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ACADEMIC MEDICAL CENTRE

Genomic
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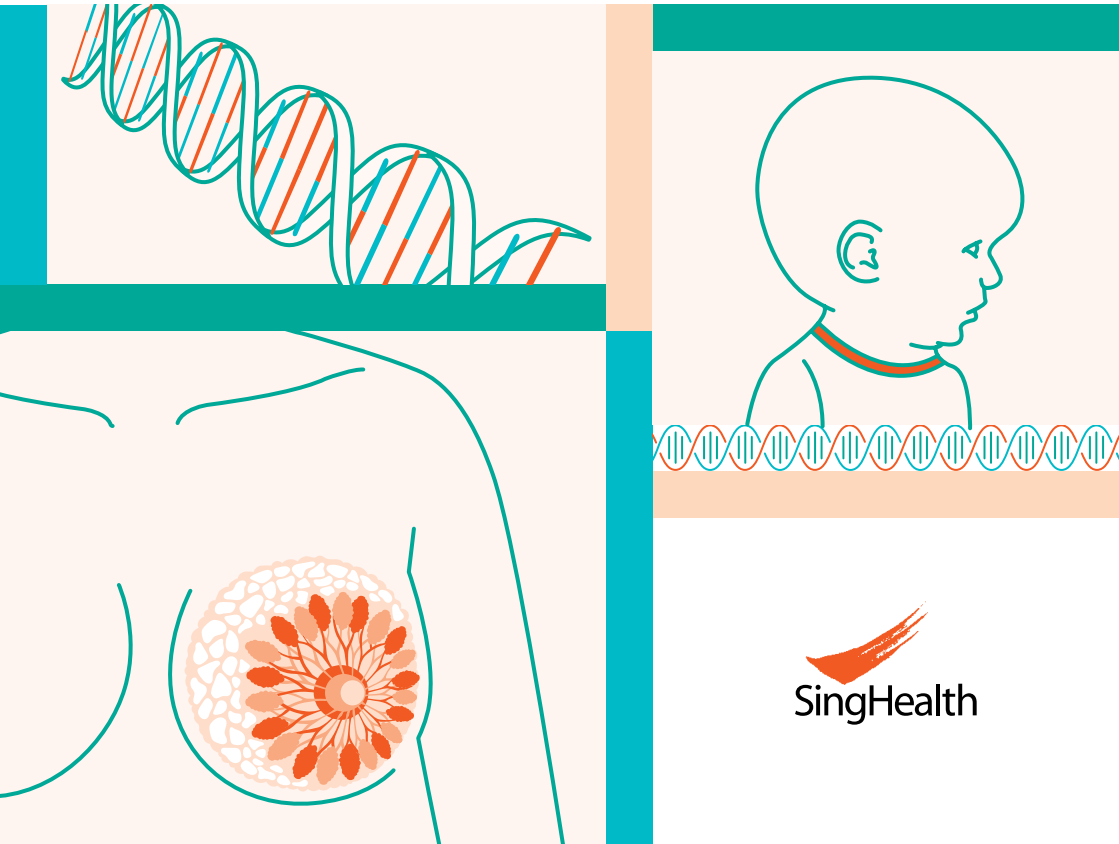
Cowden Syndrome



SingHealth

Cowden syndrome, or PTEN hamartoma tumour syndrome, is a hereditary cancer syndrome.

What is hereditary cancer?

Hereditary cancer makes up about 5-10% of all cases of cancer. Some genes function to protect us from cancer. When they are not working well, it causes hereditary cancer. We refer to genes that are not working well as faulty genes.

Individuals who carry a faulty cancer gene(s) have a higher chance of developing certain cancers over their lifetime compared to the general population. The types of cancers that they may be at increased risk of will depend on the gene(s) involved.

If you have a faulty cancer gene, you may be at increased risk of developing certain cancers. As genes are shared among family, other family members may have inherited the faulty gene and may be at increased risk of cancer too.

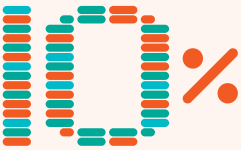
What is genetic testing?

Genetic testing is offered to individuals where a hereditary cause of their personal and/or family history of cancer is suspected.

Genes contain the instructions that our body reads to carry out different functions. Genetic testing involves analysing your genes to understand if there are faults (i.e., mutations) that may increase the risk of diseases like cancer.

How is genetic testing done?

- Genetic testing is typically a one-time blood test.
- If a blood sample cannot be taken, other sample sources (e.g., skin or saliva) may be used.

Hereditary cancer accounts for up to  **of all cases of cancer.**

What are the possible results of genetic testing?

There are 3 types of results you may receive:

Positive

Faulty gene(s) identified

General Population Risk — Elevated Risk

Increased risk of developing certain tumours and cancers (depends on faulty gene(s) involved)

Your family (parents, siblings, children and extended relatives) may have inherited the faulty gene(s) and should consider genetic testing to clarify this

Uncertain

Variant of Uncertain Significance (VUS)

Uncertain gene change(s) identified, unclear if these change(s) increase risk for tumours and cancers

General Population Risk — Elevated Risk

May be clarified by testing other family members

May be reclassified over time as 'positive' or 'negative' when more information is known

Negative

No faulty gene(s) identified

General Population Risk — Elevated Risk

Tumour and cancer risk is similar to that of general population

Test limitations will be explained in the context of your personal and family history of tumours and cancers

PTEN hamartoma tumour syndrome

PTEN hamartoma tumour syndrome (PHTS) is a hereditary condition caused by a faulty (disease-causing) *PTEN* gene.

'Hamartoma' is a general term for a benign, or non-cancerous, tumour-like growth. *PHTS* is a broader term which includes Cowden syndrome (CS).

***PTEN* is a gene that makes an important protein to control cell growth and division.** When a fault occurs in the *PTEN* gene, the protein cannot be made properly and cell growth becomes uncontrollable, which often leads to the development of benign tumours or cancer.

In rare cases, individuals with faults in other genes like *AKT1* and *PIK3CA* can present with features similar to CS. Genetic testing can clarify where the gene fault lies.

What is Cowden syndrome?

CS occurs in an estimated **one in 200,000 people**. Individuals with CS may develop both benign and malignant (cancerous) tumours in the breasts, uterus, thyroid, gastrointestinal tract, skin, tongue and gums.

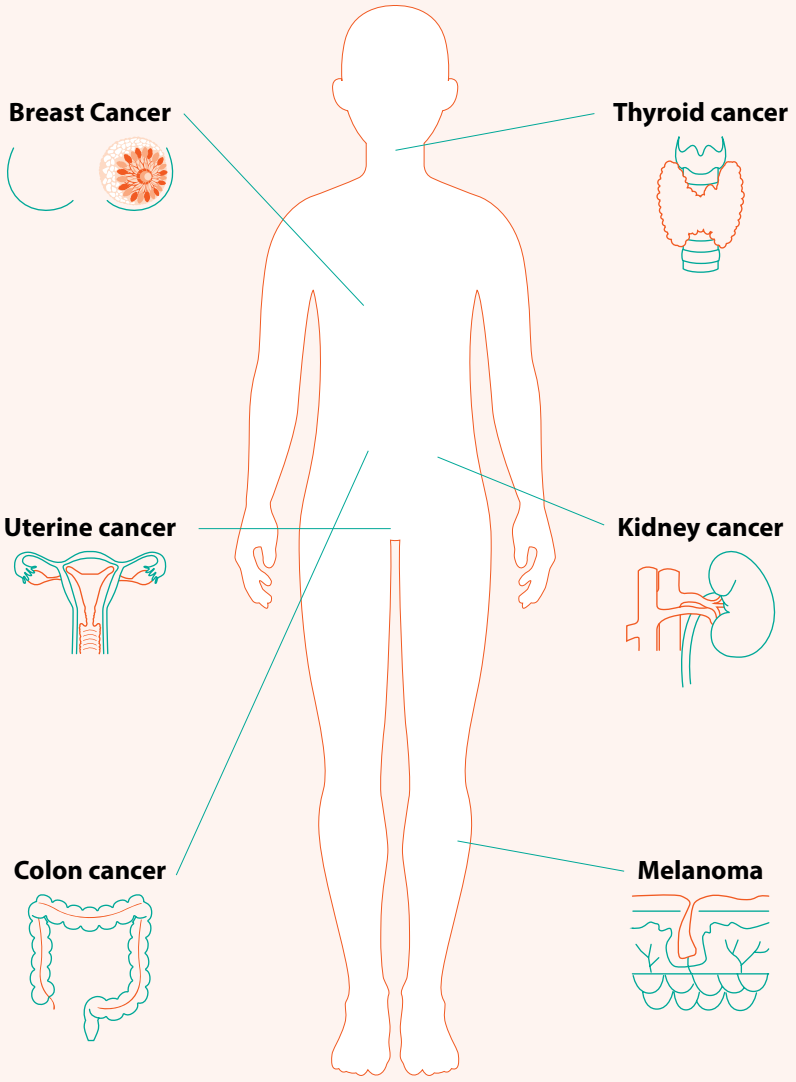
People with CS are also at higher risk of developing various cancers.

Lifetime cancer risks for individuals carrying a faulty *PTEN* gene

Cancer type	PTEN carriers	General population risk
Breast (female)	40 - 60%	13%
Thyroid	6 - 38%	1%
Uterine (endometrial)	19 - 28%	3%
Renal (kidney)	2 - 24%	2%
Colon	9 - 32%	4%
Melanoma (skin)	5%	2%

Note: The cancers associated with a faulty PTEN gene and their risk estimates may change as more information is available.

The common cancers in individuals with a faulty *PTEN* gene



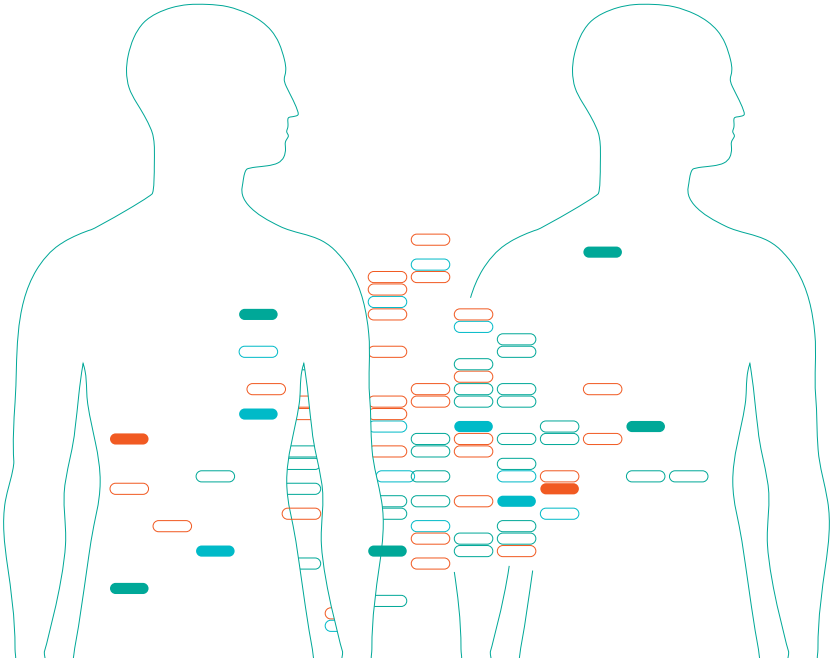
Other non-cancer features associated with CS include:

- A large head size (macrocephaly)
- Benign tumours of the thyroid, breast and endometrium
- Bumps/growths on the skin (trichilemmomas) or in the mouth (papillomatosis)
- Polyps (growths) in the colon or intestines
- Autism
- Developmental delay
- Blood vessel malformations or haemangiomas (strawberry marks)
- Benign tumours (lipomas) commonly found on the upper back and shoulders

How is CS diagnosed by doctors?

Individuals can be diagnosed with CS through a physical examination and clinical evaluation by a doctor with experience in managing the condition, to assess if the clinical diagnostic criteria of CS is met.

If a patient is found to meet clinical testing criteria or to have features suggestive of CS, genetic testing may be offered.



How is CS inherited?

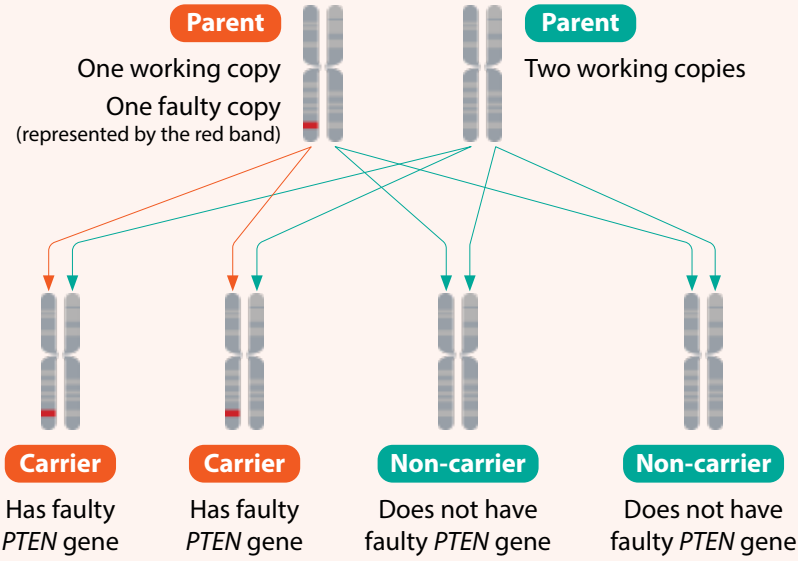
Cowden syndrome follows a **dominant inheritance pattern**. This means that having one copy of a faulty *PTEN* gene will result in the diagnosis of CS and an increased risk of tumours/cancer. It affects both males and females.

Everyone has 2 copies of each gene in their body's cells:

1 copy comes from our father

1 copy comes from our mother

Dominant inheritance pattern



- A parent with a faulty gene(s) has a 50% chance of passing down their faulty gene(s) to their children.
- A child, sibling or parent of a family member with a faulty gene(s) has a 50% chance of also inheriting the same faulty gene(s).
- Extended relatives may also inherit the faulty gene(s).

Who should undergo testing for CS?

Genetic testing is usually recommended for individuals who meet one or more of the criteria below:

- Clinically diagnosed with CS
- A family member who has a clinical diagnosis of CS/PHTS for whom testing has not been performed AND meets:
  - Any two major criteria; ***OR***
  - One major and two minor criteria; ***OR***
  - Three minor criteria
- A previously identified faulty *PTEN* gene in the family

Major criteria

- Breast cancer
- Uterine (endometrial) cancer
- A certain type of thyroid cancer (follicular)
- Multiple benign growths in the intestine or on nerves
- Rare benign brain tumour (Lhermitte-Duclos disease)
- Large head size (macrocephaly)
- Penile freckling
- Lesions on skin (trichilemmomas)
- Abnormal thickening of the hands and feet (palmoplantar keratosis)
- Lesion in mouth (mucosal papillomatosis)

Minor criteria

- Colon cancer
- Multiple benign growths in the oesophagus (oesophageal glycogenic acanthosis)
- Intellectual disability
- A certain type of thyroid cancer (papillary thyroid cancer)
- Thyroid lesions, such as adenoma, nodule(s) or goiter
- Kidney cancer (renal cell carcinoma)
- Autism
- Blood vessel anomalies (haemangiomas)
- Benign soft tissue tumour (lipoma)
- Single benign growth in the intestine or on nerves (gastrointestinal hamartoma or ganglioneuroma)
- Multiple benign lumps in the testicles (testicular lipomatosis)

Note: The criteria outlined here may change as more information is available.

How can your genetic test result help you?

1. Personalised management

Your genetic test result may help confirm a clinical diagnosis of CS. Understanding if you have CS provides you with options for managing your risk of tumours/cancer.

For example, screening options may be recommended to you which can help to detect tumours/cancer at its earliest, most treatable and manageable stage.

In some cases, you may choose to undergo surgery that can help to reduce your risk of developing cancer (not standard management). For individuals planning a family, dedicated reproductive options may also be available.

2. Familial implications

Your genetic test result can also help you understand if other family members are at risk of CS. They can subsequently consider their own testing (predictive testing) to clarify their carrier status to determine tumour and cancer risks.

Family members who ***have inherited*** the same faulty gene may be at increased risk of tumours and cancer and can benefit from management options such as screening (to detect tumours and cancer at an early and manageable stage) or surgery (to reduce their risk of cancer).

Family members who ***did not inherit*** the faulty gene can avoid unnecessary screening and worry. Their children will also not be at risk.

What can I do to manage my increased risk of cancer?

Screening

Screening helps to detect (and in some cases treat) tumours and/or cancer at an early and manageable stage.

General

- Physical examination by a doctor with experience in managing CS

Breast cancer (for females)

- Practice breast self-awareness
- Regular clinical breast examination
- Breast mammograms and/or magnetic resonance imaging (MRI) scans

Uterine (endometrial) cancer (for females)

- Prompt reporting of symptoms (e.g., abnormal uterine bleeding)
- Consider endometrial biopsies (limited evidence of benefit)

Kidney cancer

- Consider kidney ultrasounds

Skin cancer

- Examinations by a skin doctor (dermatologist)

Screening (continued)

Colorectal cancer

- Colonoscopies

Thyroid cancer

- Thyroid ultrasounds

Your managing doctor(s) will discuss screening recommendations with you in greater detail, which may be tailored based on your personal and medical history. The age and onset for screening may depend on your personal and/or family history of cancer. Screening guidelines may change as more information is known.

Risk-reducing surgery

In some cases, risk-reducing surgery may be offered to help reduce the risk of cancer.

Breast cancer (for females)

- Consider risk-reducing surgery to remove breast tissue (bilateral mastectomy)

Uterine (endometrial) cancer (for females)

- Consider risk-reducing surgery (hysterectomy) to remove the womb (uterus) in certain cases, upon family completion

Your managing doctor(s) will discuss these options with you in greater detail. These surgeries reduce cancer risk significantly but do not remove the risk entirely.

Frequently Asked Questions (FAQs)

Q: Who is the best person in the family to undergo genetic testing?

A: Genetic testing is usually offered to **the family member whose personal history is most suggestive of a hereditary cancer syndrome** (e.g., someone with a personal history of tumours/cancer at a young age or clinical presentations suggestive of CS).

It is usually not advisable to test someone without a history of cancer, tumours or clinical features.

The genetic test results of an asymptomatic individual may have limitations:

- If they were to receive a negative result, it may not mean that there is no hereditary cause of tumours/cancer in the family. The individual being tested may not have inherited it, but others in the family may have, or the faulty gene may not have been identified yet.
- The result is only useful to the asymptomatic person being tested and their children, but not to their parents, siblings and other second-degree family members.

Once the faulty gene in the family is identified, genetic testing can be offered to other family members, including those who do not have cancer. This would help in understanding if they have inherited the faulty gene and if so, tailoring their management to manage or reduce their risks.

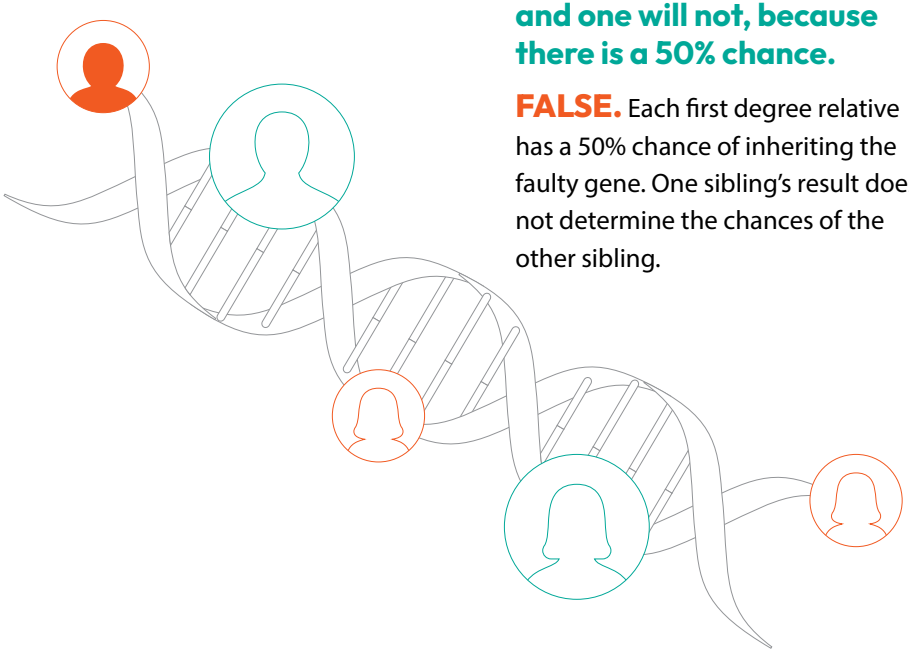
Q: Is testing recommended in children?

A: As children with CS may develop medical issues or tumours/cancer at a young age, genetic testing for CS is recommended in young children. However, genetic testing is only offered when the child has a personal history suggestive of CS, or if a faulty gene is identified in the family (i.e., a parent has CS).

Common Myths & Misconceptions

If my genetic test result is positive, it means that I have or will have cancer, or my cancer will recur.

FALSE. Results from a genetic test do not determine the likelihood of a tumour/cancer being present or tumour/cancer recurrence. Instead, a genetic test that indicates you have CS means you may face an increased risk of tumours/cancer developing over your lifetime.



If I test positive, it means that my children will also have CS.

FALSE. If you have a genetic test result confirming a diagnosis of CS (a faulty *PTEN* gene is identified), it means that your children have a 50% (1 in 2) chance of inheriting the same faulty *PTEN* gene.

I have two brothers, so one will inherit the faulty gene and one will not, because there is a 50% chance.

FALSE. Each first degree relative has a 50% chance of inheriting the faulty gene. One sibling's result does not determine the chances of the other sibling.

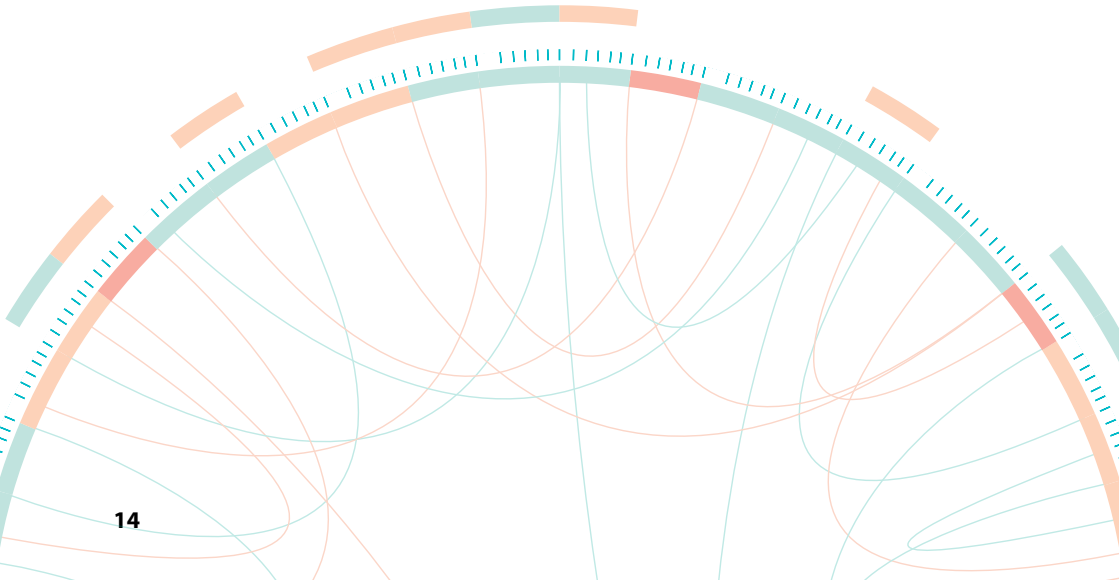
Common Myths & Misconceptions

I only need to tell my brothers, sisters and children. My extended relatives (aunties, uncles, cousins) are too far removed so I do not need to let them know.

FALSE. Distant relatives can inherit the faulty gene. It is important to let them know so that they can consider their own genetic testing (predictive testing) to understand their risk of developing tumours/cancer.

I (or my relative) already had cancer, so I (or my relative) need not undergo genetic testing.

FALSE. Individuals who have been diagnosed with cancer previously should still consider genetic testing, especially if their personal history is suggestive of CS. They may be at risk of developing another tumour/cancer, for which there are early screening strategies that can help detect tumours/cancer at a early and manageable stage.



If you have any questions, please contact:

Cancer Genetics Service,
National Cancer Centre Singapore
30 Hospital Boulevard, Singapore 168538
Mondays to Fridays: 8.30am to 5.30pm
Weekends and Public Holidays: Closed

Tel: **6436 8000**
Email: **cgsgroup@nccs.com.sg**
Website: **www.nccs.com.sg/patient-care/specialties-services/cancer-genetics-service**

Cancer Helpline

Tel: **6225 5655**
Email: **cancerhelpline@nccs.com.sg**

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Acknowledgements

Editors

Ms Jeanette Yuen

Dr Chiang Jianbang

Authors

Dr Joanne Ngeow

Dr Zhang Zewen

Ms Tarryn Shaw

Ms Li Shao-Tzu

Ms Goh Hui Xuan

Mr Benjamin Fong

Information contributed by:

SingHealth DukeNUS ACADEMIC MEDICAL CENTRE

Genomic Medicine Centre

KK Women's and Children's Hospital
6294 4050
www.kkh.com.sg

Singapore General Hospital
6321 4377
www.sgh.com.sg

Changi General Hospital
6850 3333
www.cgh.com.sg

Sengkang General Hospital
6930 6000
www.skh.com.sg

National Cancer Centre Singapore
6436 8088
www.nccs.com.sg

National Heart Centre Singapore
6704 2000
www.nhcs.com.sg

National Neuroscience Institute
6321 4377 (SGH Campus)
6330 6363 (TTSH Campus)
www.nni.com.sg

Singapore National Eye Centre
6227 7266
www.snec.com.sg

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