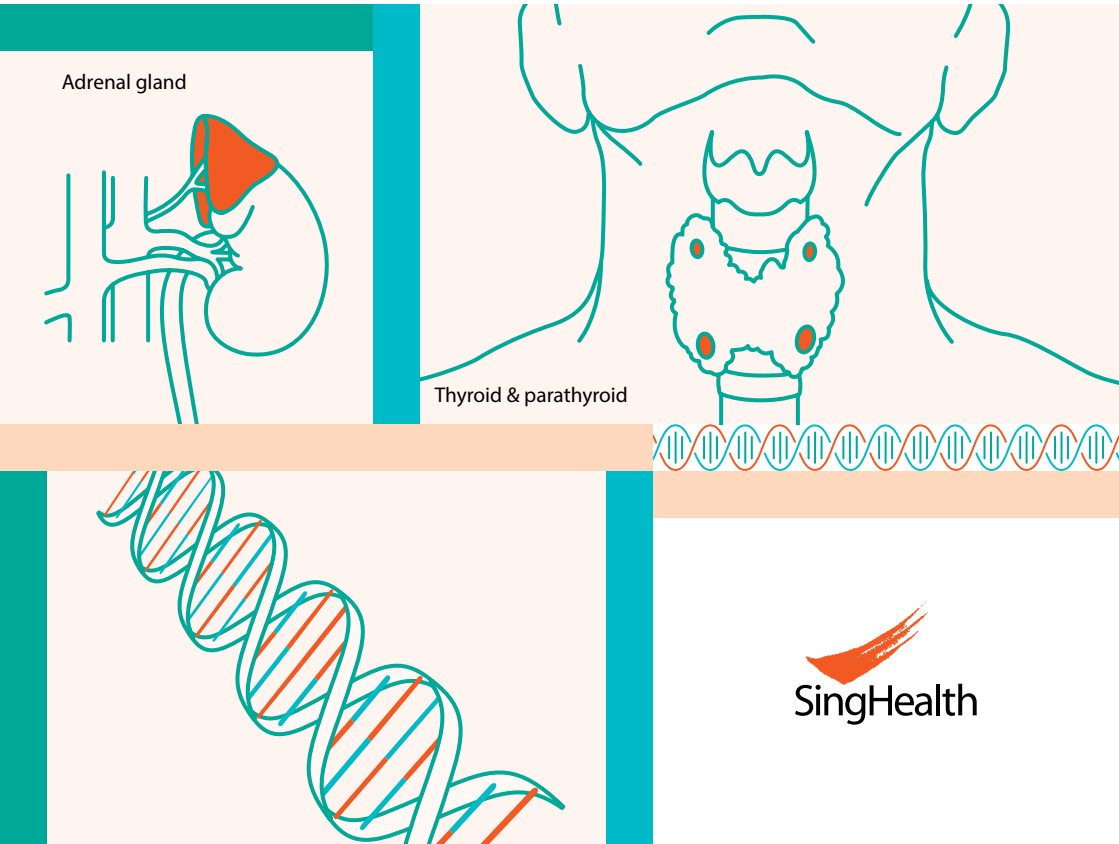
SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE

Genomic
Medicine Centre

Multiple Endocrine Neoplasia Type 2 (MEN2)



SingHealth

Multiple Endocrine Neoplasia Type 2 is a hereditary cancer syndrome.

What are hereditary tumours and cancers?

Hereditary tumours and cancers develop because of the presence of a faulty gene. Some genes function to protect us from cancer/tumour growth. When they are not working well, it causes an increased risk of tumours/cancers developing. We refer to genes that are not working well as faulty genes.

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

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

What is genetic testing?

Genetic testing is offered to individuals where a hereditary cause of their personal and/or family history of tumours/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 tumours/cancers developing.

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.

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

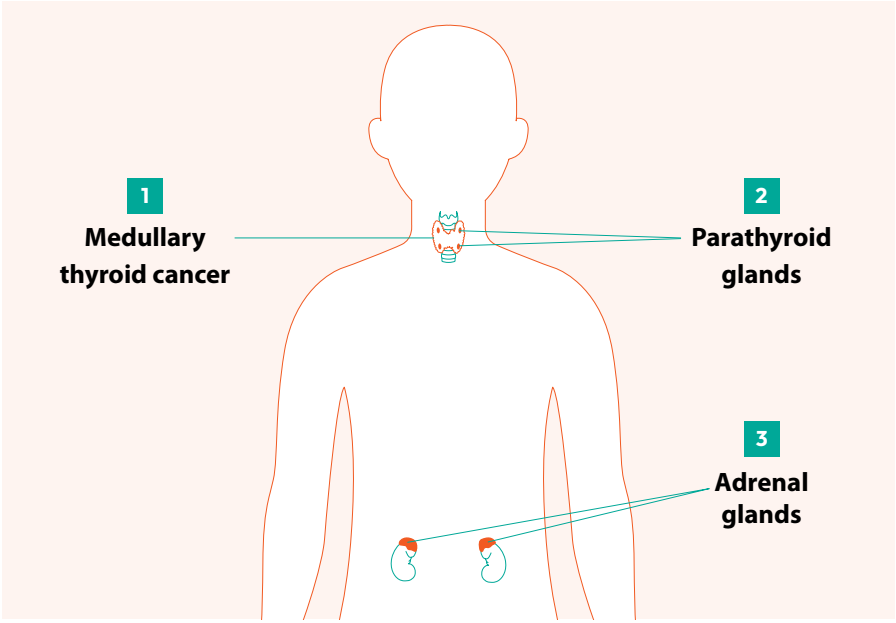
Tumour and cancer risk is similar to that of general population

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

What is Multiple Endocrine Neoplasia Type 2?

Multiple Endocrine Neoplasia Type 2 (MEN2) is a hereditary condition associated with an increased risk for developing tumours and cancers of the endocrine (hormone producing) glands.

What are the tumours and cancers commonly associated with MEN2?



Medullary thyroid cancer

Medullary thyroid cancer is a cancer of the thyroid gland. It is the most common tumour caused by MEN2. The thyroid is a small gland in the front of the neck, just below the voice box.

The symptoms of medullary thyroid cancer include:

- A painless lump in the neck
- Changes in swallowing or breathing (due to the tumour pressing on the windpipe)

Overactive / enlarged parathyroid glands (hyperparathyroidism)

The parathyroid glands are located just behind the thyroid gland, infront of the neck. If you have MEN2A, the parathyroid glands may become large and overactive (hyperparathyroidism). This mostly happens from ages 20 to 40.

Parathyroid glands produce a hormone called parathyroid hormone (PTH) which helps to control the body's calcium levels. People with overactive parathyroid glands may make too much PTH, which can result in high levels of calcium in the blood.

This can make you:

- Nauseous
- Thirsty
- Constipated
- Need to pass urine often
- Drowsy or confused

The high levels of PTH can also cause bones to become weaker and more prone to fracture. High calcium levels can also affect the kidney, possibly leading to the development of kidney stones and kidney damage, which can be avoided if you are diagnosed and seek treatment early.

Phaeochromocytoma

Phaeochromocytoma (PCC) is a tumour of the adrenal glands, the small glands above the kidneys. It is usually noncancerous.

People with MEN2A or MEN2B can develop PCC, and one or both of the adrenal glands may be affected. PCC can cause the adrenal gland to make large amounts of hormones such as adrenaline (epinephrine) and adrenaline-like hormones.

Adrenaline regulates the heart rate and blood pressure, and too much of it can cause symptoms such as:

- Severe headaches
- Fast heart palpitations
- Excessive sweating
- Feeling anxious
- High blood pressure, or fluctuating blood pressure

All patients with medullary thyroid cancer, phaeochromocytoma or paraganglioma diagnosis are recommended to have genetic testing.

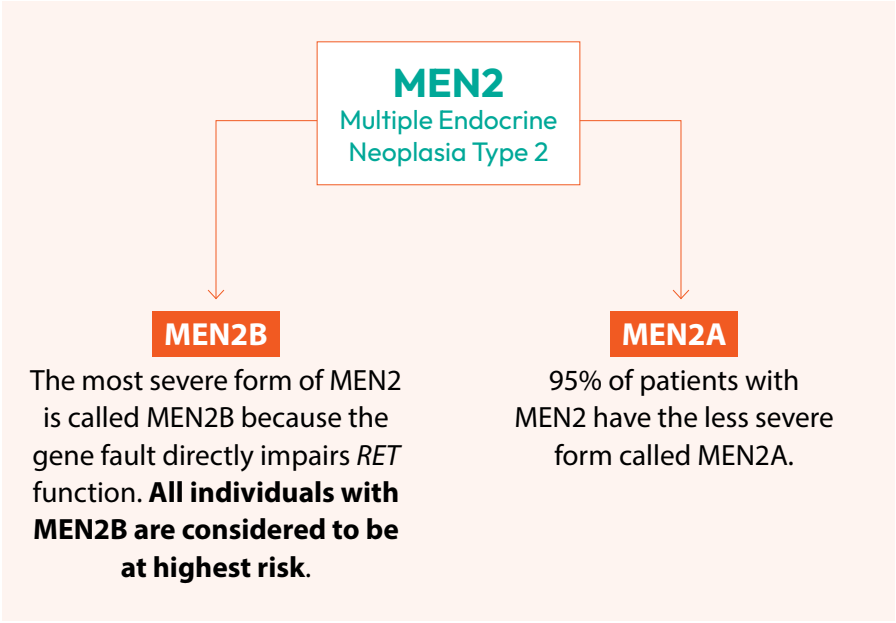
What causes MEN2?

People with MEN2 are born with a faulty (i.e., disease-causing) *RET* gene.

When working properly, the *RET* gene provides instructions to produce a protein involved in signalling within cells. This signalling is needed to ensure normal development and controlled growth of cells.

If there is a fault (i.e., mutation) within the *RET* gene, it can become dysfunctional, resulting in the production of an overactive protein which can signal cells to grow and divide uncontrollably, resulting in tumour formation and cancer.

The location of the fault within the *RET* gene can determine the age, likelihood and aggressiveness of the medullary thyroid cancer that may develop. Its management will be based on where the location of the fault is in the *RET* gene.



What are the tumour and cancer risks associated with MEN2?

Lifetime tumour and cancer risks or individuals with a faulty *RET* gene		
Cancer/tumour type	**Risk for individuals with a faulty *RET* gene**	
MEN2A		
Medullary Thyroid Cancer	• 4 - 8% by age 10 • 25 - 50% by age 28	• 80% by age 50 • Almost 100% by age 70
Phaeochromocytomas	• 25 - 88%	
Hyperparathyroidism	• 2 - 30%	
MEN2B		
Medullary Thyroid Cancer	• 100% by age 10	
Phaeochromocytomas	• 50% (lifetime)	
Hyperparathyroidism	• Same as population risk	

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

Depending on your genetic result and personal/family history of cancer, your personal risk levels may differ from the values shown above.

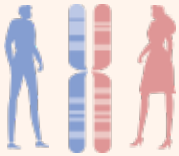
There is a classification system that determines the medullary thyroid cancer risk level based on where the fault in the *RET* gene is located. It is best to ask your genetics service to understand your risk level in more detail.

Your managing doctors will also advise you on the medical care that might or might not be beneficial for you, according to your risk level.

How is MEN2 inherited?

MEN2 follows a **dominant inheritance pattern**. This means that having one faulty copy of the *RET* gene can result in an increased risk of tumours/cancer. It can affect both males and females.

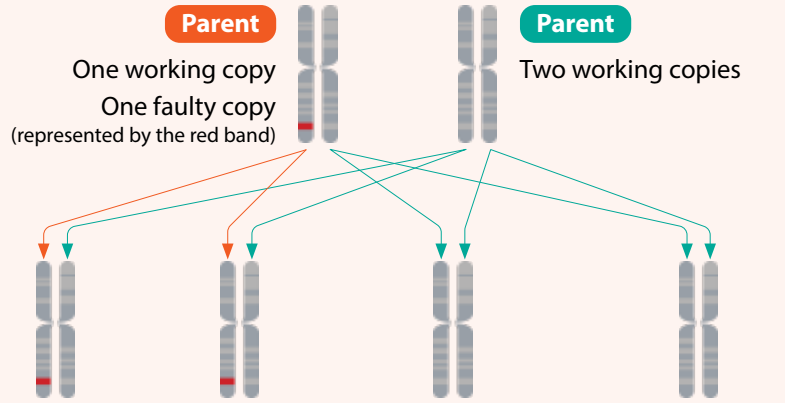
Everyone has 2 copies of each gene in their body's cells:



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 genetic testing for MEN2?

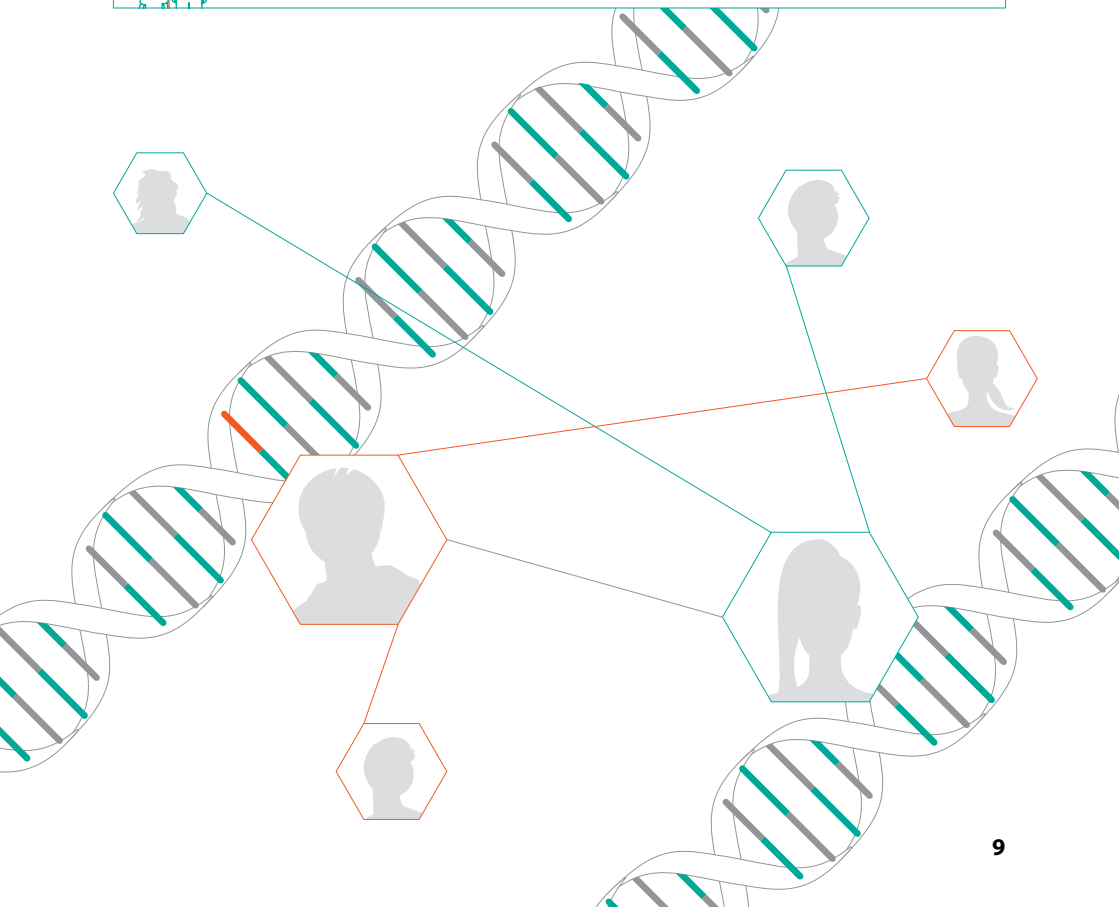
You should consider genetic testing if you or your family members meet one or more of the following criteria:

- Medullary thyroid cancer

- Paraganglioma or phaeochromocytoma

- Family history of any of the above

- Family members who have been previously identified to have MEN2



How can your genetic test result help you?

1. Personalised management

In individuals who are diagnosed with medullary thyroid cancer, genetic testing is important to determine if the cause of it is sporadic (spontaneous) or hereditary.

If the cause is hereditary:

- **Genetic testing** can confirm the correct genetic diagnosis and help guide surveillance and medical management based on the risks associated with the particular condition.
- **Surveillance** can help detect tumours and cancer at an early and manageable stage, and avoid irreversible or serious medical complications.
- **Surgery** can be advised in some cases to reduce your risk of tumours/cancer.
- **Reproductive options** may also be available for individuals planning a family.

It is important to identify the type of faulty *RET* gene you may have, as the various types carry different tumour/cancer risks which would affect how doctors plan for your medical management.

2. Familial implications

Your genetic test result can also help you understand if other family members are at risk of MEN2. 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 *RET* 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 *RET* 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 tumours and cancer?

Screening

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

Medullary thyroid cancer

- Blood test to check calcitonin levels
- Thyroid ultrasound and physical examination

Hyperparathyroidism

- Blood tests to check for parathyroid hormone and calcium levels

Phaeochromocytomas

- Physical examination
- Blood pressure measurement
- Urine test to check hormone levels
- Further imaging (computed tomography [CT] / magnetic resonance imaging [MRI]) may be ordered

Your managing doctor(s) will discuss screening recommendations with you in greater detail. The age and onset for screening is dependent on your risk level, and may change according to personal and/or family history of tumours/cancer. Screening guidelines may change as more information is known.

Risk-reducing surgery

Risk-reducing surgery may be offered to help reduce the risk of cancer/tumours.

Medullary thyroid cancer

- Removal of the thyroid

Hyperparathyroidism

- Consider removal of parathyroid alongside thyroid surgery

Your managing doctor(s) will discuss these options with you in greater detail. The time and age of surgery is usually advised according to your risk level and your personal and/or family history of tumours/cancers.

Frequently Asked Questions (FAQs)

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

A: In order to determine if a hereditary cause exists in the family, genetic testing is usually initially offered to **the family member whose personal history is most suggestive of MEN2** (e.g., someone with a personal history of medullary thyroid cancer at a young age or clinical presentations suggestive of MEN2).

It is usually not advisable to test someone without a history of cancer / tumours / clinical features unless a hereditary cause has already been identified in the family.

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

- If they were to receive a negative result, it may not mean that there is no hereditary cause of cancer/tumours 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 a tumour/cancer. This will help them understand if they have inherited the faulty gene change and if so, tailor their management to manage or reduce their risks.

Common Myths & Misconceptions

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

FALSE. The genetic test result cannot determine the likelihood of tumour/cancer recurrence or the presence of a tumour/cancer. A positive result only indicates that you have been diagnosed with MEN2 and are at an increased risk of developing tumours/cancer.

If I or my child tests positive, it means that my children/ grandchildren will develop tumours/cancer.

FALSE. If you or your child has a positive genetic test result where a faulty *RET* gene is identified, it means that each of your children/ grandchildren has a 50% (1 in 2) chance of inheriting the faulty *RET* gene.

My child looks a lot like me, so he/she must have inherited the faulty gene(s) since I have it.

FALSE. Genes that govern your appearance are different from the *RET* gene that causes MEN2. All first-degree relatives (siblings, children and parents) have a 50% (1 in 2) chance of inheriting the faulty *RET* gene, regardless of whether they look like you or not.

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

FALSE. Each first-degree relative (parents, siblings and children) has a 50% (1 in 2) chance of inheriting the faulty gene(s). The genetic test result of one sibling does not impact the chances of the other sibling.

If you have any questions, please contact:

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Mondays to Fridays: 8.30am to 5.30pm
Weekends and Public Holidays: Closed

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Scan the QR code for online resources by the Cancer Genetics Service.

If you wish to support the Cancer Genetics Service's education, research and patient support efforts, please scan the QR code to make a donation.

Acknowledgements

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