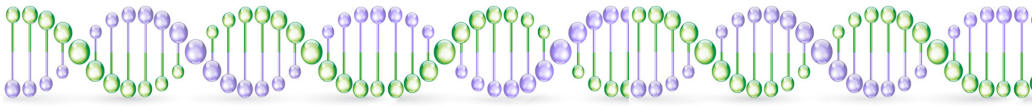
Information Sheet



Lynch syndrome and the Mismatch repair genes

Lynch syndrome affects between 1:600 and 1:2000 people and is responsible for 3% of bowel and uterine cancers. It is caused by mistakes (mutations) affecting the mismatch repair genes: MLH1, MSH2, MSH6 and PMS2.

Lynch syndrome was initially described in a single family by Dr Aldred Scott Warthin in 1895. It was referred to as a "family cancer syndrome" in the 1960's by Dr Henry T. Lynch and given the name Lynch syndrome.

Many other names have been applied to Lynch syndrome over the years and all are now obsolete. These old names include:

- Lynch Syndrome I and II, which were used to distinguish families with just colon cancer from those families whose cancer history included other Lynch syndrome related cancers such as uterine cancer
- Turcot syndrome which includes families whose cancer history included brain tumours (glioblastoma in particular)
- Muir Torre syndrome which includes families whose cancer history included sebaceous adenocarcinoma
- Hereditary Non Polyposis Colorectal Cancer syndrome (HNPCC).

The term Hereditary Non Polyposis Colorectal Cancer syndrome (HNPCC) was created to distinguish Lynch syndrome from Familial Adenomatous Polyposis (FAP) syndrome. (FAP is an inherited cancer syndrome that results in 100s or even 1000s of polyps). It was abandoned because Lynch syndrome does causes polyps and Lynch syndrome is associated with a high risk of other cancers, such as uterine and ovarian cancer, not just colon cancers.

What causes Lynch syndrome?
Lynch syndrome is caused by an inherited (germline) mutation (pathogenic variant) affecting any one of the 4 mismatch repair genes: MLH1, MSH2, MSH6 and PMS2. There is also the EPCAM gene, which sits next to the MSH2 gene. When EPCAM is damaged in a certain way, the MSH2 gene can't work properly.

The mismatch repair genes MLH1, MSH2, MSH6 and PMS2 produce proteins that function as "spell checkers", looking for a fixing and particular type of error, called a mismatch, which can occur when DNA is copied during cell division.

The proteins work in pairs: the protein made by MLH1 pairs with PMS2 and the protein made by MSH2 pairs with MSH6.

What is a DNA mismatch?
DNA is made up of 4 "letters" A, T, C and G, which are then grouped into 3s (codons), with each group of 3 coding either for one of the 20 amino acids (the building blocks of proteins) or a "stop codon". (For an easy to understand but detailed account of how DNA is translated into proteins, see the link on our website to Nature.com's educational Scitable website.)

Each letter pairs with the same partner to make up the rung of the DNA ladder: an A always matches with a T and a C always matches with a G.

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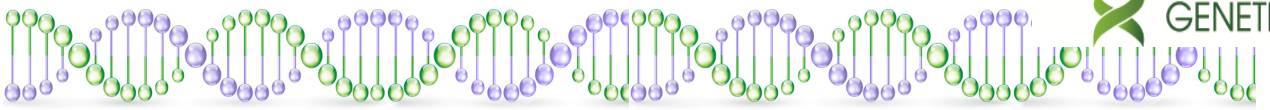

Why do DNA mismatches matter?
Here's an example to explain why mismatch repair to keep the DNA code accurate is so important.

The 3 letter code TGT codes for the amino acid Cysteine. Cysteine is a small, straight, charged amino acid.

Changing the last letter to:

- C (TGC) still codes for Cysteine (there is redundancy in the code). A synonymous variant.
- A (TGA) codes for a stop codon (the protein chain will stop). A nonsense variant.
- G (TGG) codes for Tryptophan (a different amino, which is very large, uncharged and has rings.) A missense variant.

These changes may affect how the protein folds and therefore its function. If they do, these variations in the code are called pathogenic variants (or mutations for short). Cancers develop when key genes that tell cells when to grow, when to die and how to behave are damaged. So… fixing DNA mismatches protects us from cancer and that's why Lynch syndrome is associated with an increased risk of cancer.

How is Lynch syndrome diagnosed?
Lynch syndrome is diagnosed via a blood or saliva test to detect a germline (inherited) mutation affecting one of the 4 mismatch repair genes MLH1, MSH2, MSH6 or PSM2. Mutations in EPCAM also cause Lynch syndrome because the MSH2 gene can't work properly.

Who should be tested for Lynch syndrome?
If the Lynch syndrome gene is damaged, the protein won't be made. Tumours in Lynch syndrome characteristically show loss of immunohistochemical staining for one of the mismatch repair proteins (MMR IHC testing).

Today, all colon and uterine cancers and most bladder and ovarian cancer should undergo MMR IHC testing to see if Lynch syndrome is a possible cause for that cancer. (Note: The proteins work in pairs (MLH1 with PMS2 and MSH2 with MSH6) and if the dominant protein is missing, its partner will be missing as well).

How likely is cancer in Lynch syndrome?
Men with Lynch syndrome have a 40% lifetime risk of bowel cancer while women have a 35% lifetime risk cancer of the bowel and/or the uterus and a 10% lifetime risk of ovarian cancer. These risk estimates vary between the different genes MLH1, MSH2, MSH6 and PMS2 and don't take into account the very significant risk reduction achieved by screening such as colonoscopies.

Both men and women have an increase in risk of cancer of the small bowel, stomach, pancreas and the kidneys, bladder and ureters. Some families also have brain tumours and sebaceous adenocarcinomas.

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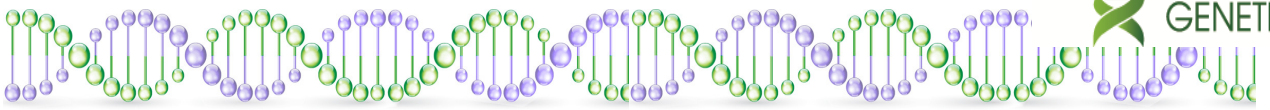

How is Lynch syndrome treated?
Management guidelines to reduce cancer risk in Lynch syndrome are now well established.

- Screening colonoscopies should commence at age 25 or 30 and be performed every 1 to 2 years.
- There is no useful screening for ovarian or uterine cancer. Instead, the uterus, fallopian tubes and ovaries should be removed at age 40, after completion of childbearing.
- Screening for the rarer cancers caused by Lynch syndrome has not been shown to be effective and is not required. The exception is gastroscopies to screen for stomach cancers in families where this type of cancer has occurred.
- Low dose aspirin has been shown to reduce colon cancer risk and should be discussed with your doctor

How much does it cost to get tested for Lynch syndrome?
Tumour testing is Medicare funded.

If there is loss of staining for any of the mismatch repair proteins on MMR IHC testing, then genetic testing is Medicare funded. This is to determine whether the damage was inherited (a germline mutation) or just occurred in the cancer cells (a somatic mutation).

If a mutation (Class 4 or Class 5 variant) is detected in a Lynch syndrome gene, then predictive testing for this mistake is available for adult blood relatives and is also Medicare funded.

In some families, self-funded testing, via a panel that includes MLH1, MSH2, MSH6, PMS2 and EPCAM and costing $450, may be considered if testing can't be performed in the relative who had the cancer.

Does this sound like you or your family?
Have you had a young onset colon or uterine cancer? Has a tumour demonstrated loss of staining on MMR IHC testing or has a mismatch repair gene mutation been detected in a blood relative? Medicare funded genetic testing is likely to be available.

Make an appointment with Dr Hilda High at Sydney Cancer Genetics. It is a confidential opportunity to discuss your personal and family history of cancer and genetic testing can be organised, if needed.

More information is available on our website, including links to the following:

- Lynch Syndrome Australia is an Australian based charity that has run information days in the past and has links to international support groups
- The Cancer Genetics section of the Cancer Institute's eviQ website provides up-to-date Australian-based management guidelines
- The US National Library of Medicine website has more information about this syndrome.

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