ensure the best possible outcomes for both mothers and babies.

These services are operated by the Maternal Fetal Medicine section of the department. Given the increasing complexity of cases seen and the growing number of joint clinics, CHiRP will also optimise and streamline the coordination and operations of these services together with the other perinatal services of prenatal diagnosis under one centre.

Currently the centre is a virtual one, but we hope to be able to have a well-sited physical space to house these services under one roof in the near future.

From left to right:
Seated:
Dr Tan Eng Loy, Francine Tu Chen Chen, Assoc Prof Tan Lay Kok, Latifah Nur Binte Mohamed Taufik, Assoc Prof Devendra Kanagalingam

Standing:
Dr Tan Wei Ching, Dr Yang Liying

CENTRE for HIGH-RISK PREGNANCIES CHiRP

OUR CLINICS & REFERRAL CRITERIA

CLINICS	WHO TO REFER / SERVICES
High-Risk Clinic	• Patients with bad obstetric history • Patients at risk of preterm labour • Placenta praevia • Placenta accreta • Two or more previous caesarean sections • VBAC • Hyperemesis gravidarum
Gestational Diabetes Joint Clinic	• Type 1 diabetes • Type 2 diabetes • Gestational diabetes
Cardiology Joint Clinic	Pre-existing cardiac conditions, such as: • Congenital heart disease • Valvular disease • Aortopathies • Ischaemic heart disease • Arrhythmias • Cardiomyopathy • Heart failure • New onset cardiac issues
Rheumatology Obstetric Clinic	All rheumatological conditions, such as: • Systemic lupus erythematous (SLE) • Scleroderma • Rheumatoid arthritis • Vasculitides • Mixed connective tissue disease
Obstetrics & Gynaecology Haematology Clinic	• Complex anaemias (e.g., thalassaemias) • Platelet disorders (e.g., immune thrombocytopaenia (ITP)) • Thrombosis • Thrombophilias • Patients requiring long-term anticoagulation
Obstetric Kidney Clinic	• All pre-existing kidney disorders • Renal transplant patients • Dialysis patients
Obstetric Medicine Clinic	General medical disorders including: • Hypertension • Thyroid disorders • Neurological conditions • Epilepsy • Dermatology • Complex multiple medical co-morbidities
Fetal Medicine Clinic	• Counselling for prenatal screening and diagnosis (including NIPT & CMA) • Diagnosis and management of fetal anomalies including echocardiography and neurosonography, and intrauterine growth restriction • Management of monochorionic twins and higher-order multiple pregnancy • Rhesus iso-immunisation, fetal infections and intrauterine fetal therapy

CASE STUDIES

CASES SEEN AT OUR HIGH-RISK CLINICS

CHiRP's range of joint clinics were thoughtfully developed to care for patients and the specific needs they may have. The case studies below illustrate the scale and spectrum of complicated cases that these clinics are equipped to manage.

CLINICS

- **High-Risk Clinic**
- **Gestational Diabetes Joint Clinic**
- **Cardiology Joint Clinic**
- **Rheumatology Obstetric Clinic**
- **Obstetrics & Gynaecology Haematology Clinic**
- **Obstetric Kidney Clinic**
- **Obstetric Medicine Clinic**
- **Fetal Medicine Clinic**

CASE A

Mdm L. is a 30-year-old with a complex medical background of **type 1 diabetes mellitus, rheumatoid arthritis, Hashimoto's hypothyroidism and depression.** She was receiving long-term care from various medical specialties.

When she became pregnant for a second time, her antenatal care was undertaken at the **Gestational Diabetes Joint Clinic (GDJC)** where she would see the consultant endocrinologist, consultant obstetrician, dietitian and diabetic nurse in a one-stop joint service. She was placed on a basal-bolus insulin regimen with close obstetric monitoring for fetal anomalies and growth. She was reassured about the safety of and rationale for continuing the thyroxine for hypothyroidism, as well as the hydroxychloroquine for her rheumatoid arthritis. Subsequently, she developed obstetric cholestasis.

She had a successful induction of labour and delivered a healthy appropriately-grown baby boy.

CASE B

Mdm T. is a 35-year-old who has **systemic lupus erythematous (SLE) complicated by immune thrombocytopaenia (ITP) and Raynaud's phenomenon.** Her previous pregnancy was complicated by severe early-onset pre-eclampsia requiring caesarean delivery which in turn was complicated by a deep vein thrombosis.

For the second pregnancy, she was managed by our **Rheumatology Obstetric Clinic,** a one-stop clinic where she saw both the consultant rheumatologist and consultant obstetrician. Clearly a very high-risk pregnancy, she was placed on low-dose aspirin and her medications were reviewed, reassuring her that hydroxychloroquine, prednisolone, and low molecular weight heparin were safe and important to maintain the SLE in remission for the benefit of the pregnancy, and also to prevent the formation of thrombosis.

She had close monitoring of both her condition and her baby's development, and required a course of intravenous immunoglobulin during the pregnancy, before having a healthy term baby delivered by a planned caesarean section at 37 weeks.

CASE C

Mdm N. is a 20-year-old with **compound heterozygosity for sickle cell anaemia and beta thalassaemia.**

Transfusion-dependent, she had an unplanned pregnancy which was referred early to the **Obstetrics & Gynaecology Haematology Clinic,** where her antenatal care was undertaken jointly by a consultant haematologist and consultant obstetrician.

The complexity of her medical issues, superimposed on the physiological changes of pregnancy, required a coordinated multidisciplinary effort with other disciplines including cardiology, anaesthesia and neonatology. The risks of sickling crisis and thrombosis with potentially adverse consequences to pregnancy, including fetal growth restriction, were closely anticipated, and she was placed on prophylactic anticoagulation.

The team managed to bring her pregnancy till 37 weeks when she was delivered by elective caesarean section.

CASE D

Mdm L. is a 27-year-old in her second pregnancy, with a significant medical history of a **surgically corrected tetralogy of Fallot.**

She was managed by the **Cardiology Joint Clinic,** where she was seen jointly by a consultant cardiologist and a consultant obstetrician at every session. This facilitated timely serial echocardiographic assessments of her cardiac function, as well as simultaneous monitoring of her obstetric and baby's wellbeing.

She was counselled and monitored for cardiac complications such as heart failure, arrhythmias, cyanosis and syncope, and a multidisciplinary delivery plan was carried to fruition with a term normal vaginal delivery at 39 weeks.

CASE E

Mdm C. is a 36-year-old with **diabetic nephrosclerosis with impaired renal function** (serum creatinine 100 µmol/L) and significant **proteinuria, hypertension, anaemia and depression.**

This being her first pregnancy, she was managed by the **Obstetric Kidney Clinic** where she was seen jointly by a consultant nephrologist and a consultant obstetrician. She was counselled on the high-risk nature of the pregnancy, and was closely monitored for the progression of her renal function while controlling her hypertension and anaemia. She was also tracked for fetal growth restriction and possible development of pre-eclampsia.

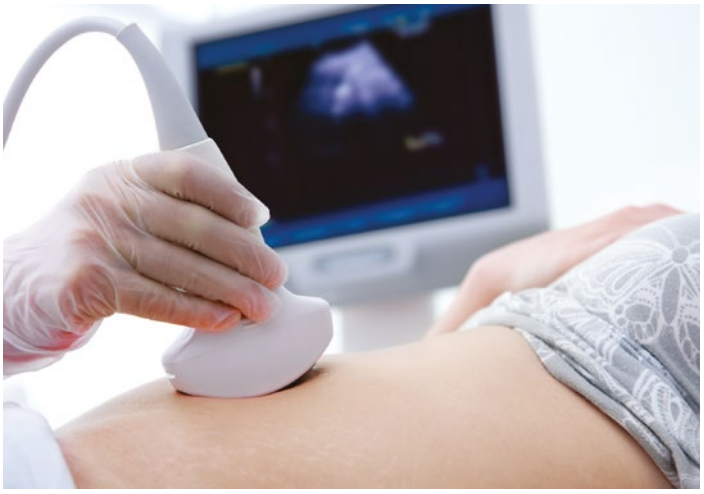
Despite the increased risk of preterm birth, the team managed to bring her pregnancy to 37 weeks when she had a successful induction of labour and gave birth to a healthy 2.4kg baby.

HOW GPS CAN REFER

The Centre welcomes GP referrals for patients with any of the aforementioned conditions. To refer a patient to any of these clinics, please contact CHiRP at:

Tel: 6321 4516
Fax: 6321 4837
Email: gdmogsgh@sgh.com.sg

For more information on CHiRP, scan the QR to visit the website.



Our Care Team

1 2 3 4 5 6 7

1. **Assoc Prof Tan Lay Kok**
   Director & Maternal Medicine Lead;
   Senior Consultant

2. **Assoc Prof Devendra Kanagalingam**
   Peripartum Lead;
   Senior Consultant

3. **Dr Tan Eng Loy**
   Education and Training Lead;
   Senior Consultant

4. **Dr Tan Wei Ching**
   Fetal Medicine Lead;
   Senior Consultant

5. **Dr Yang Liying**
   Research Lead;
   Consultant

6. **Francine Tu Chen Chen**
   Coordinator and Nursing Lead

7. **Latifah Nur Binte Mohamed Taufik**
   Senior Staff Nurse

Using Advanced Genomic Technologies to Improve Healthcare Outcomes

The SingHealth Duke-NUS Genomic Medicine Centre (SDGMC)

was established to bring clinical genomics to institutions across the SingHealth cluster. The Centre aims to be a global leader in delivering clinical care, with use of advanced genomic technologies to improve patient diagnostics, therapeutics and healthcare outcomes.

Clinical genomics is the use of information stored in our DNA (i.e., our genes) to understand the mechanism underlying the individual's disease. The improved understanding of genomics, triggered by the rapid decline in cost of sequencing, has fuelled the development of therapies that would be most beneficial to the individual. This has enabled the move from a "one size fits all" approach to medicine, to a more individualised form of precision medicine.

ABOUT THE GENOMIC MEDICINE CENTRE

SDGMC brings together expertise from the various SingHealth institutions and Duke-NUS Medical School, and aims to work closely with other sub-specialists across the cluster to provide multidisciplinary care in a seamless and timely manner.

The Centre boosts genomic expertise and standardise clinical pathways across medical specialties in SingHealth. Specialty genetics clinics have been set up in SingHealth hospitals and institutions for patients with genetic disorders or conditions with a suspected genetic basis. In these clinics, patients and their family members undergo risk assessment, genetic testing and genetic counselling by a team of qualified specialists, geneticists and genetic counsellors.

RESEARCH AND INNOVATION

Research is an integral aspect in advancing genomics care. SDGMC endeavours to collaborate with local institutions such as Duke-NUS, A*STAR, National University of Singapore (NUS) and Nanyang Technological University (NTU) to conduct research to discover new biomarkers and genetic disorders for improved diagnosis and novel treatment. A genetics registry would also be established to serve as a centralised repository for the in-depth study of various conditions, which would in turn aid in better management of genetic disorders.

EDUCATION

An ongoing quarterly workshop, 'Genetics Education for Medical Professionals', is conducted to equip clinicians with practical knowledge on the use of genetics in clinical practice. This helps them better identify, and make appropriate referrals for, patients with genetic conditions. SDGMC intends to expand on this to build an education platform that would increase the number of genomic-trained professionals across SingHealth.

Our Services

- Genetic testing for specified disease
- Carrier testing / testing of family members
- Presymptomatic testing
- Reproductive counselling
- Telegenetics
- Evaluation for possible genetic disorder and subsequent management
- Risk assessment and multidisciplinary risk management clinics
- Research, clinical trials patient registry and support groups

For GP referrals, please contact the SingHealth Duke-NUS Genomic Medicine Centre:

KK Women's and Children's Hospital
6692 2984

National Cancer Centre Singapore
6436 8288

Website: www.singhealth.com.sg/genomic-medicine-centre

Our Executive Committee

1 2 3 4 5 6

Head
1. **Asst Prof Saumya Shekhar Jamuar**
Senior Consultant,
Genetics Service, KKH

Deputy Head
2. **Adj Assoc Prof Tan Ee Shien**
Head & Senior Consultant,
Genetics Service, KKH

Director, Bioinformatics
3. **Asst Prof Lim Weng Khong**
Chief Information Officer,
SingHealth Duke-NUS Institute of Precision Medicine

Director, Education
4. **Adj Asst Prof Ting Teck Wah**
Consultant,
Genetics Service, KKH

Director, Research
5. **Adj Assoc Prof Sonia Davila**
Assistant Director,
SingHealth Duke-NUS Institute of Precision Medicine

Service Chief, Cancer Genetics
6. **Assoc Prof Joanne Ngeow Yuen Yie**
Head,
Cancer Genetics Service, NCCS

Specialist Promotions & Appointments

Singapore General Hospital
SingHealth

Appointments: 6326 6060 | Email: gpnetwork@sgh.com.sg

NEW APPOINTMENT

Dr Mathur Sachin
Director, Trauma Service; Senior Consultant
Dept
General Surgery

PROMOTIONS – CONSULTANTS

Dr Ho Ying Ci
Consultant
Dept
Anaesthesiology

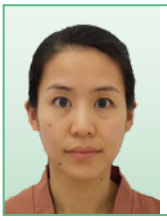
Dr Sim Yilin, Eileen
Consultant
Dept
Anaesthesiology

Dr Wan Paul Weng
Consultant
Dept
Emergency Medicine

Dr Teo Chi Yuan, Esmeralda
Consultant
Dept
Haematology

Dr Kang Yong Chiang
Consultant
Dept
Hand and Reconstructive Microsurgery

Dr Goh Xian-Yang, Charles
Consultant
Dept
Nuclear Medicine & Molecular Imaging



Dr Vanessa Tan Yee Jueen
Consultant
Dept
Otorhinolaryngology – Head & Neck Surgery

Dr Lie Sui An
Consultant
Dept
Surgical Intensive Care

Dr Lee Qingwei, Shaun
Consultant
Dept
Vascular Surgery

APPOINTMENT – CONSULTANT

Dr Liew Tau Ming
Consultant
Dept
Psychiatry

APPOINTMENTS – ASSOCIATE CONSULTANTS

Dr Anusha Kannan
Associate Consultant
Dept
Anaesthesiology

Dr Lin Wenjie
Associate Consultant
Dept
Colorectal Surgery

Dr Kwee Ann Kerwen
Associate Consultant
Dept
Endocrinology

Dr Chia Zi Yang
Associate Consultant
Dept
Orthopaedic Surgery

Dr Tan Bingchao, Alfred
Associate Consultant
Dept
Vascular & Interventional Radiology

Dr Nick Ng Zhi Peng
Associate Consultant
Dept
Vascular Surgery

Specialist Promotions & Appointments

Sengkang General Hospital
SingHealth

Appointments: 6930 6000 | Email: appointments@skh.com.sg

APPOINTMENTS – ASSOCIATE CONSULTANTS

Dr Lam Sze Jia
Associate Consultant
Dept
Emergency Medicine

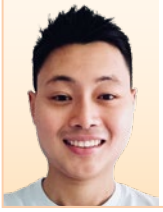
Dr Koh Minghe Moses
Associate Consultant
Dept
General Medicine, Rehabilitation Medicine

Dr Guo Weiwen
Associate Consultant
Dept
General Medicine, Renal Medicine

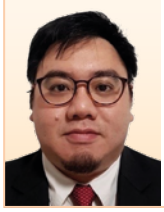
Dr Lee Pei Shan
Associate Consultant
Dept
General Medicine, Renal Medicine

Dr Lum Huey Ming Johnathan
Associate Consultant
Dept
General Medicine, Gastroenterology

Dr Tan Wee Beng Alvin
Associate Consultant
Dept
General Medicine, Geriatric Medicine



Dr Marc Wong Hai Liang
Associate Consultant
Dept
General Medicine, Internal Medicine



Dr Allen Wong Wei Jiat
Associate Consultant

Plastics, Reconstructive & Aesthetics Surgery Services

Dr Thomas Chan Kong Ngai
Associate Consultant
Dept
Urology

KK Women's and Children's Hospital
SingHealth

Appointments: 6692 2984 | Email: centralappt@kkh.com.sg

NEW APPOINTMENTS

Prof Chan Kok Yen Jerry
Academic Vice Chair (Research), SingHealth Duke-NUS Obstetrics and Gynaecology Academic Clinical Programme (OBGYN ACP)

Dr Lew Eileen
Chairman

Division of Clinical Support Services

Dr Manisha Mathur
Academic Deputy Vice Chair (Postgraduate Education), SingHealth Duke-NUS Obstetrics and Gynaecology Academic Clinical Programme (OBGYN ACP)

Dr Mohammad Ashik bin Zainuddin
Head

Sports Medicine Service

Dr Suzanna bte Sulaiman
Academic Deputy Vice Chair (Clinical), SingHealth Duke-NUS Obstetrics and Gynaecology Academic Clinical Programme (OBGYN ACP)

Dr Tewani Komal Girish
Head

Women's Palliative Care Service

Dr Veronique Celine Viardot-Foucault
Director

Clinical Endocrinology

Dr Ann Margaret Wright
Head

Peripartum Unit

PROMOTIONS – CONSULTANTS

Dr Chan Jiahui, Charmaine
Consultant

Cardiology Service

Dr Mervin Loi V-Ter
Consultant

Children's Intensive Care Unit

Dr Lee Mi Li Jean Jasmin
Consultant

Family Medicine Service

Dr Ho Weng Yan
Consultant

Dept
Gynaecological Oncology

Dr Thain Pei Ting, Serene
Consultant

Dept
Maternal Fetal Medicine

Dr Simrita Kaur Khurana
Consultant

Dept
Neonatology

Dr Tan Yi Hua
Consultant

Respiratory Medicine Service

Dr Huang Youjin, Eugene
Consultant

Dept
Urogynaecology

APPOINTMENTS – SENIOR CONSULTANTS

Dr Grace Benjamin Moshi
Senior Consultant

Dept
Pathology and Laboratory Medicine

Dr Por Yong Chen
Senior Consultant

Dept
Plastic, Reconstructive and Aesthetic Surgery

APPOINTMENTS – ASSOCIATE CONSULTANTS

Dr Tan Xian-Ting, Christelle
Associate Consultant

Dept
Child Development

Dr Chan Boon Hui
Associate Consultant

Dental Service

Dr Ang Yi Shan
Associate Consultant

General Paediatrics Service

Dr Cheah Sue Mei
Associate Consultant

General Paediatrics Service

Dr Tan Hui Yin Jessica
Associate Consultant

General Paediatrics Service

Dr Raymond Reinaldo Tanugroho
Associate Consultant

General Paediatrics Service

Specialist Promotions & Appointments

APPOINTMENTS – ASSOCIATE CONSULTANTS

Dr Fong Wen Yan, Nikki
Associate Consultant

Genetics Service

Dr Ngoh Seow Fen, Adeline
Associate Consultant

Neurology Service

Dr Long Huiyi, Melody
Associate Consultant

Dept
Paediatric Anaesthesia

Dr Ong Han Lim
Associate Consultant

Dept
Paediatric Surgery

Dr Tan Hon Sen (Chen Fengcheng)
Associate Consultant

Dept
Women's Anaesthesia

National Heart Centre Singapore
SingHealth

Appointments: 6704 2222 | **Email: central.appt@nhcs.com.sg**

PROMOTIONS – CONSULTANTS

Dr Koh Si Ya Natalie
Consultant

Dept
Cardiology

Sub-specialty
Echocardiography

Dr Muhammad Bin Idu Jion
Consultant

Dept
Cardiology

Sub-specialties
Interventional Cardiology, Nuclear Cardiology

APPOINTMENTS – ASSOCIATE CONSULTANTS

Dr Lim Chiw Yeh
Associate Consultant

Dept
Cardiology

Dr Yan Limin
Associate Consultant

Dept
Cardiology

Dr Zameer Bin Abdul Aziz
Associate Consultant

Dept
Cardiothoracic Surgery

Sub-specialty
Cardiac Surgery (Adult)

National Neuroscience Institute
SingHealth

Appointments:
(SGH Campus) 6326 6060
(TTSH Campus) 6330 6363
(CGH) 6788 3003

Email:
gpnetwork@sgh.com.sg
appointments@nni.com.sg

NEW APPOINTMENTS

Assoc Prof Low Chyi Yeu David
Deputy Medical Director (Clinical), Head & Senior Consultant

Dept
Neurosurgery (TTSH Campus)

Sub-specialties
Neuro-Oncology, Paediatric Neurosurgery, Hydrocephalus, Epilepsy Surgery

Dr Ling Ji Min
Head & Consultant

Dept
Neurosurgery (CGH)

Sub-specialties
Spine Surgery, General Neurosurgery

PROMOTIONS – SENIOR CONSULTANTS

Dr Ng Su Lyn Adeline
Senior Consultant
Dept
Neurology (TTSH Campus)
Sub-specialties
Behavioural Neurology, Cognitive Neurology

Dr Tan Yee-Leng
Senior Consultant
Dept
Neurology (TTSH Campus)
Sub-specialty
Epilepsy

Dr Kalpana Prasad
Senior Consultant
Dept
Neurology (TTSH Campus)
Sub-specialty
Neuromuscular Disease

Dr Sheila D/O Srinivasan
Senior Consultant
Dept
Neurology (TTSH Campus)
Sub-specialty
Epilepsy

PROMOTION – CONSULTANT

Dr Lee Chee Hoe Lester
Consultant
Dept
Neurosurgery (TTSH Campus)
Sub-specialties
General Neurosurgery, Spine Surgery

Singapore National Eye Centre
SingHealth

Appointments: 6322 9399 | **Email: appointments@snec.com.sg**

APPOINTMENTS – ASSOCIATE CONSULTANTS

Dr Chiam Pei Yu Nathalie
Associate Consultant
Dept
Cataract and Comprehensive Ophthalmology
Sub-specialty
Ophthalmology

Dr Beau James Fenner
Associate Consultant
Dept
Cataract and Comprehensive Ophthalmology
Sub-specialty
Ophthalmology

Dr Foo Chao Ming Reuben
Associate Consultant
Dept
Cataract and Comprehensive Ophthalmology
Sub-specialty
Ophthalmology

Dr Lee Yi Fang
Associate Consultant
Dept
Cataract and Comprehensive Ophthalmology
Sub-specialty
Ophthalmology

Dr Ng Wei Yan
Associate Consultant
Dept
Cataract and Comprehensive Ophthalmology
Sub-specialty
Ophthalmology

Dr Tan Peng Yi
Associate Consultant
Dept
Cataract and Comprehensive Ophthalmology
Sub-specialty
Ophthalmology

Recruitment

Embark on a Life-Changing Journey with a Career at SingHealth

If you are a qualified doctor, a challenging career awaits you at SingHealth.

Interested applicants are to email your CV with full personal particulars, educational and professional qualifications (including housemanship details), career history, present and expected salary, names of at least two professional references, contact numbers and e-mail address together with a non-returnable photograph.

Please email your CV to the respective institutions' email addresses/online career portals with the Reference Number DM2012.

Singapore General Hospital

Departments seeking:
Resident Physicians and Staff Registrars
- Anaesthesiology
- Diagnostic Radiology
- Family Medicine & Continuing Care
- Emergency Medicine
- Surgical disciplines such as General Surgery, ENT-HNS, O&G, Breast, SPRinT, Colorectal, Vascular Surgery, Urology, Orthopaedics, Hand and Plastic

Consultants
- Acute Care Surgery/Trauma
- Anatomical Pathology
- Geriatric Medicine
- Surgical Oncology (Sarcoma, Peritoneal and Rare Tumours)

Website: www.sgh.com.sg
Career Portal: www.sgh.com.sg/careers
Email: careers.medical@sgh.com.sg

KK Women's and Children's Hospital

Departments/Services seeking:
Senior Consultants/Consultants/ Associate Consultants (Gynaecologic & Breast Pathologist, Microbiologist, Chemical Pathologist and Paediatric Pathologist)
- Pathology & Laboratory Medicine

Senior Consultants/Consultants/ Associate Consultants
- Diagnostic & Interventional Imaging

Consultants/Associate Consultants
- Child Development

Staff Registrars
- Paediatric Surgery

Family Physician
- Family Medicine

Resident Physicians
- Emergency Medicine
- Orthopaedic Surgery
- Otolaryngology
- Paediatric Surgery

Website: www.kkh.com.sg
Email: medical.hr@kkh.com.sg

National Neuroscience Institute

Departments seeking Resident Physicians and Service Registrars
- Neurology
- Neuroradiology
- Neurosurgery

Website: www.nni.com.sg
Email: nni_hr@nni.com.sg

National Heart Centre Singapore

Departments seeking Resident Physicians
- Cardiology
- Cardiothoracic Surgery

Website: www.nhcs.com.sg
Email: joyce.soh.y.h@nhcs.com.sg

Sengkang General Hospital

Departments seeking:
Resident Physicians and Staff Registrars
- Anaesthesiology
- Cardiology
- Emergency Medicine
- Surgery
- General Medicine (with interest in Dermatology, General Medicine and Palliative Medicine)
- Intensive Care Medicine
- Orthopaedic Surgery (with interest in Hand Surgery and Orthopaedic Surgery)
- Otorhinolaryngology – Head & Neck Surgery
- Plastic, Reconstructive & Aesthetic Surgery Services
- Urology

Senior Consultant, Consultant, Associate Consultant
- Radiology
- Pathology
- Urology

Website: www.skh.com.sg
Career Portal: www.skh.com.sg/careers/Pages/careers.aspx
Email: careers@skh.com.sg

SingHealth Community Hospitals

(Sengkang Community Hospital, Outram Community Hospital and Bright Vision Hospital)

Department seeking:
Consultant, Associate Consultant, Staff Registrars, Resident Physicians
- Family Medicine

Website: http://www.singhealthch.com.sg/
Career Portal: www.singhealth.com.sg/SCH/careers/Pages/Careers.aspx
Email: schrecruitment@singhealthch.com.sg

HOTLINES

SingHealth

GP Fast Track Appointment Hotlines

Singapore General Hospital	6326 6060	KK Women's and Children's Hospital	6692 2984	National Heart Centre Singapore	6704 2222
Changi General Hospital	6788 3003	National Cancer Centre Singapore	6436 8288	National Neuroscience Institute	6330 6363
Sengkang General Hospital	6930 6000	National Dental Centre Singapore	6324 8798	Singapore National Eye Centre	6322 9399

www.singhealth.com.sg

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