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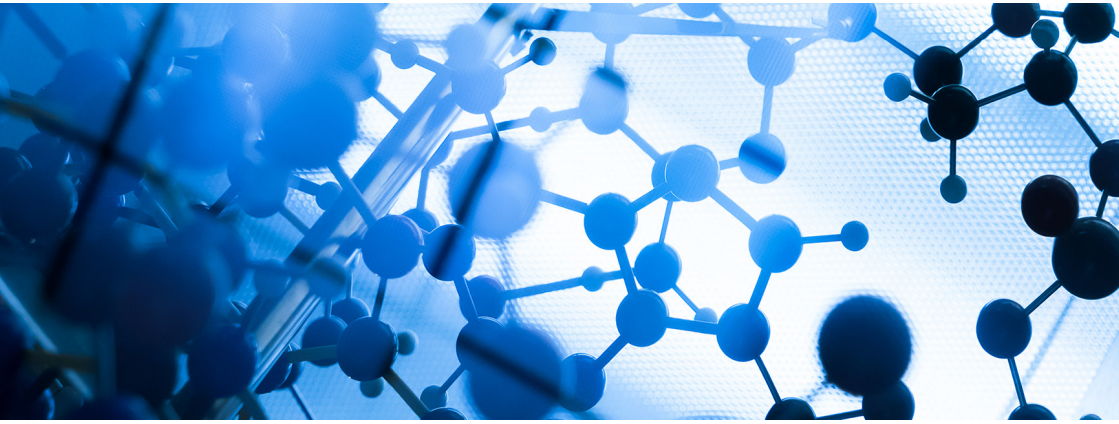
LYNCH SYNDROME



DIAGNOSTIC GENETIC TESTING

LYNCH SYNDROME
DIAGNOSTIC TESTING

This booklet has been written for people who have a personal history of bowel and/or related cancers that could be explained by an inherited factor and who are considering having genetic testing. This leaflet contains general information about the condition, but it needs to be considered in combination with our clinic discussions and the covering letter that relates to the specific history in your own family.

WHY HAVE I BEEN OFFERED DIAGNOSTIC GENETIC TESTING?

It is uncommon for cancer to be caused genetic spelling mistakes (technically known as pathogenic variants) in high risk genes. However, in about 5%-10% of people who develop bowel, or related cancers, we know that genetic spelling mistakes in high risk genes do play a role. People are usually offered genetic testing because the results of 'tumour tissue studies' suggest that a condition called Lynch syndrome may be a cause of the cancer in the family.

WHAT ARE TUMOUR TISSUE STUDIES?

Tissue studies are tests on samples of a tumour removed at the time of surgery or biopsy. They can help to identify the cancers which are more likely to be caused by an underlying genetic variant. The results can help us recognise families where genetic testing may be useful, and to advise on the most appropriate screening for you and your relatives.

There are two tests that can be done. They are called Mismatch Repair Immunohistochemistry (MMR IHC) and Microsatellite instability (MSI) testing. The tests are looking for clues to suggest whether Lynch syndrome is a possible cause of the cancer.

WHAT IS LYNCH SYNDROME

Lynch syndrome, which is sometimes referred to as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is a hereditary condition which is associated with an increased risk of developing certain types of cancer. Men and women who have Lynch syndrome have an increased risk of developing colorectal cancer, which is cancer of the large bowel (colon) and rectum. Women who have Lynch syndrome also have an increased risk of developing cancer of the lining of the womb (endometrium). Individuals with Lynch Syndrome also have increased risks of some other cancer types, these risks are discussed further below. Lynch syndrome is caused by pathogenic (disease causing) variants in the mismatch repair (MMR) genes.

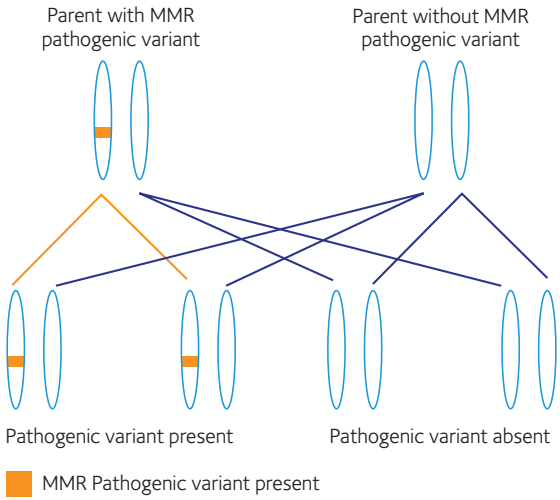
WHAT ARE MISMATCH REPAIR (MMR) GENES?

The MMR genes help to protect us from developing certain forms of cancers. A pathogenic (disease causing) variant can affect the function of the gene and this can increase the chance of developing these forms of cancer, which may occur at a younger age than these cancers usually occur in the general population. There are four MMR genes which have been linked to Lynch syndrome; these are MLH1, MSH2, MSH6 and PMS2. The risks of different cancers vary depending on which gene is affected and so not everyone with Lynch syndrome will have the same screening recommendations.

HOW IS LYNCH SYNDROME INHERITED?

All of our genes come in pairs; we inherit one copy from our mother and the other from our father. When we have children we randomly pass on one of each pair. If a person has a pathogenic variant in one copy of a MMR gene, each of his or her children (male or female) has a 50% (1in 2) chance of inheriting it.

AUTOSOMAL DOMINANT INHERITANCE



CAN I HAVE A TEST TO SEE IF THE CANCERS IN MY FAMILY ARE DUE TO LYNCH SYNDROME?

Yes. As you have previously developed cancer and analysis of your tumour tissue has suggested that a diagnosis of Lynch syndrome may be likely, we can offer diagnostic genetic testing. A genetic test involves taking a sample of blood, which is then sent off to a laboratory where the relevant genes are analysed.

THERE ARE THREE POSSIBLE OUTCOMES OF HAVING A GENETIC TEST:

1. We find a pathogenic variant that we are confident is associated with Lynch syndrome This would explain the cause of the cancers in your family, and would allow testing for other family members in order to clarify their risks. It may also make a difference to your treatment.
2. We do not find any pathogenic variants in the MMR genes. This is the most likely outcome, and it would mean that a diagnosis of Lynch Syndrome is unlikely. In this scenario we would not need to offer any genetic testing to your relatives.
   However, recommendations for screening for you and your relatives can still be made. This is because there is still a possibility

that the cancer has been caused by a genetic variant which we were unable to identify through the testing.

3. We find a variant but we cannot be confident that it is associated with Lynch Syndrome. These types of variants are called 'variants of uncertain significance'. We do not offer testing for variants of uncertain significance for other family members. However, over time more information may become available so that we can be clearer about whether or not the is pathogenic or benign. In the meantime, we can still make screening recommendations for you and the family based on family history.

DOES EVERYONE WITH LYNCH SYNDROME DEVELOP CANCER?

No, not everyone with Lynch Syndrome will develop cancer. Individuals with Lynch syndrome are at an increased risk of developing certain cancers, compared to the general population.

We do not yet know why some people with Lynch syndrome develop cancer, and some do not. Lifestyle or other genetic factors are likely to play a role. Knowledge about what can be done to reduce the risk of cancer developing, or identifying it at the earliest and most treatable stage, is always improving.

DOES ASPIRIN REDUCE THE RISK OF DEVELOPING COLORECTAL CANCER?

Several research studies have reported that individuals with Lynch Syndrome who take aspirin long term have lower rates of bowel cancer, compared to those who were taking a placebo. Studies are still ongoing to try and establish the optimal dose of aspirin. Currently we recommend that people should take 150mg of Aspirin if they have a BMI less than 25kg/m^2 (approximately 70kg or 11 stone). 300mg is recommended for anyone over that weight following a discussion with their GP regarding any possible contraindications.

WHAT ARE THE CANCER RISKS ASSOCIATED WITH LYNCH SYNDROME?

This table outlines the approximate cancer risks by age 70 associated with each of the four MMR genes and compares that risk to the population risk.

Cancer Site	MLH1 Carriers	MSH2 Carriers	MSH6 Carriers	PMS2 Carriers	General Population
Colorectal Cancer	50-65%	35-75%	20-70%	15-20%	5-6%
Endometrial Cancer (women)	20-25%	30-40%	25-70%	15%	2%
Ovarian Cancer (women)	10-15%	10%	1-2%	1-2%	1-2%
Gastric	<10%	<10%	<1%	<1%	<1%
Urinary Tract	3-5%	10-30%	<1%	<1%	<1%
Small Bowel	3-5%	3-5%	<1%	<1%	<1%

IF I HAVE LYNCH SYNDROME SHOULD I HAVE ADDITIONAL SCREENING?

Cancer	Risk Management Options
Bowel	• 2 yearly Colonoscopies from from 25 for MLH1 & MSH2 carriers from 35 for MSH6 & PMS2 carriers
Gastric	• There is no convincing evidence to support the use of endoscopy (Oesophago-gastro-duodenoscopy OGD as a screening test for gastric cancer, in all Lynch Syndrome families but it may be recommended in some situations (eg. where there is a significant family history)
	• Screening for Helicobacter pylori (an organism found in the stomach of some individuals) is known to be associated with gastric cancer generally. A one-off screen for H. Pylori & treatment (if needed) - usually a course of antibiotics can be arranged by your GP.
Gynaecological	• Endometrial cancer surveillance may sometimes be offered. A referral to gynaecology to discuss options is recommended from 35
	• Ovarian screening is not routinely recommended
	• Some women with Lynch syndrome opt to have a total abdominal hysterectomy (removal of the womb) with bilateral salpingo-oophorectomy (removal of both ovaries and fallopian tubes) as this reduces the risk of developing endometrial and ovarian cancer significantly.

WHAT ARE THE IMPLICATIONS OF DIAGNOSTIC GENETIC TESTING?

Some people can experience a range of emotions when they are told they have a pathogenic variant that increases their chance of cancer. They may feel angry, shocked, anxious, or guilty about possibly passing Lynch syndrome on to children. Some people may also feel guilty if they do not have Lynch syndrome when other close family members do.

Genetic testing in a family can affect other family members; as it may identify others who are at potentially at increased risk of cancer. Communicating this information can be difficult for many people. We can provide support and advice as necessary, along with relevant written information on the practicalities of how people can seek referral to our service. We are happy to discuss what genetic testing and screening recommendations would be available to an individual but they are under no obligation to undertake genetic testing.

IS THERE AN ALTERNATIVE TO GENETIC TESTING?

You may decide not to have genetic testing. Whether or not you are tested, you should talk to your clinician about screening options. If you decide not to have genetic testing at this stage you could consider storing a DNA sample, so that genetic testing could be available to relatives in the future. Genetic testing is only undertaken in living individuals with their consent, a stored sample would not be tested without your permission.

ARE THERE ANY SUPPORT GROUPS FOR PEOPLE WITH LYNCH SYNDROME?

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

The health professionals involved in your case are:

Genetic Counsellor: _____

T: _____

Consultant: _____

T: _____

BT21 1959

If you have any feedback or comments regarding the contents of this leaflet we would be pleased to receive them at genetic.medicine@belfasttrust.hscni.net