University Hospitals Bristol and Weston
NHS Foundation Trust

Patient information service
Clinical genetics

Lynch syndrome

Diagnostic testing for MMR gene alterations

This leaflet has been written for people who have a personal history of colorectal or related cancers that could be explained by an inherited cause, and who are considering having genetic testing. It has been written for use alongside a clinical genetics appointment and may answer some of your questions.

Why have I been offered a diagnostic genetic test?

Cancer is common in the general population and around 1 in 2 people in the UK will develop a cancer during their lifetime.

Colorectal (bowel) cancer develops in around 1 in 15 (7%) males and 1 in 18 (6%) females during their lifetime. Most cases of colorectal cancer are diagnosed after the age of 60.

It is rare for cancer to be caused by an alteration in a high-risk gene. However, in about 5 to 10% of people who develop colorectal or related cancers, a specific gene alteration (pathogenic variant) plays a part.

People are offered a diagnostic genetic test for Lynch syndrome either because they have a personal and/or family history that is suggestive of Lynch syndrome or because tumour tissue studies have shown that Lynch syndrome may be the cause of the cancer in their family.

What is Lynch syndrome?

Lynch syndrome is an inherited condition that causes people to have an increased risk of developing certain types of cancer. It is sometimes called hereditary non-polyposis colorectal cancer (HNPCC).

Both males and females who have Lynch syndrome have an increased risk of developing colorectal cancer (cancer in the large bowel/colon or rectum). They also have increased risks of developing some other cancers.

Females who have Lynch syndrome also have an increased risk of

developing cancer of the endometrium (lining of the womb) and may have an increased risk of developing cancer of the ovaries.

Lynch syndrome is caused by an alteration in a mismatch repair (MMR) gene.

What are mismatch repair (MMR) genes?

Our genes are found in almost every cell in our body. They are the instructions that tell our bodies how to grow and function.

The MMR genes help to protect us from developing certain types of cancer. An alteration can stop the gene from working properly. This can increase the chance of developing colorectal and related cancers and cause these cancers to happen at a younger age.

There are four MMR genes that are associated with Lynch syndrome: MLH1, MSH2, MSH6 and PMS2.

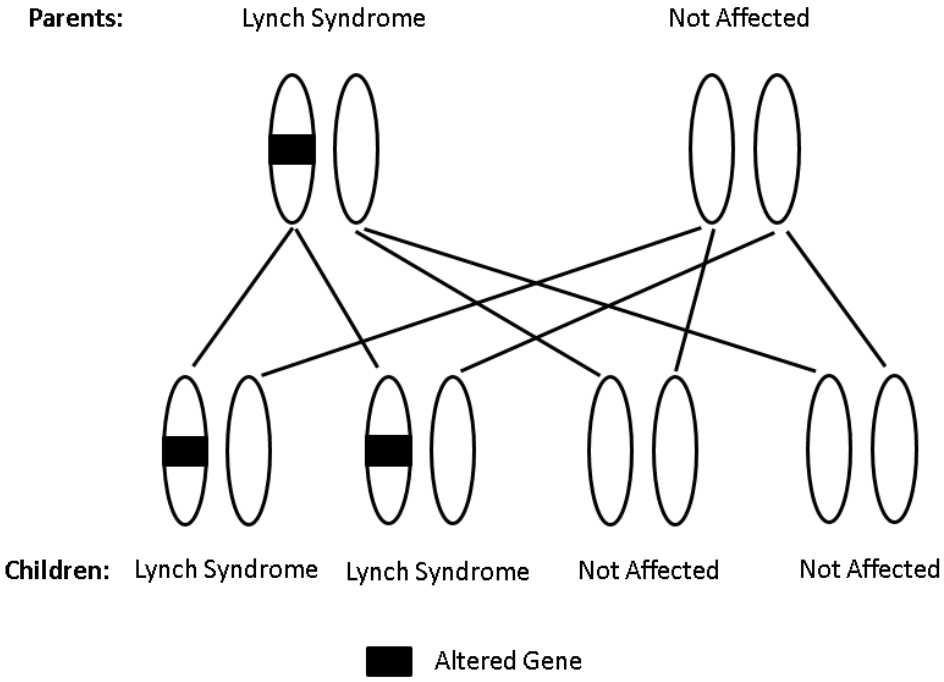
How are the MMR genes inherited?

All our genes come in pairs. We inherit one of each pair from our mother and the other from our father. This means that the children (male or female) of a person with an alteration in one of the MMR genes have a 1 in 2 (50%) chance of inheriting it.

If a person has not inherited an alteration in an MMR gene they cannot pass it on to their children.

Alterations in the MMR genes are inherited in an autosomal dominant manner. This means that having one altered copy of the gene is enough to cause an increased chance of developing Lynch syndrome-related cancers.

Autosomal dominant inheritance:



Can I have a test to see if the cancers in my family are due to Lynch syndrome?

Possibly. Currently, genetic testing is usually offered to people who have had tumour tissue studies and the results suggest that Lynch syndrome is likely to be the cause, or who have a strong personal and family history of colorectal and/or other Lynch syndrome-related cancers. Your genetic healthcare professional will discuss if you are eligible to have a genetic test.

If you are offered a diagnostic genetic test for Lynch syndrome, this involves having a blood or saliva sample collected. This is sent to a laboratory and the four MMR genes are analysed for alterations.

What are the possible outcomes of a genetic test?

There are three possible outcomes of having a diagnostic genetic test:

1. A gene alteration (pathogenic variant) is found which confirms the diagnosis of Lynch syndrome in the family. Appropriate screening recommendations will be made for you and your relatives based on this gene alteration.
   Genetic testing for this gene alteration would be available for other at-risk family members. To have a genetic test, they would need to be referred to their local clinical genetics service.

2. No gene alterations are found in any of the MMR genes. This is the most likely outcome. This could mean that the cancers in you and your family may have happened by chance. However, we cannot rule out the possibility that there may be some kind of hereditary predisposition which we cannot pick up with our present techniques and knowledge. Appropriate screening recommendations will be made for you and your relatives based on the family history of cancer.

3. A variant of uncertain significance (VUS) is found. This means that we have found an alteration in one of the MMR genes, but we do not know whether or not it prevents the gene from working properly. It is therefore unclear whether it causes an increased cancer risk. This is because as well as disease causing alterations within genes, there are also naturally occurring (harmless) variations. While we are usually good at telling the difference between the two we may occasionally find a change we do not know the significance of.
   Genetic testing is not usually offered to relatives for this type of gene alteration. However, we would encourage you or your family to re-contact clinical genetics in the future for an update

because as our knowledge improves we may be able to review the significance of the variant.

What if a relative with colorectal or a related cancer is not available for testing? Can I be tested even if I have never had cancer?

Genetic testing for Lynch syndrome is usually first offered to a person in the family who has been diagnosed with cancer, rather than an individual who has not had cancer themselves. This is because the test results can be more difficult to understand and interpret in a person that has never had cancer.

However, in some families it may be possible to test a tumour sample from an affected relative who has passed away. Tumour testing can help to clarify the likelihood that Lynch syndrome is the cause of the cancer in the family.

In some families, genetic testing for Lynch syndrome is offered to an unaffected family member if there are no living, affected relatives. Your genetic counsellor or geneticist will talk to you about this if it is an option available for you.

Does everyone who inherits an MMR gene alteration develop cancer?

No. The chance of developing Lynch syndrome-related cancers is not 100%.

We do not yet know why some people with an alteration develop cancer and some do not. Other environmental and genetic factors are likely to play a role.

It is important to note that developing cancer is not the same as dying from cancer. Even if cancer develops, there is a good chance that it can be treated effectively if it is found early.

What are the cancer risks for someone with Lynch syndrome?

This table shows the increased cancer risks over the lifetime of males and females who have Lynch syndrome. It also shows the lifetime risks of these cancers in the general population.

Approximate cancer risks for males with Lynch syndrome*

Cancer type	General population	Lynch syndrome (MMR genes)			
		MLH1	MSH2	MSH6	PMS2
Colorectal	7%	60%	50%	20%	15%
Upper gastrointestinal	5%	20%	20%	10%	Similar to population
Ureter or kidney	3%	5%	20%	Similar to population	Similar to population
Urinary Bladder	2%	10%	15%	10%	Similar to population
Brain	Less than 1%	Less than 1%	10%	2%	Similar to population
Prostate	18%	Similar to population	25%	Similar to population	Similar to population

Approximate cancer risks for females with Lynch syndrome*

Cancer type	General population	Lynch syndrome (MMR genes)			
		MLH1	MSH2	MSH6	PMS2
Colorectal	6%	50%	50%	20%	10%
Endometrial	3%	40%	50%	40%	15%
Ovarian	2%	10%	15%	10%	Similar to population
Upper gastrointestinal	4%	10%	15%	5%	Similar to population
Ureter or Kidney	2%	5%	20%	5%	Similar to population
Urinary bladder	Less than 1%	5%	10%	1%	Similar to population
Brain	Less than 1%	2%	5%	1%	Similar to population

Remember: 1% means 1 in 100 people will develop this cancer in their lifetime.

*These risk figures have been taken from the Cancer Genetics Group guidance documents (2019) and may change with new information in the future.

What screening is available for people with Lynch syndrome?

Colorectal (bowel)

Regular screening by colonoscopy can detect early signs of colorectal cancer and remove adenomas (noncancerous growths or polyps) in the bowel wall which can lead to colorectal cancer. A colonoscopy uses a thin tube-like telescope to look inside

the large bowel and rectum. People with Lynch syndrome are recommended to have a colonoscopy every 2 years from age 25 (MLH1 and MSH2) or 35 (MSH6 and PMS2) up to at least age 75. This should continue even if an individual has a series of normal colonoscopies.

Gastric

There is no effective screening for gastrointestinal cancer. Helicobacter pylori is a bacteria that is found in the stomach of some people and is known to be associated with an increased risk of developing stomach cancer in the general population. Therefore, people with Lynch syndrome are advised to be screened for an H. pylori infection which can simply be treated with antibiotics. This can be arranged by the GP.

Other cancers

There is currently no proven, effective screening for endometrial, ovarian or other Lynch syndrome-related cancers. However, screening for ovarian cancer may be available privately.

Risk reducing surgery

Some females with Lynch syndrome choose to have a total hysterectomy with bilateral salpingo-oophorectomy (BSO; surgical removal of the uterus, ovaries and fallopian tubes). This surgery significantly reduces the risk of developing endometrial and ovarian cancer.

Individuals with a PMS2 gene alteration may be advised to have only the uterus removed and not the ovaries because their ovarian cancer risk is not thought to be greatly increased.

Symptom awareness*

Cancer	Symptoms
Colorectal	Bleeding from the anus, blood in stools (poo), change in normal bowel habits to diarrhoea or looser stools, lasting longer than 4 to 6 weeks, unexplained weight loss, abdominal pain, and fatigue.
Endometrial	Vaginal bleeding after the menopause, heavy periods, bleeding between menstrual cycles, and vaginal discharge.
Ovarian	Symptoms can be quite vague, but include pain in the lower abdomen or side, feeling bloated, abdominal swelling, abdominal pain, abnormal vaginal bleeding (postmenopausal or in between cycles), back pain, and constipation.
Urinary tract and bladder	Blood in urine (pee), mass in abdomen, weight loss, fatigue, persistent pain in side, and urinary frequency or urgency.
Upper GI tract	Persistent indigestion, feeling full early, pain or difficulty with swallowing, fatigue, dark tarry stools, nausea, pain in the back/stomach, unexpected weight loss, and yellowing of the skin and whites of the eyes.

*These symptoms have been taken from the Cancer Genetic Group guidance for Lynch syndrome (2019)

If you experience any of these symptoms, it is important that you report this promptly to your GP. It is important to remember that many of these symptoms can also be caused by factors other than cancer.

What are the implications of diagnostic genetic testing?

Some people feel a range of emotions when they are told that they have a gene alteration which increases their chance of developing cancer. They may feel angry, shocked, anxious, or guilty about the possibility of passing the gene alteration on to their children.

Genetic testing may also affect the relationships within families. Other family members may need to be told that they too are at an increased risk of developing cancer and may be eligible for genetic testing and/or screening. We can help support family communication when necessary.

Will genetic testing affect my insurance?

Currently, many insurance companies have agreed not to ask about genetic testing for the majority of policies but they can ask about health related issues which may be linked to Lynch syndrome. This position may change in the future. You can talk to you genetic health professional about genetic testing and insurance.

Do I have to have a genetic test?

You may decide not to have a genetic test, or that you want to take some time before making a decision. Whether or not you have a diagnostic genetic test, you should speak to your genetic health professional about your screening options.

Research for people with a family history of cancer

There may be research studies that you could take part in if you wish. It is important to remember that research studies may not benefit you directly, but may help future generations. Talk to your genetic health professional about research opportunities.

Support for people with Lynch syndrome

There is a UK based support group for people with Lynch syndrome that can provide information and peer support. Their website is www.lynch-syndrome-uk.org

The clinical genetic health professionals involved in your care:

Consultant…….

Telephone……

Area covered……

Genetic counsellor……

Telephone……

Area covered……

CG number……

Contact us

Clinical Genetics Department
St Michael's Hospital
Southwell Street
Bristol
BS2 8EG

Telephone: 0117 342 5107

Notes

As well as providing clinical care, our Trust has an important role in research. This allows us to discover new and improved ways of treating patients.

While under our care, you may be invited to take part in research. To find out more please visit: **www.uhbw.nhs.uk**

Help us prevent the spread of infection in hospital. Please make sure your hands are clean. Wash and dry them thoroughly/use the gel provided. If you have been unwell in the last 48 hours please consider whether your visit is essential.

Smoking is the primary cause of preventable illness and premature death. For support in stopping smoking contact **NHS Smokefree** on **0300 123 1044**.

Drinkline is the national alcohol helpline. If you're worried about your own or someone else's drinking, you can call this free helpline in complete confidence. **Drinkline** on **0300 123 1110.**

For access all patient leaflets and information please go to the following address: **http://foi.avon.nhs.uk/**

Bristol switchboard: 0117 923 0000

Weston switchboard: 01934 636 363

www.uhbw.nhs.uk

For an interpreter or signer please contact the telephone number on your appointment letter.

For this leaflet in large print or PDF format, please email patientleaflets@uhbw.nhs.uk.

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