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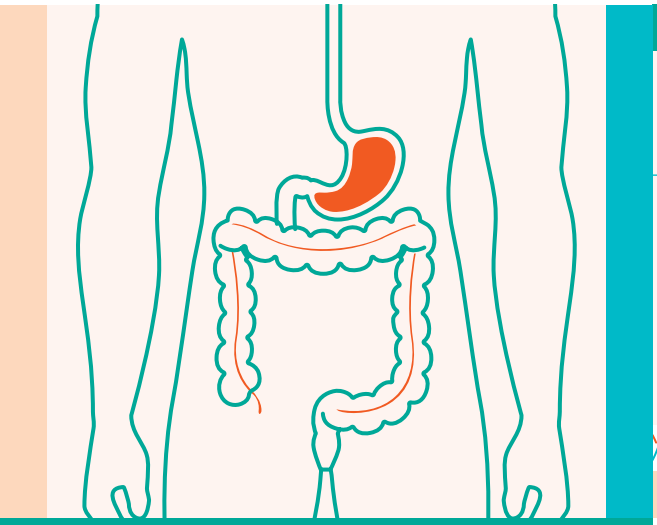
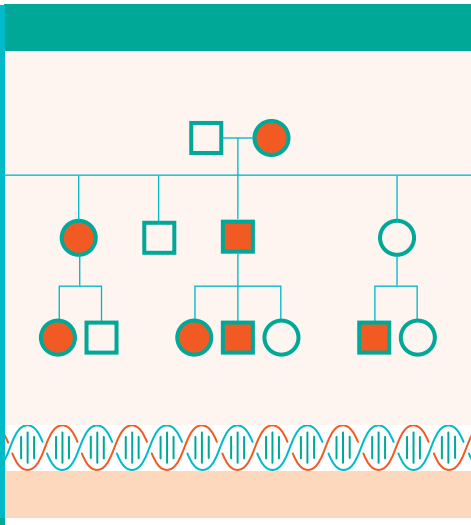
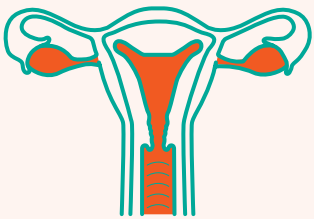
Lynch Syndrome







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Lynch 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.

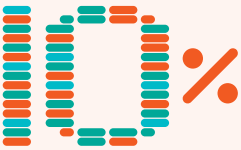
What is genetic testing?

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

What is Lynch syndrome?

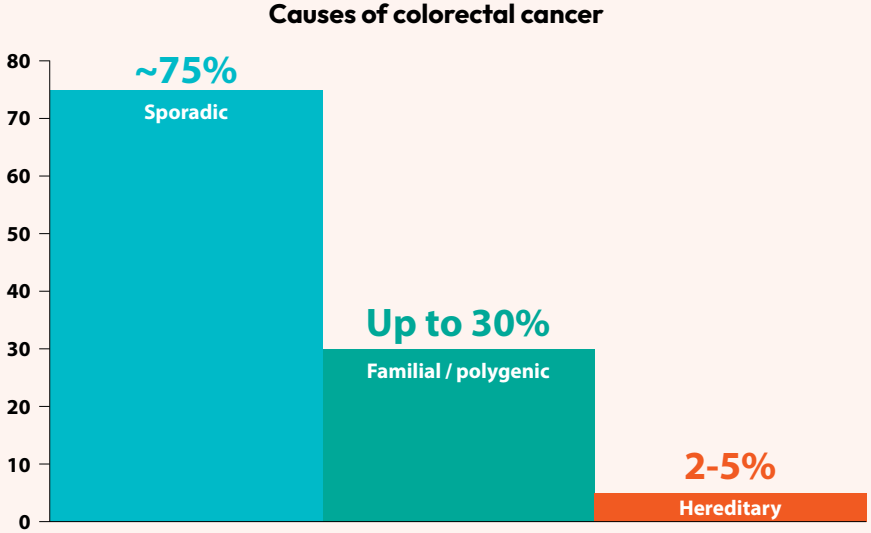
Lynch syndrome is an adult-onset hereditary condition that runs in families. It is associated with an increased risk of developing colorectal cancer as well as other cancers.

Approximately 2-5% of all colorectal cancer cases is associated with a hereditary cancer syndrome.

How common is Lynch syndrome?

Estimates suggest that **one in 300 people** may carry a faulty copy of a DNA mismatch repair (MMR) gene associated with Lynch syndrome.

Approximately, up to 5% of colorectal cancer and 3% of endometrial (uterine) cancer cases are caused by Lynch syndrome.



Sporadic

Largely caused by chance events, driven by age and environmental factors

Familial / polygenic

A combination of genes and environmental factors resulting in an elevated cancer risk

Hereditary

There are different hereditary cancer syndromes associated with an increased risk of colorectal cancer, of which Lynch syndrome is the most common

What are the cancer risks associated with Lynch syndrome?

Lynch syndrome is associated with a faulty (disease-causing) copy of MMR genes, namely *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*.

Individuals who have Lynch syndrome (carriers) face an increased risk of cancers, but it does not mean that they will definitely develop cancer. Carriers face different cancer risks depending on which faulty gene they have.

Cancer risks associated with Lynch syndrome as compared to the general population[1-2]

Cancer type	*MLH1* carrier risk	*MSH2 & EPCAM* carrier risk	*MSH6* carrier risk	*PMS2* carrier risk	General population risk
Colorectal	46 - 61%	33 - 52%	10 - 44%	9 - 20%	5%
Uterus (endometrial) (females)	34 - 54%	21 - 57%	16 - 49%	13 - 26%	3%
Ovarian (females)	4 - 20%	8 - 38%	≤ 1 - 13%	1 - 3%	1.3%
Breast (females)	May be increased				13%
Prostate (males)	4 - 14%	4 - 24%	3 - 12%	5 - 12%	12%
Renal pelvis and/or ureter	0.2 - 5%	2 - 28%	0.7 - 6%	≤ 1 - 4%	–*
Bladder	2 - 7%	4 - 13%	1 - 8%	≤ 1 - 2%	2.4%
Gastric	5 - 7%	0.2 - 9%	≤ 1 - 8%	–*	0.9%
Small bowel	0.4 - 11%	1 - 10%	≤ 1 - 4%	0.1 - 0.3%	0.3%
Pancreas	6%	0.5 - 2%	1.6%	≤ 1 - 2%	1.6%
Biliary tract	2 - 4%	0.02 - 2%	0.2 - 1%	0.2 - 1%	0.2%
Brain	0.7 - 2%	3 - 8%	0.8 - 2%	0.6 - 1%	0.6%

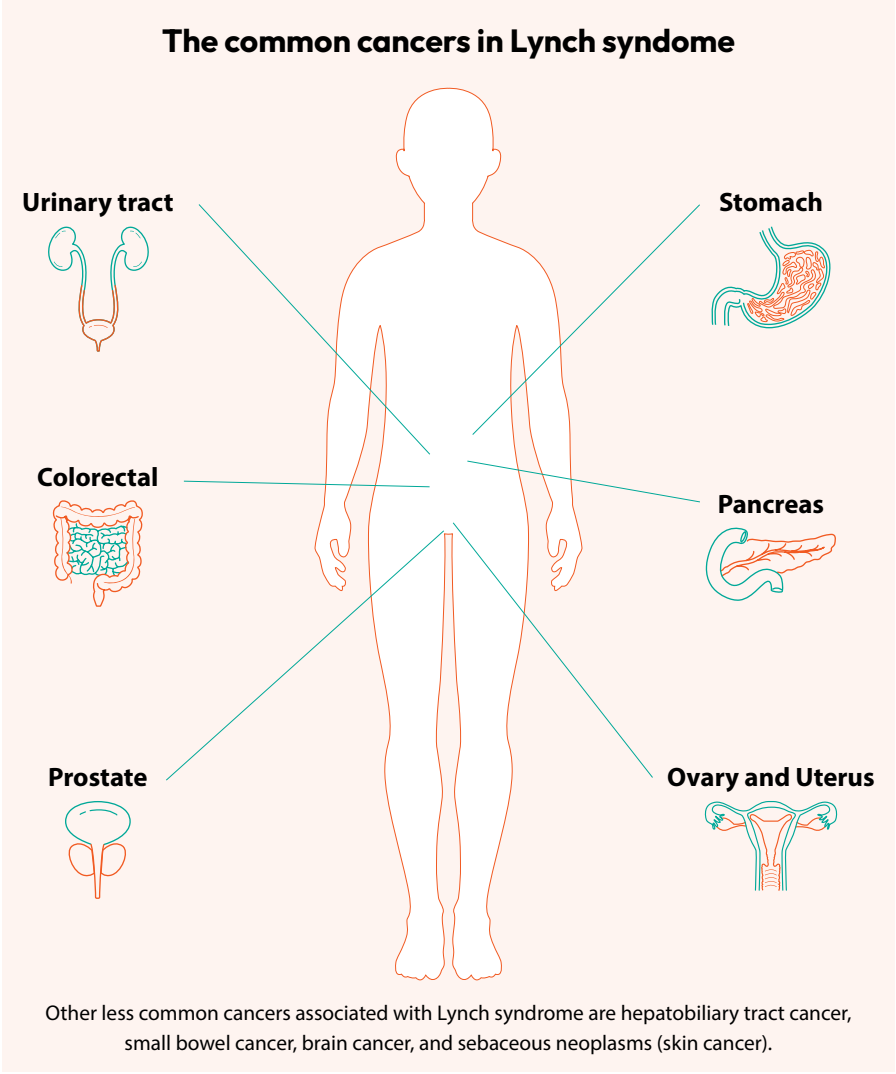
**inadequate data*

Note: The conditions associated with Lynch syndrome and their risk estimates may change as more information is available.

References

1. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2020. 2020 July 21; National Comprehensive Cancer Network.*
2. *Dominguez-Valentin, M. et al (2020). Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genetics in Medicine, 22(1), 15–25. https://doi.org/10.1038/s41436-019-0596-9*

Lynch syndrome increases the risk of cancer in both males and females.



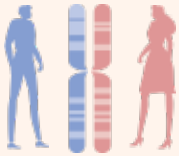
Other less common cancers associated with Lynch syndrome are hepatobiliary tract cancer, small bowel cancer, brain cancer, and sebaceous neoplasms (skin cancer).

There are other genes aside from MMR genes that increase the risk of colorectal cancer (e.g., *APC*, *POLE*, *POLD1*, *PTEN*, *CHEK2*, *MUTYH*, *NTHL1*, *MSH3*) as part of other genetic conditions. Genetic testing for colorectal cancer will usually include testing of such genes as well.

How is Lynch syndrome inherited?

Lynch syndrome follows a **dominant inheritance pattern**. This means that having one faulty copy of any MMR gene (i.e., *MLH1, MSH2, MSH6, PMS2* and *EPCAM*) can result in an increased risk of cancer.

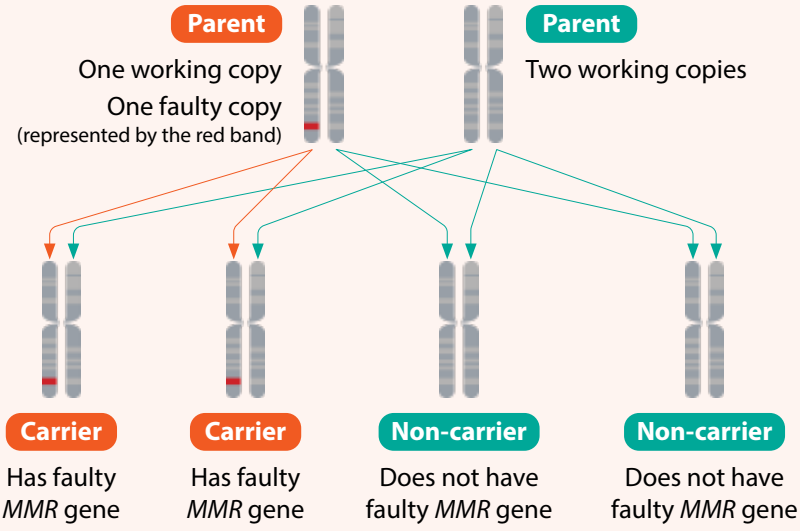
Everyone has 2 copies of each gene in their body's cells:



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 Lynch syndrome?

Occasionally, **tumour or cancer testing** may reveal results that can help guide if Lynch syndrome testing is needed for you. These tumour tests include:

1. Immunohistochemistry (IHC) testing for MMR proteins

- IHC testing can determine which MMR proteins are present or absent within the tumour
- The absence or loss of any MMR proteins is suggestive of Lynch syndrome and genetic testing may be offered to you

2. Microsatellite instability (MSI) testing

- Microsatellites are regions of repeated DNA that show instability if the MMR proteins do not function properly
- MSI testing evaluates for the presence of functional MMR proteins
- Tumours that are MSI-high (i.e., high microsatellite instability) are suggestive of Lynch syndrome and genetic testing may be offered to you

You may be recommended to undergo additional tests to determine if genetic testing is needed for you.

Your **personal and/or family history of cancer** can also help guide if genetic testing for Lynch syndrome is needed. If you or your family members meet one or more of the following criteria, you can consider genetic testing:

- Colorectal/uterine cancer diagnosed at or under the age of 50
- Colorectal/uterine cancer diagnosed with loss of MMR proteins on IHC tumour testing
- Colorectal/uterine cancer diagnosed with MSI-high result on tumour tissue
- Combination of colorectal/uterine cancer and another Lynch syndrome-related cancer*
- Two or more family members on the same side of the family diagnosed with any Lynch syndrome-related cancer*, with one diagnosed at or under the age of 50
- Three or more family members on the same side of the family diagnosed with any Lynch syndrome-related cancer* at any age
- A previously identified faulty MMR gene in the family

***Lynch syndrome-related cancers:**

- Colorectal
- Uterine (endometrial)
- Ovarian
- Gastric
- Renal pelvis and/or ureter
- Bladder
- Biliary tract
- Pancreatic
- Brain/central nervous system
- Prostate
- Breast

Note: This list may change as more information is available

How can your genetic test result help you?

1. Personalised management

Your genetic test result may help to personalise your management options based on your cancer risk.

If you have a cancer diagnosis

- Can help guide important treatment and sometimes surgical decisions
- Indicates what other cancers you are at risk of and how to manage these risks

If you are currently cancer-free

- Can help guide relevant screening to detect cancer at its earliest, most treatable stage
- Can help guide decisions regarding relevant cancer risk-reducing procedures like surgery (not standard management)
- Can help carriers consider dedicated reproductive options when family planning

2. Familial implications

Your genetic test result can also help you understand if other family members are at risk of Lynch syndrome. 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 MMR 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 MMR 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

Colorectal

- Annual colonoscopies
- Aspirin can be considered to reduce cancer risk

Uterine (endometrial)

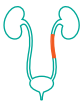
- Pelvic examinations and endometrial biopsies
- Prompt and early reporting of symptoms is encouraged (e.g., abnormal uterine bleeding or postmenopausal bleeding)

Ovaries

- Pelvic examinations
- Prompt and early reporting of symptoms is encouraged (e.g., pelvic or abdominal pain, bloating, increased abdominal girth, difficulty eating, early satiety, or urinary frequency or urgency)

Gastric

- Upper gastrointestinal (GI) endoscopy
- Testing and treatment of H. pylori infections



Urinary tract

- Urine tests
- Early reporting of symptoms (e.g. blood in urine) is encouraged

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

Risk-reducing surgery

These options are not standard management practices but may be offered on a case-by-case basis. Surgery is generally offered to patients who have been diagnosed with cancer and require surgery as part of their treatment plan.

Colorectal

- Surgery to remove parts of / the entire colon

Uterus

- Surgery to remove the uterus

Ovaries

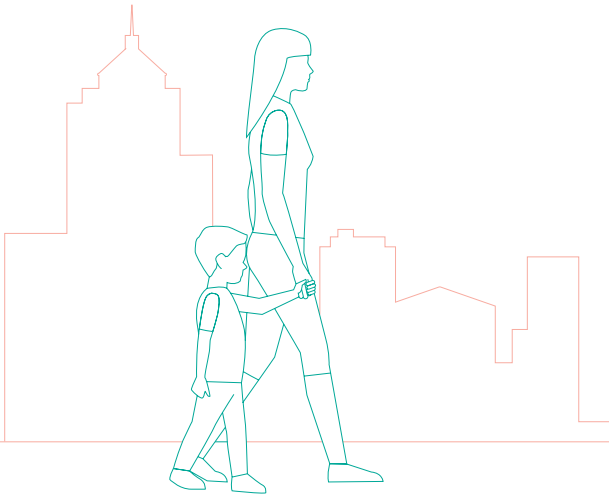
- Surgery to remove both ovaries and fallopian tubes

Individuals can consider removing both the uterus and ovaries at the same time to reduce the risk of cancer.

These options will be discussed in detail with you by your managing doctor(s). These surgeries reduce the risk of cancer significantly but do not remove the risk completely.

Lifestyle adjustments

- Promote avoidance/cessation of smoking
- Keep a healthy diet and active lifestyle
- Practise sun-smart behaviour such as using sunscreen

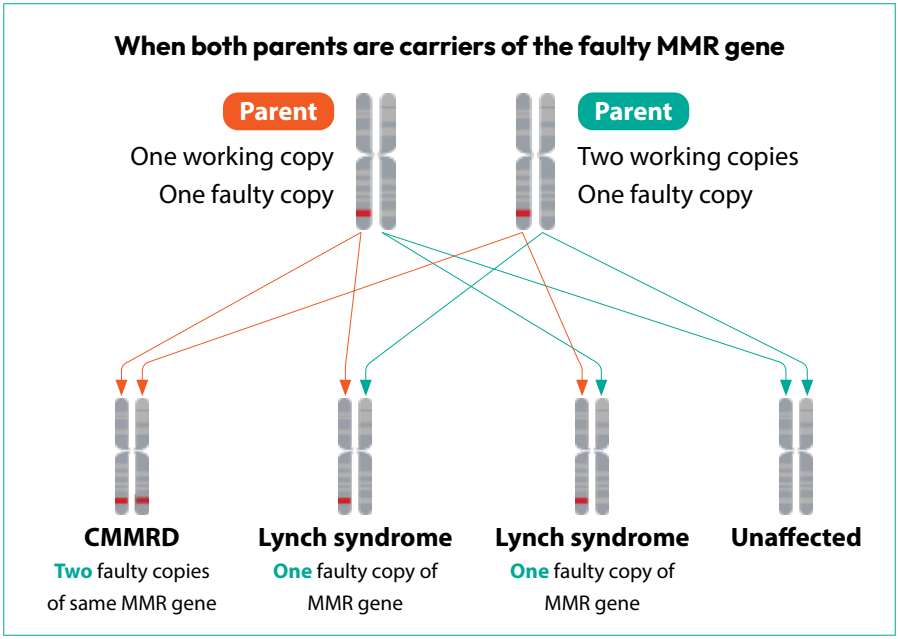


Reproductive options

Couples who are both carriers of the same faulty MMR gene can consider assisted reproductive options when planning a pregnancy. Their children have a 1 in 4 chance (25%) of inheriting two faulty copies of the same MMR gene – one from each parent – resulting in a condition known as **constitutional mismatch repair deficiency (CMMRD) syndrome** as shown below. Those who inherit two faulty copies of the same MMR gene have CMMRD.

Individuals with CMMRD are at risk of developing blood malignancies, brain tumours, and colon, small bowel, uterine, gastric, urologic and other types of cancer. They may develop multiple cancers throughout their lifetime and may present early in childhood.

We recommend people with Lynch syndrome to speak to a genetic counsellor prior to family planning and pregnancy to find out how their partners can undergo genetic testing to understand their carrier status, and to understand their options for assisted reproductive techniques.



Frequently Asked Questions (FAQs)

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

A: Genetic testing is recommended foremostly for **the family member whose cancer diagnosis is most suggestive of a hereditary cause** (e.g., young or unusual cancer). Those with a history of cancer are more likely to have inherited a faulty gene(s) over those without such history.

If a hereditary cause is identified, testing can be subsequently offered to at-risk relatives who do not have cancer or are asymptomatic. In some cases, testing an affected family member is not possible and genetic testing can be offered to asymptomatic individuals.

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 in the family. The individual being tested may not have inherited it, but others in the family may have, or the faulty gene(s) 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.

Q: Is testing recommended in children?

A: Genetic testing for adult-onset conditions like Lynch syndrome is **not recommended in individuals under the age of 21**.

Genetic testing in children is only offered when they have a personal history of certain cancers, or if the faulty gene(s) identified in the family is known to increase the risk of cancer during childhood.

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. Your genetic test result cannot determine the likelihood of cancer recurrence or the presence of cancer. A positive result only indicates an increased risk of getting cancer or of a new cancer developing.

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

FALSE. If you have a positive genetic test result where a faulty gene(s) is identified, it means each of your children has a 50% (1 in 2) chance of inheriting the faulty gene(s). It affects both males and females.

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 Lynch syndrome (MMR) genes like *MLH1, MSH2, MSH6, PMS2* and *EPCAM*. All first-degree relatives (siblings, children, parents) have a 50% (1 in 2) chance of inheriting the faulty MMR gene(s).

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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Acknowledgements

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Reg. No.: 200002698Z
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