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ACADEMIC MEDICAL CENTRE

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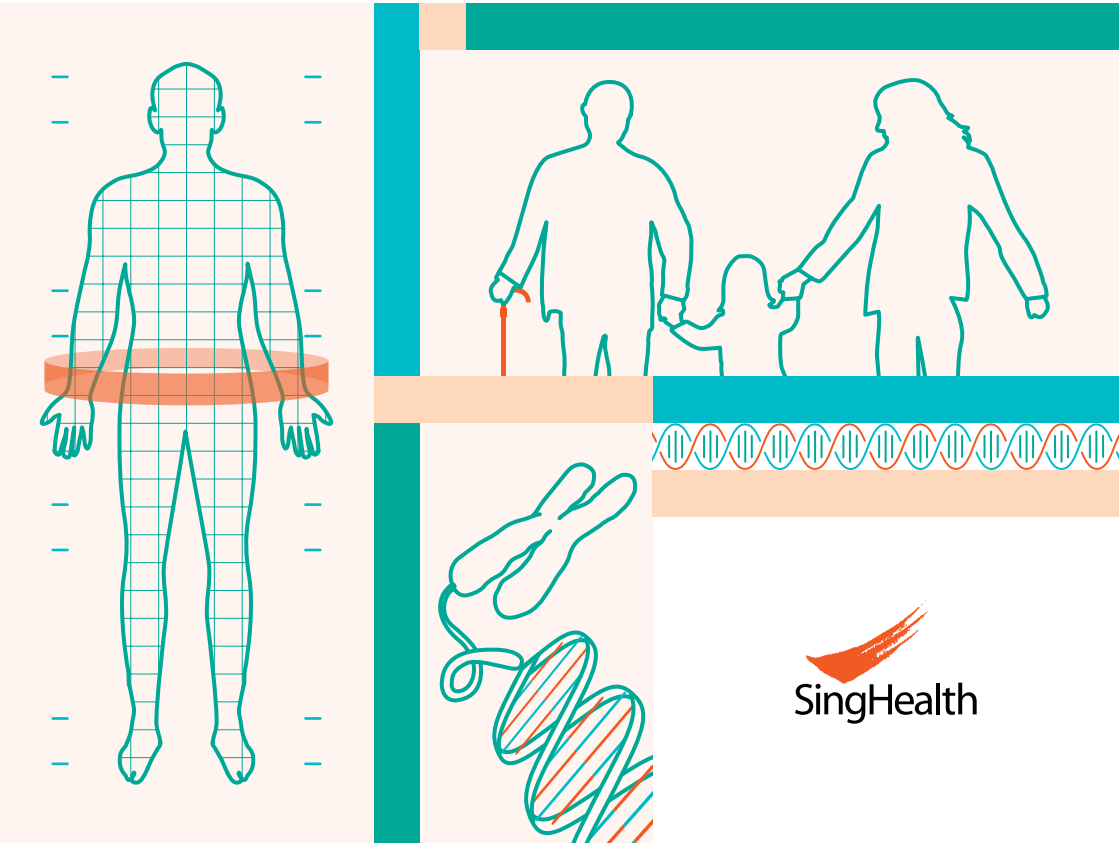
# Li-Fraumeni Syndrome



SingHealth

# Li-Fraumeni 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.

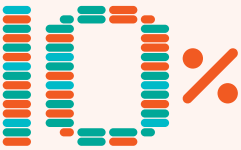
## What is genetic testing?

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

### 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

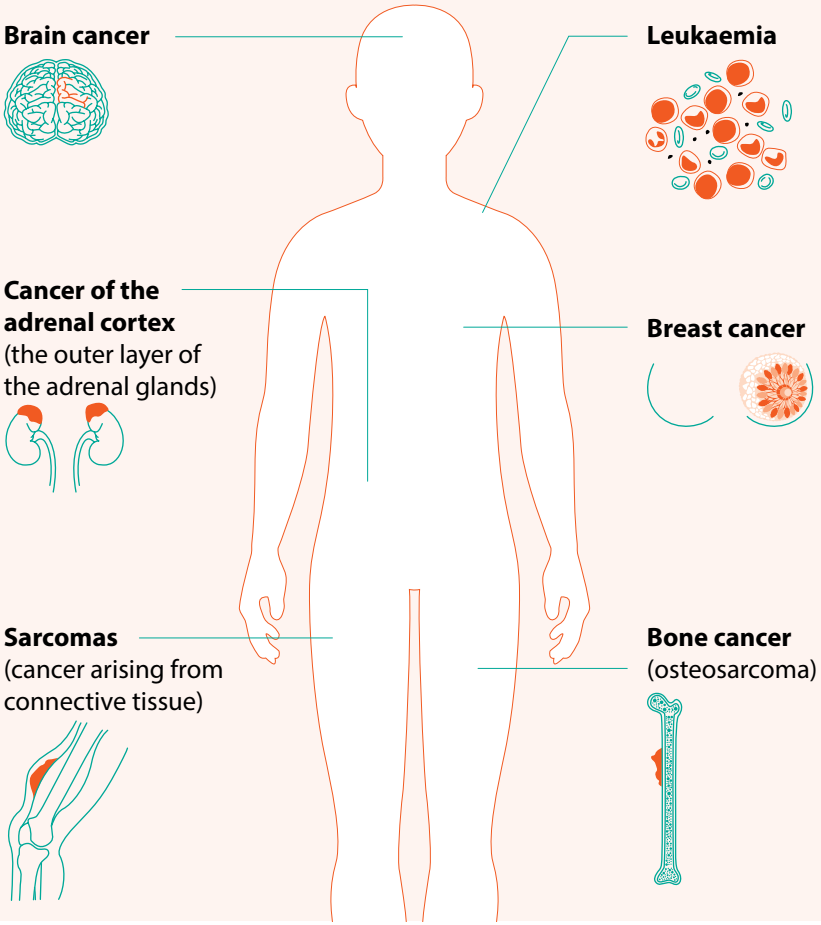
Tumour and cancer risk is similar to that of general population

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

## What is Li-Fraumeni syndrome?

Li-Fraumeni syndrome (LFS) is a hereditary condition associated with higher risks of a range of childhood- and adult-onset cancers. This condition can be passed down in a family and is caused by a faulty (disease-causing) *TP53* gene.

**The most common types of cancers associated with LFS include sarcomas (cancers arising from connective tissue) and:**



## What are the cancer risks associated with LFS?

| Cancer risks for individuals aged 20 and under with a faulty *TP53* gene | | |
|---|---|---|
| **Cancer type** | **LFS risk (up to age 20)** | **General population risk (up to age 20)** |
| **Overall cancer** | Females: 15 - 27%<br>Males: 25 - 39% | < 0.4% |
| **Soft tissue cancer** (sarcoma) | Females: 2.5 - 5%<br>Males: 6 - 12% | 0.02% |
| **Bone cancer** (osteosarcoma) | Females: 2.5 - 7.5%<br>Males: 7.5 - 12.5% | Rare |
| **Brain** (various) | Up to 8% | 0.04% |
| **Cancer of the adrenal cortex** (adrenocortical carcinoma) | Up to 9% | Rare |

The risk of other cancers including leukaemia, Wilms tumour, neuroblastoma, and lung, colorectal, stomach and pancreatic cancers may also be increased (risk figures not quantified).

*Note: The conditions associated with LFS and their risk estimates may change as more information is available. Published literature may overestimate cancer risks. These figures are based on retrospective analysis which may be biased towards families with an excess of cancer diagnoses.*

| Lifetime cancer risks for individuals with a faulty *TP53* gene | | |
|---|---|---|
| **Cancer type** | **LFS risk (up to age 70)** | **General population risk (up to age 70)** |
| **Overall cancer (female)** | > 95% | 22% |
| **Overall cancer (male)** | > 90% | 23% |
| **Breast (female)** | 85% | 13% |
| **Soft tissue cancer** (sarcoma) | 50% | Rare |
| **Bone cancer** (osteosarcoma) | 10% | Rare |
| **Brain cancer** | 20 - 30% | Rare |
| **Colorectal cancer** | Up to 24% | 4% |
| **Gastric cancer** | 1 - 16% | ~1% |
| **Cancer of the adrenal cortex** (adrenocortical carcinoma) | Increased | Rare |
| **Others: Lung, prostate, renal, melanoma and pancreatic cancers** | Increased | – |
| **Risk of second primary cancer** | 50% by 10 years | 8% |

*Note: The conditions associated with LFS and their risk estimates may change as more information is available. Published literature may overestimate cancer risks. These figures are based on retrospective analysis which may be biased towards families with an excess of cancer diagnoses.*

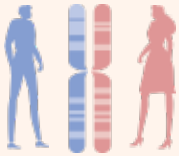
## How is LFS inherited?

LFS follows a **dominant inheritance pattern**. This means that individuals who have one faulty copy of the *TP53* gene have an increased risk of cancer. It can affect both males and females.

## How common is LFS?

The estimated frequency of LFS ranges between **one in 5,000 to 20,000 people**. These rates may change as more information is known.

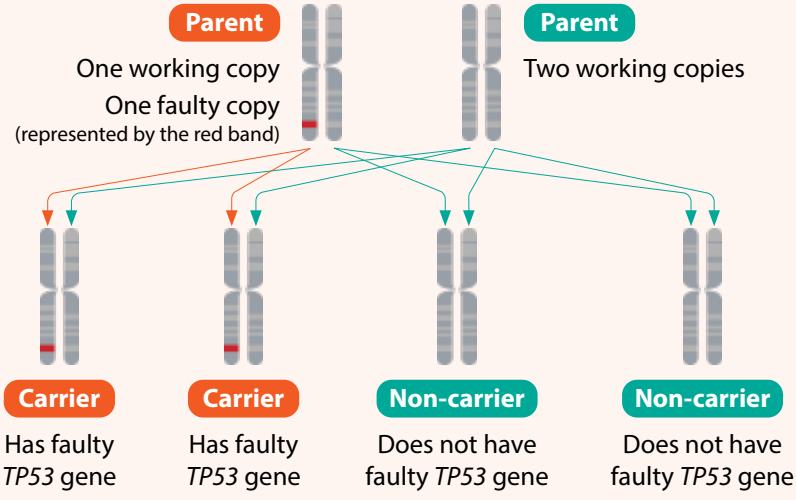
Everyone has 2 copies of each gene in their body's cells:



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 LFS?

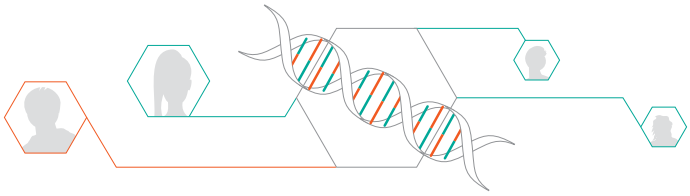
You should consider genetic testing if you or your family members meet one or more of the following criteria:

1. Sarcoma diagnosed before the age of 45
2. Sarcoma diagnosed at any age, with a relative diagnosed with cancer before the age of 45 or a sarcoma diagnosed at any age
3. Breast cancer diagnosed before the age of 31
4. A LFS-related condition* diagnosed before the age of 46 and a family history of cancer
5. Two or more LFS-related conditions* in the same individual
6. Two or more family members on the same side of the family with a LFS-related condition* before the age of 56
7. Adrenocortical cancer or rhabdomyosarcoma at any age
8. Tumour in the choroid plexus (membrane surrounding the brain) at any age
9. A previously identified faulty *TP53* gene in the family
10. A *TP53* gene fault identified at high frequency on tumour testing

While LFS may run in families, up to 25% of individuals with LFS may have acquired a faulty *TP53* gene at birth (*de novo*). Therefore, genetic testing may also be offered in the absence of relevant family history and/or if an individual's personal history is suspicious for LFS.

***LFS-related conditions:**

- Soft tissue cancer (sarcoma)
- Bone cancer (osteosarcoma)
- Central nervous system tumour
- Breast cancer (often early-onset)
- Adrenocortical tumour
- Leukaemia
- Bronchoalveolar cancer
- Colorectal cancer



## How can your genetic test result help you?

### 1. Personalised management

Your genetic test result may confirm whether your personal and/or family history is due to a hereditary condition like LFS, and clarify what your lifetime cancer risks may be. This information can be useful for doctors to personalise your medical care to help manage or reduce cancer risks.

#### If you have a cancer diagnosis

- Helps guide important treatment and/or surgical decisions
- Indicates what other cancers you are at risk of and how to manage these risks

#### If you are currently cancer-free

- Helps guide management and relevant screening options for you to detect cancer at its earliest, most treatable stage
- Helps guide your lifestyle and screening decisions (e.g., unnecessary radiation exposure should be avoided)
- Helps guide decisions regarding relevant cancer risk-reducing interventions (e.g., surgery)
- Allows individuals with LFS to consider dedicated reproductive options for family planning

### 2. Familial implications

Your genetic test result can also help you understand if other family members are at risk of LFS. 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 *TP53* 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 *TP53* 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 cancers?

### Screening for LFS from birth

Unnecessary radiation exposure for screening or therapeutic purposes should be avoided where possible.

**General assessments**

- Regular physical examinations
- Full neurological assessments
- Early reporting of symptoms

**Adrenocortical carcinoma (ACC)**

- Ultrasound of abdomen and pelvis
- Additional blood tests may be recommended

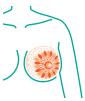
**Soft tissue and bone sarcoma**

- Ultrasound of abdomen and pelvis
- Whole-body MRI

**Brain tumour**

- Brain MRI

### ≥ 18 yr Screening for LFS from the age of 18 onwards



**Breast cancer**

- Breast awareness and self-examination
- Clinical breast examination
- Breast MRI
- Consider hormone therapy (tamoxifen/raloxifene)

≥ 18 yr

## Add-on screening for LFS from the age 18 onwards (continued)

**Melanoma**

- Dermatological examination

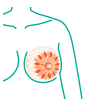
**Gastric/colorectal cancer**

- Upper gastrointestinal endoscopy and colonoscopy

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

## Risk-reducing surgery

In some cases, individuals can consider interventions such as surgery to reduce their risk of cancer.



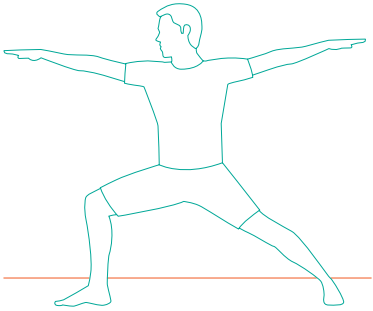
**Breast cancer**

- Bilateral mastectomy: Surgery to remove breast tissue (greatest benefit when performed under the age of 40)

This will be discussed in detail with you by your managing doctor(s). The surgery may reduce the risk of cancer significantly, but does not remove the risk completely.

## Lifestyle adjustments

- Avoid smoking
- Avoid excessive alcohol consumption
- Keep a healthy diet and active lifestyle
- Avoid sun exposure and practise sun-smart behaviour such as using sunscreen



# 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 cancer diagnosis is most suggestive of hereditary cancer syndrome** (e.g., someone with a personal history of a cancer at a young age). It is usually not advisable to test someone without a history of cancer/tumours.

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 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 *TP53* gene in the family is identified, genetic testing can be offered to other at-risk family members (including those who do not have cancer) to manage their risks.

## Q: Is testing recommended in children?

**A:** Genetic testing for LFS is recommended in young children due to an increased risk of childhood cancer from a young age. However, testing for LFS in children is only offered when the child has a personal history of certain cancers, or if a faulty *TP53* gene is identified in the family.

# 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.** Results from a genetic test do not determine the likelihood of cancer recurrence or the presence of a tumour/cancer. Instead, a positive result from your genetic test indicates that there is an increased risk of cancer.

## I only have brothers, so I do not need to tell them – this condition can only pass through females.

**FALSE.** The faulty gene for LFS can be passed to and through both females and males. There are cancer risks for both genders. It is important for both females and males to undergo testing to understand if they have inherited the faulty gene.

Brothers and sisters who inherit the gene fault have a 50% (1 in 2) chance of passing it on to any children (daughters and sons) they have.

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

**FALSE.** If you have a positive genetic test result (a faulty gene is identified), it means that your children have a 50% (1 in 2) chance of inheriting that gene fault.

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

**FALSE.** Genes that govern your appearance are different from cancer-related genes like *TP53* that cause LFS. All first-degree relatives (siblings, children, parents) have a 50% (1 in 2) chance of inheriting the faulty *TP53* gene.

# Common Myths & Misconceptions

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

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

## I only need to tell my brothers, sisters and children. My distant 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 responsible for LFS. It is important to let them know so that they can consider genetic testing to understand their risk of developing 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 they have a personal history suggestive of LFS.

Individuals with LFS are also at higher risk of developing multiple primary tumours, for which there are early screening strategies that can help detect tumours/cancer at an early and manageable stage. Their genetic testing result can also help doctors make important treatment decisions.

**If you have any questions, please contact:**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## Acknowledgements

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