Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC) syndrome is caused by pathogenic (or harmful) variants in one of five known genes: MLH1, MSH2, MSH6, PMS2, and EPCAM. Seeing any of the following in a family could increase the chance for Lynch syndrome:

- Early-onset colorectal cancer (occurring before the age of 50 years)
- Early-onset uterine cancer (occuring before the age of 50 years)
- Multiple individuals diagnosed with colorectal and/or uterine cancer over several generations on the same side of the family
- One individual diagnosed with more than one type of cancer in their lifetime
- Patterns of stomach, small intestinal, ovarian, urinary tract, pancreatic, and glioma/glioblastoma (type of brain cancer), in addition to colorectal, or uterine cancer

Pathogenic variants that cause Lynch syndrome are inherited in an autosomal dominant pattern, meaning that children of someone with Lynch syndrome each have a 50% chance to also have Lynch syndrome and the related increased risks for cancer. Women and men both have the Lynch syndrome genes and have the same chances to inherit and pass down pathogenic variants in these genes, therefore both sides of the family are important to look at when trying to determine if someone has a higher chance to have Lynch syndrome.

Cancer type	**Risk in the general population**	**Risk in Lynch syndrome**
Colorectal	5.5%	Up to 80%
Uterine/Endometrial	2.7%	Up to 60%
Ovarian	1.2%	Up to 24%
Stomach	<1%	Up to 13%
Small intestine	<1%	Up to 6%
Urinary tract (specifically renal pelvic type)	<1%	Up to 7%
Hepatobiliary tract	<1%	Up to 4%
Pancreatic	<1%	Up to 6%
Brain cancer	<1%	Up to 3%
Skin (specifically sebaceous adenoma/carcinoma type)	<1%	Up to 9%

It is important to remember that there are 5 genes that are known to cause Lynch syndrome

and each of these genes have their own unique cancer risk numbers. The MLH1, MSH2, and EPCAM genes are associated with a higher risk of cancers (as described in the above table), while the MSH6 and PMS2 genes are still associated with an increased risk for cancer, just not as high as with MLH1, MSH2, and EPCAM. All individuals who have Lynch syndrome should be offered additional surveillance and screening regardless of which of the five genes is causing their Lynch syndrome.

GENETIC TESTING FOR LYNCH SYNDROME

Genetic testing for pathogenic variants that cause Lynch syndrome has been available for many years, and the testing methods have changed and improved over time. There are several different ways to approach to testing in these genes, depending on the history and any prior testing that may have been done. Different approaches include:

- *Single site analysis*: Testing specific to a known pathogenic variant in the family
- *Full gene sequencing and rearrangement analysis*: Comprehensive testing to search for all currently detectable variants in the genes.
- *Gene panels*: Newer, more broadly based gene tests that would include not only the Lynch syndrome genes, but other genes known or suspected to be associated with increased cancer risks

IMMUNOHISTOCHEMISTRY (IHC) TESTING FOR LYNCH SYNDROME

This testing is different from other types of genetic tests because it is done specifically on a person's cancer/tumor. Some hospitals complete this testing on all patients diagnosed with colon or uterine cancer as part of their treatment, while other facilities do not. The IHC test for Lynch syndrome (also called mismatch repair deficiency) is a screening test, meaning that it cannot tell us with 100% certainty whether or not someone has Lynch syndrome. It also may not find all patients that truly have Lynch syndrome. More commonly, positive results from IHC screening end up being a false positive, meaning that the person's tumor looks like Lynch syndrome, but this is later ruled out by genetic testing. Individuals who have an abnormal IHC screening test should be referred to speak with a genetic counselor to discuss the results and help determine if genetic testing for Lynch syndrome is indicated and something that the patient wants to do. Many patients do not know if an IHC screening test was performed on their cancer, but you can ask your doctor about this information.

WHO SHOULD BE OFFERED TESTING FOR LYNCH SYNDROME?

Other than someone's personal history of cancer, another piece of information that we can

use to help determine if someone is at a higher risk to have Lynch syndrome is your family history. The National Comprehensive Cancer Network (NCCN) is a group of medical professionals that regularly meet to look over any updates in research studies and determine recommendations for who should be considered at a higher risk for one of these pathogenic gene variants, and thus should be offered genetic testing.

Cancers that are associated with Lynch syndrome include: colon cancer, uterine cancer, ovarian cancer, pancreatic cancer, stomach cancer, small intestinal cancer, hepatobiliary cancer, brain cancer (specifically glioblastoma), urinary tract cancer (specifically renal pelvic type), and sebaceous skin tumors/cancer.

You should consider genetic counseling and possibly genetic testing if you see these cancers within your family history (make sure to include yourself in your family history if you have been diagnosed with cancer), specifically if you see:

- Colon cancer or uterine cancer under the age of 50
- An individual diagnosed with two separate colon cancers in their lifetime
- An individual diagnosed with two or more of the Lynch syndrome-associated cancers (listed above)
- An individual with colon cancer AND a close relative who has been diagnosed with a Lynch-syndrome associated cancer (listed above), with one of the cancers being diagnosed under the age of 50
- An individual with colon cancer AND two or more individuals within the same side of the family with a Lynch syndrome-associated (listed above) cancer at any age

These are some loose guidelines for who may be at an increased risk, but a medical professional, such as a genetic counselor, will be able to meet with you to further examine your family history and help determine if you meet criteria for genetic testing.

CANCER SCREENING AND RISK MANAGEMENT FOR LYNCH SYNDROME

If you are tested and found to have Lynch syndrome, it is recommended to discuss your management plan with your healthcare team, and if available, to seek consultation through a specialized high-risk clinic. General recommendations are included here based on the updated guidelines of the NCCN, but may be tailored to your specific medical and family history.

All individuals with Lynch syndrome should have a colonoscopy every 1-2 years to look for colon polyps which may grow into colorectal cancer. This screening should start around age

20-25. The good news is that this screening for colon cancer is highly effective in reducing the chance that someone would develop colon cancer and reduces the severity of colon cancer.

An endoscopy (EGD) to look at the stomach and duodenum (the first part of the small intestine immediately beyond the stomach) may be considered for those who have a family history of stomach or small intestinal cancer or have other risk factors for these cancers (i.e. Asian descent).

Women at increased risk for uterine and ovarian cancer due to having Lynch syndrome are encouraged to consider prophylactic (preventative) removal of the uterus, ovaries, and fallopian tubes once they are certain they would not like any future pregnancies. For women who do not elect preventive surgery, screening for these cancers may include biopsies of the uterus, checking CA-125 blood levels to screen for ovarian cancer, and transvaginal ultrasound. However, these screenings have not proven to be effective and are not recommended by many medical organizations.

In families with Lynch syndrome and a history of pancreatic cancer, individualized screening may be offered based on the history, but no specific guidelines currently exist.

An annual urine test can be considered to screen for urinary tract cancers starting around age 30-35.

Individuals with Lynch syndrome should have regular physical exams with primary cancer physician including a neurological evaluation.

Click here to learn more about scheduling a genetic counseling appointment for questions about hereditary cancer predisposition.

Resources:

A Guide for Patients and Their Families (from the Center for Disease Control)

Hereditary Colon Cancer Takes Guts (A Patient's Guide to Lynch Syndrome)

Lynch Syndrome International