Liverpool Women's
NHS Foundation Trust

Predictive Genetic testing for Lynch Syndrome
Information for people who have a Lynch syndrome gene alteration in the family

Cancer is common in the general population with 1 in 2* people being diagnosed with a cancer in their lifetime and most cancer occurs just by chance. Our suspicions of an inherited explanation for the cancers in a family are raised if the same or similar cancers occur in several family members on the same side of the family, usually across different generations and at a younger age than expected. This is why genetic testing would be offered to a family.

*Cancer research UK (2015) estimated lifetime risk of being diagnosed, people born after 1960

What are genes and chromosomes?

Humans are made up of trillions of cells. At the centre of almost all of your cells is a ball-shaped structure called the nucleus, inside of which are 46 thread-like structures called chromosomes. Chromosomes are long strands of DNA (DeoxyriboNucleic Acid). It is estimated that if a strand of DNA was stretched out, it would be around two meters long, even though the average cell is smaller than a pinhead.

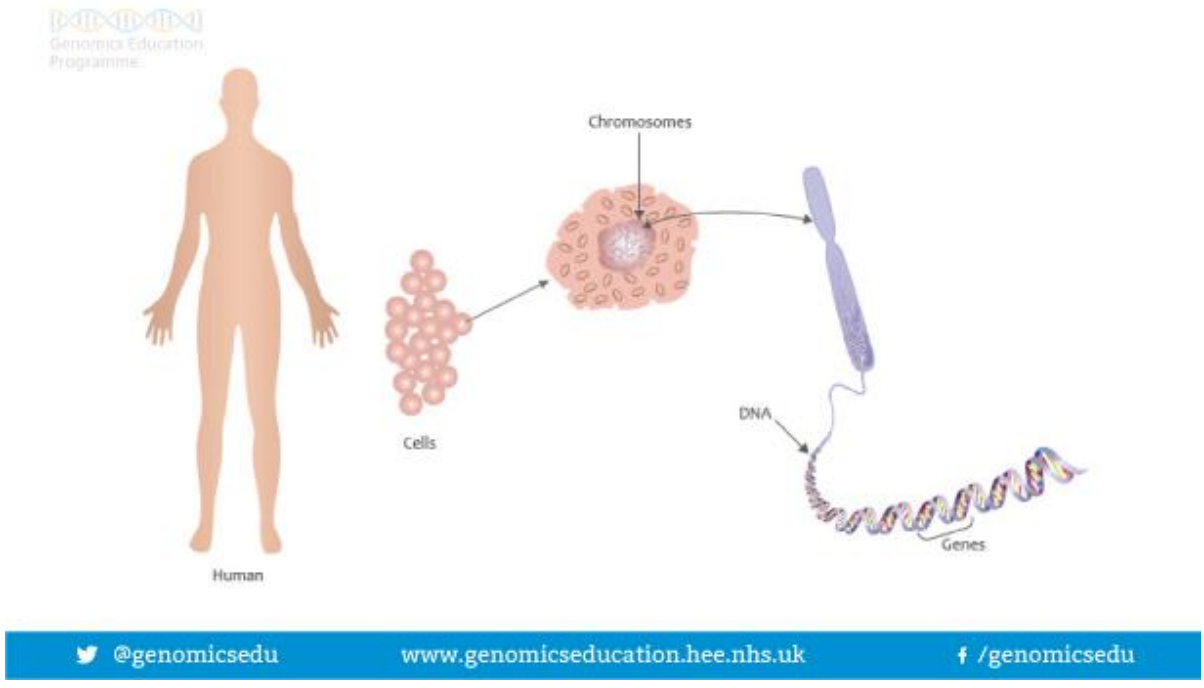

Image source: https://www.genomicseducation.hee.nhs.uk/image-library/

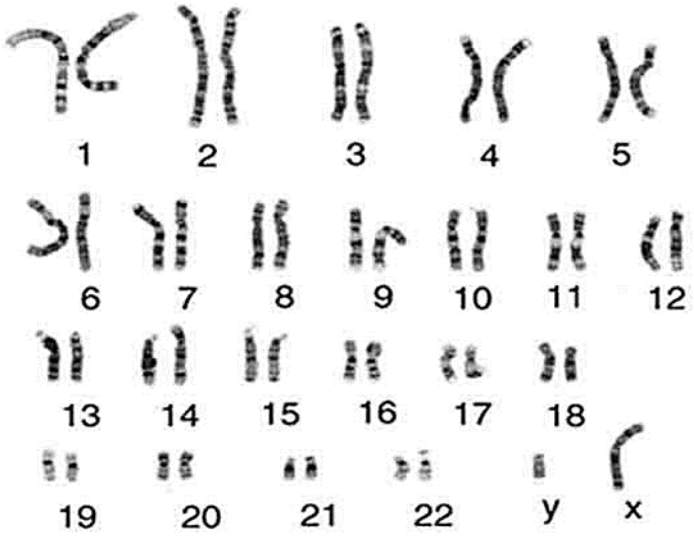

Image Source: https://cpmc.coriell.org

We have 23 pairs of chromosomes; one of each pair is inherited from your mother and one of each pair from your father. Chromosomes 1-22 are arranged in size order with number 1 being the largest and 22 the smallest. The 23rd pair of chromosomes determines a person's sex. Most males are XY and most females are XX. Chromosomes contain an estimated 20-30,000 pairs of genes that make us who we are. As we have pairs of chromosomes we therefore have pairs of genes.

Genes are often called the blueprint for life because they tell each of your cells what to do and when to do it. For example, some genes determine how tall you will be; some what colour your hair will be; some genes are responsible for maintenance in our bodies and some for our development, and so on. Genes do this by making proteins. In fact, a gene may act by being a 'recipe' or a code for making a certain protein. In order for a gene to do the job it is supposed to do, the 'recipe' or code needs to be written correctly. If the 'recipe' is wrong, the protein is either not made, or is made incorrectly so cannot do the job it is supposed to do. This is sometimes called a gene alteration, a spelling mistake or a gene mutation.

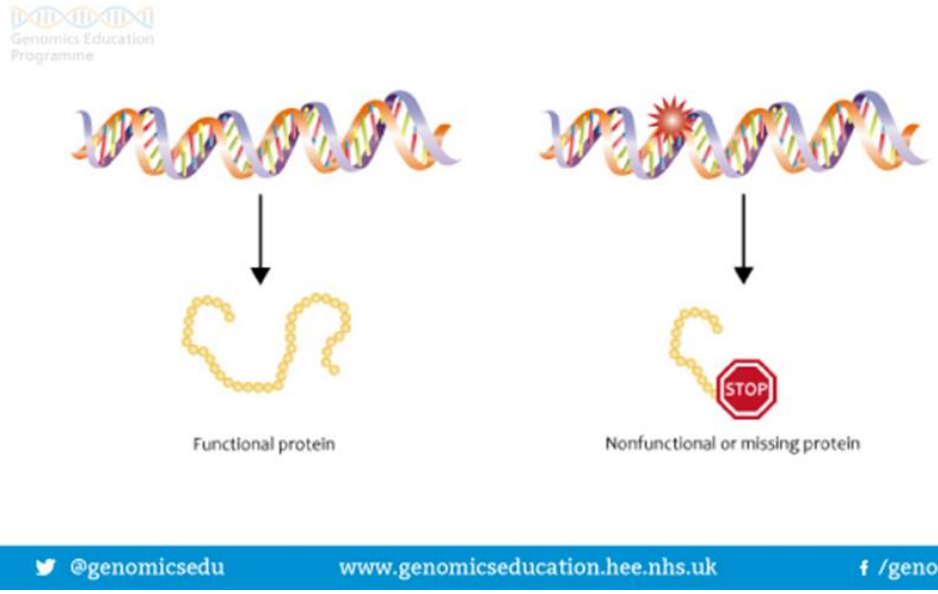

Image source: https://www.genomicseducation.hee.nhs.uk/image-library/

What is Lynch syndrome?

Lynch syndrome is a hereditary condition that causes people to have an increased risk of developing certain types of cancer and is caused by a gene alteration. Lynch syndrome also used to be known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC).

What genes are associated with Lynch syndrome?

There are currently 4 genes that we know of that, if they are altered, can be associated with the development of Lynch syndrome. These genes are known as MLH1, MSH2, MSH6 and PMS2. In fact we all have 2 copies each of these genes and they have a very important role to protect certain parts of our body from developing cancer. These genes are called mis-match repair genes and help protect us from developing cancer by detecting and correcting errors that can occur in DNA when cells copy themselves (DNA replication errors). They are like a quality control system that will either repair the mistakes in the DNA or gets rid of the cell with the mistake to stop it being copied anymore. If there is an alteration in one of our Lynch syndrome genes this quality control system is less effective and the person then has an increased *susceptibility* to developing cancer. But having an alteration in a Lynch Syndrome gene does not mean a person will definitely go on to develop cancer.

What are the main cancer risks associated with having a Lynch syndrome gene alteration?

Associated risks	**General Population risk**	**Different gene mutations carry different risks- these figures are provided from the Institute of Cancer Research/Royal Marsden mutation carrier guidelines**			
		MLH1	**MSH2**	**MSH6**	**PMS2**
Bowel cancer	Men 1 in 15 = 7%*	57%	51%	18%	13%
	Women 1 in 18 = 5.7%*	48%	47%	20%	12%
Ovarian cancer	2% = 1 in 50 women*	11%	17%	11%	similar to population
Endometrial cancer	2.8% = 1 in 36*	37%	49%	41%	13%

*Cancer research UK (2015) estimated lifetime risk of being diagnosed, people born after 1960.

There may also be a small risk of developing other cancers including kidney (renal) cancer and pancreatic cancer but not enough to warrant routine screening. However, screening for these cancers may be offered if family members have developed these cancers. There is also a low risk of other cancers for which screening is not offered however, it would be important to have a low threshold for seeking medical help for any concerning or persistent symptoms.

What can be done to help manage these risks?

For each of the high risk cancers, screening and surgical options are discussed. Different options are available to men and women, and options can also differ dependent on what age you are.

Screening for people with Lynch syndrome

	Type of screening	**MLH1**	**MSH2**	**MSH6**	**PMS2**
For men and women	**Colonoscopy**	2 yearly 25-75 years review at 75	2 yearly 25-75 years review at 75	2 yearly 35-75 years review at 75	2 yearly 35-75 years review at 75
	Gastric	H Pylori one off screening from 25	H Pylori one off screening from 25	H Pylori one off screening from 25	H Pylori one off screening from 25
	Aspirin	Discuss with GP the pros and cons of taking aspirin, further details below	Discuss with GP the pros and cons of taking aspirin, further details below	Discuss with GP the pros and cons of taking aspirin, further details below	Discuss with GP the pros and cons of taking aspirin, further details below
For women only in addition to above		Offer risk-reducing hysterectomy with BSO once childbearing complete no earlier than 35-40. HRT should be offered until 51 in women who have not had ER +ve breast cancer All women should attend for their regular cervical smears	Offer risk-reducing hysterectomy with BSO once childbearing complete no earlier than 35-40. HRT should be offered until 51 in women who have not had ER +ve breast cancer All women should attend for their regular cervical smears	Offer risk-reducing hysterectomy with BSO once childbearing complete no earlier than 35-40. HRT should be offered until 51 in women who have not had ER +ve breast cancer All women should attend for their regular cervical smears	Consider hysterectomy alone once childbearing complete- no earlier than 45. All women should attend for their regular cervical smears

What does bowel screening involve?

This is an internal examination of the large bowel, also known as colonoscopy. The purpose of a colonoscopy is to look for cancer and polyps.

Polyps are quite common in the general population, but they are very common in people with Lynch syndrome. Most polyps are harmless and will not cause any trouble. However, the occasional polyp may grow over many years and develop into a cancer, as illustrated:

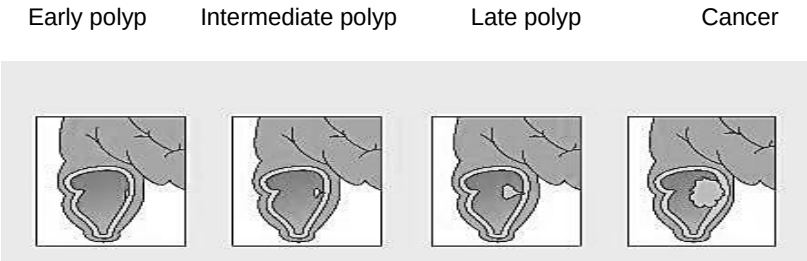

Image source: NHS National Genetics and Genomics Education Centre

It may be possible to prevent a cancer from forming by removing polyps. Removal of polyps is usually carried out during a colonoscopy.

How is Helicobacter pylori screened for?

People with Lynch syndrome should also be tested for the presence of a bacterium called Helicobacter pylori (H.pylori) and this can be done through your GP. H.pylori can live in the gut and can lead to chronic gastritis which in turn could lead to an increased risk of stomach cancer for people who carry a Lynch syndrome gene alteration. H.pylori can be detected by a breath test, blood test or stool sample and if found, eradicated with a course of antibiotics.

Why should I discuss aspirin use with my GP?

Aspirin taken daily for 2 years or more could reduce the risk of colorectal cancer in people with Lynch syndrome (LS), says National Institute for Clinical Excellence, NICE guidance 151. Aspirin is not licensed for this purpose so if it is prescribed for cancer risk reduction this is called an 'off-label' use of aspirin.

The best dose of aspirin is not yet clear but the UK Cancer Genetics Group recommend those between 25 and 65 years consider taking 150mg if 70kg or under and 300mg for people who weigh more than 70kg. These recommendations are likely to be updated over the coming years as more evidence becomes available.

PLEASE REMEMBER; Aspirin is a drug that can have serious side effects. It should never be taken without first being reviewed by your GP to make sure there is no reason you should not take it. We are not recommending consideration of aspirin usage to anyone without Lynch syndrome.

Can I have screening for ovarian and endometrial cancer rather than surgery?

Screening for ovarian cancer involves regular blood tests approximately 3-4 times a year, to measure a marker in the blood called CA125 and also by annual ultrasound scan from the age of 35.

Screening for endometrial screening involves an annual transvaginal ultrasound scan and endometrial sampling (sampling of the lining of the womb).

However, ovarian and endometrial screening does not always reliably inform us of cancers early enough in order for them to be treated effectively. Therefore for women with Lynch syndrome, we encourage them to consider surgery to help manage their risk of gynecological cancers as detailed above.

What else can I do to help protect my health?

We suggest that individuals at increased familial risk of colorectal cancer should be strongly encouraged not to smoke, to maintain a normal BMI, to moderate their consumption of red and processed meat, and to exercise regularly.

How are Lynch syndrome gene alterations passed down (inherited) through families?

The way Lynch Syndrome gene alterations are inherited is called DOMINANT inheritance. This is caused by an alteration in only one copy of a Lynch syndrome gene. Even though we each have 2 copies of Lynch syndrome genes a normal copy cannot compensate for an altered copy and a person with one altered Lynch syndrome gene has an increased risk of developing cancer.

If a parent carries an altered Lynch Syndrome gene, each of their children has a 50%, or 1 in 2 chance of having inherited the altered gene and therefore having an increased risk of developing cancer. For each child, regardless of their sex the risk is the same = 50:50.

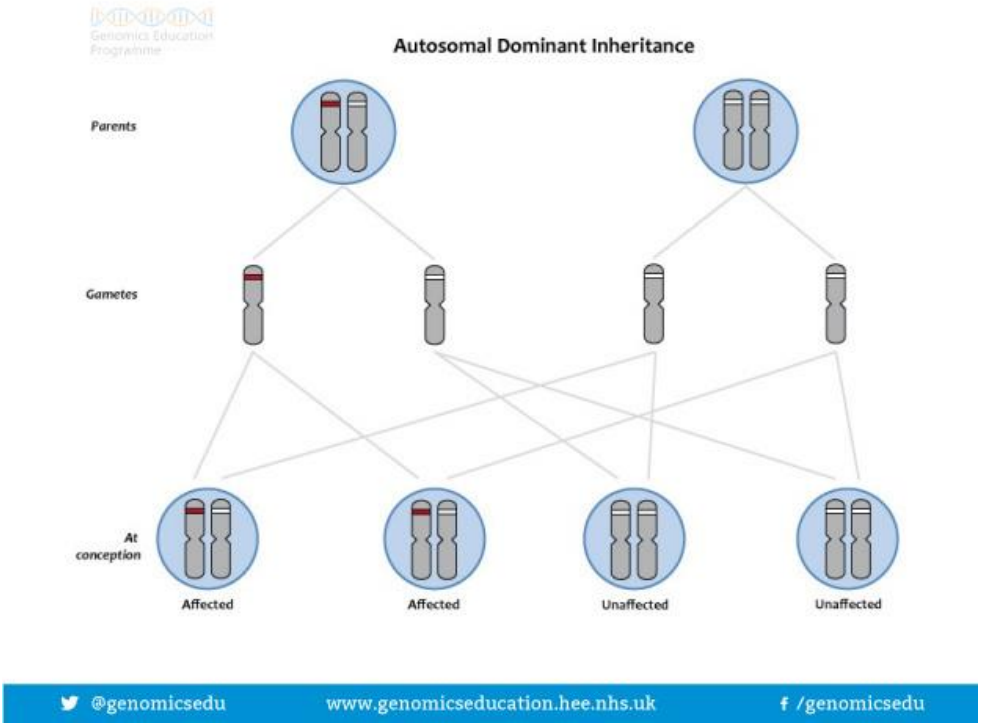

Image source: https://www.genomicseducation.hee.nhs.uk/image-library/

What is predictive testing?

Predictive testing is offered to family members who are known to be at risk of inheriting a gene alteration that has been identified in the family but are currently well. Predictive testing is usually offered over a series of appointments to allow the opportunity to consider options and choices with time for reflection in-between. How many appointments a person requires varies considerably from person to person and is negotiated on an individual basis with your genetic counsellor team. The overall aim of the predictive testing process is to help prepare you for your results whatever they are.

- **What are the issues to think about when deciding whether or not to have a gene test?**

A genetic test can establish whether you have an alteration in a gene which could affect your health. It can be difficult to make a decision about whether or not to have a genetic test. We all have gene alterations. Many of these do not affect our health. It is still quite unusual for a person to know they have an alteration in a specific gene.

There are reasons for and against having a genetic test. Within one family, relatives often have different views. You should try to make your own decision, without feeling pressured from relatives or other influences. You will have plenty of opportunity to talk through the issues surrounding the test with the genetic counsellor or doctor.

- **How do you think you would cope if the test were to show that you have inherited the altered gene?**

For some people, knowing that they have the altered gene is preferable to living with uncertainty. Having a genetic test enables them to make decisions about the future and about screening and

measures to reduce their risk. Other people may prefer not to have the test because they may feel very anxious if the test shows that they have the altered gene.

- **How do you think you would cope if the test were to show that you have not inherited the altered gene?**

Perhaps surprisingly, it can often take people some time to get used to the knowledge that they do **not** have the altered gene. This can be particularly difficult when other relatives have a different result.

People who do not have the altered gene have the same chance of developing cancer as other people in the general population.

- **If the test were to show that you have the altered gene, this would mean that your children would also be at risk of having the altered gene. How do you think you might feel about this?**

Having a genetic test may be important to other people, such as your children. It will help them to understand their own risk and if necessary make choices about screening and risk reducing options.

It can be very difficult knowing that you could have passed on an altered gene to your children. This can be hard to deal with even if you know that you had no control over which genes you passed on.

- **If you were to have the test, would you want to tell anyone the test results?**

It is important to think about who you would want to know about your test as it is very personal information. Many people who attend our clinic find that it helps to confide in a partner, trusted friend or relative.

- **Would having the test affect your ability to get life or medical insurance?**

At present, if you have already obtained your insurance, having the test should not affect your current policies. However, it is not possible to know whether it will affect your ability to get or to change insurance policies in the future.

- **Would having the test affect your employment?**

If the test shows you have the altered gene it would be your decision whether or not to inform your present employers. Some employers might ask about this if you apply for a new job.

It is important that each family member makes the decision that is best for them. We will support you whether you decide to have the test or whether you decide against having the test. It is your decision!

- **What happens if I choose to go ahead and have a test?**

After you have the opportunity to discuss the positives and negatives of predictive testing, if you wish to have the test you will be asked to read and sign a consent form and a small blood sample will then be taken.

Once the blood is taken, the laboratory staff would test the sample to find out whether or not you have inherited the altered gene known in your family.

Test results are usually available 4-6 weeks after having your blood taken and you can choose to have your results over the phone or in a clinic appointment.

IF, FOR SOME REASON YOU, HAVE NOT RECIEVED YOUR RESULTS WITHIN 4-6 WEEKS AS EXPECTED PLEASE CALL THE LIVERPOOL CENTRE FOR GENOMIC MEDICINE ON 0151 802 5008. Please remember to have your G number and W number handy for this call so we can quickly and correctly identify you.

- **What happens if I choose not to go ahead with having a test?**

We may still recommend screening to you as explained earlier in this leaflet.

You can change your mind and decide not to have the test at any time before the result is given.

Other factors to consider

Insurance and Genetics

For some types of insurance it is necessary to provide medical information, including genetic information, to the insurers in order for them to set up your policy and work out your premiums. The types of policy that require a medical history or genetic test are likely to be, life cover, critical illness insurance and income protection insurance.

We would suggest that if yourself or family members are considering taking out new insurance policies in the future that consideration be given to the possible affect genetic test results could have on the ability to gain insurance or the premiums charged. Genetic Test results do not affect insurance policies already in place.

The Association of British Insurers (ABI) has a Code of Practice 'The Concordat and Moratorium on Genetic and Insurance'.

- *Insurance companies cannot ask for the **Predictive Genetic Test** results of individuals or family members* (unless for Huntington Disease over £500,000). *A Predictive Genetic Test is where an individual has a family member with a genetic condition, but who personally has no symptoms, signs or abnormal medical tests consistent with the condition at time of testing.*

- *If a family member has been diagnosed with a genetic condition based on a **Diagnostic Genetic Test** then you or family members will need to mention this when asked to provide your family's medical history. In many cases Diagnostic Genetic Testing is used to confirm a diagnosis when a particular condition is suspected because of symptoms, signs or abnormal non-genetic tests including unusual findings on a routine blood test or other test.*

Sources of Further Information on insurance and genetics:

The Association of British Insurers Genetics Frequently Asked Questions https://www.abi.org.uk/products-and-issues/topics-and-issues/genetics/genetics-faqs/

Genetic Alliance UK (Charity) Genetics & Insurance http://www.geneticalliance.org.uk/information/living-with-a-genetic-condition/insurance-and-genetic-conditions/

Family planning

Everyone who has an inherited genetic condition can choose from a variety of options to ensure they do not pass it on. It is a highly personal decision and there is certainly no expectation that couples have to do anything to prevent passing on a Lynch syndrome gene alteration, but for couples who wish to consider this, some of the choices can include:

- **Preimplantation genetic diagnosis (PGD)**

Pre-implantation genetic diagnosis (PGD) is a special type of in vitro fertilisation (IVF) which is available to couples who are at an increased risk of having a child with a specific genetic condition. The aim is to avoid passing on the genetic condition to the child.

More information can be obtained at https://www.guysandstthomas.nhs.uk/our-services/pgd/about-us/welcome.aspx

- **Adoption**
- **Sperm or egg donation**: dependent on who carries the gene alteration.

Our experience is however that very few couples who carry a Lynch syndrome gene alteration choose any of the above options.

We hope you find this leaflet useful and please do not hesitate to discuss any of the issues identified in this leaflet with the genetics practitioner that is looking after you:

Liverpool Centre for Genomic Medicine
Liverpool Women's Hospital NHS Foundation Trust
Crown Street
Liverpool
L8 7SS
Telephone: 0151 802 5001 or 5008 Email: lwft.clingen@nhs.net

Liverpool Women's
NHS Foundation Trust

Useful websites

Genetic Alliance UK www.geneticalliance.org.uk

Cancer research group UK (CRUK) www.cruk.org.uk

National Institute for Health Care and Excellence (NICE) https://www.nice.org.uk/Guidance/NG151 Please also see the tools and resources section for a decision aid called 'Lynch syndrome: should I take aspirin to reduce my chance of getting bowel cancer?'

http://www.capp3.org for research updates regarding aspirin and Lynch syndrome

https://www.ukcgg.org select 'info & education', then 'documents and websites' then Lynch syndrome Gene Specific Guidelines

This leaflet can be made available in different formats on request. If you would like to make any suggestions or comments about the content of this leaflet, then please contact the Patient Experience Team on 0151 702 4353 or by email at pals@lwh.nhs.uk

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