What Is Lynch Syndrome?

Lynch syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is the most common hereditary form of colorectal and uterine cancer. About 2-3% of people who have colorectal or uterine cancer have Lynch syndrome. Families with Lynch syndrome usually have several family members with colorectal or uterine cancer. People with Lynch syndrome often start to develop precancerous colorectal polyps or cancers at an earlier age than the general population, as early as 20 years old. People with Lynch syndrome also have an increased risk for cancers of the stomach, small intestine, liver, gallbladder, upper urinary tract, and uncommon brain and skin cancers. **Women with Lynch syndrome have an increased risk for endometrial and ovarian cancer.** Lynch Syndrome affects ~28,000 individuals annually in the USA.

What Causes Lynch Syndrome?

We all have about 25,000 genes in almost every cell in our body. Each of these genes is made up of a series of four chemical letters in a certain order. As the cells grow and divide, exact copies of these genes are made for each new cell that is formed. When mistakes are made during this copying process, the wrong chemical letter may end up in the new gene that is created. These "typos" are known as a **DNA mismatch.**

Some of our genes act as spellcheckers to detect and repair DNA mismatch. These mismatch repair genes help protect us from cancer by correcting any mistakes that occur when DNA is growing and dividing. However, mutations in the DNA mismatch repair genes prevent them from working properly and cancer can develop.

Lynch syndrome is caused by mutations found in five genes that are part of or associated with the DNA mismatch repair process. These genes are MLH1, MSH2, MSH6, PMS2, and EPCAM.

Lifetime Risk Of Cancer In People With Lynch Syndrome

These mutations are associated with an increased lifetime risk for colorectal cancer, CRC and other malignancies within the tumor spectrum including at least endometrial, ovarian, gastric, small bowel, urothelial, hepatobiliary tract, sebaceous and pancreatic cancers.

About 80% of people with Lynch syndrome have an alteration in either the MLH1 or MSH2 gene. MSH6 gene alterations are responsible for about 5-10% or more of families with this syndrome. PMS2 alterations are found in less than 5% of families. A small number, fewer than 5% of families with Lynch syndrome are found to have alterations in the EPCAM gene. There are also some families with Lynch syndrome who have a gene alteration that cannot be found by today's technology.

If a person has inherited an alteration that is harmful (a mutation) in one of these five genes from one of their parents, then they are at risk for developing the cancers seen in Lynch syndrome.

Below are the lifetime risks of cancer in people with gene alterations associated with Lynch syndrome.

Type of Cancer	Lynch Syndrome Risk	General Population Risk
Colorectal	52-82%	5-6%
Uterine	25-60%	2-3%
Stomach	6-13%	<1%
Ovary	4-12%	1-2%
Bile Duct	1.4-4%	<1%
Small Bowel	3-6%	<1%
Urinary Tract	1-4%	<1%
Brain	1-3%	<1%
Skin	1-9%	<1%
Pancreas	1-6%	<1%

How Do I Know If My Cancer Is Caused By A Mutation In My Mismatch Repair Genes?

The first step is to perform tumor testing. Your doctor can perform testing on a biopsy before or after surgery. There are two types of tumor testing: 1) Immunohistochemisty Testing, IHC and 2) Microsatellite Instability Testing, MSI.

IHC looks for proteins made by mismatch repair genes present in your cells by staining them in different colors and looking at them under a microscopic. A missing protein suggests a mutation in one of your mismatch repair genes.

MSI: microsatellites are small repeat sections of DNA that are prone to mistakes. If your mismatch repair genes are not working, then the mistakes in microsatellites cannot be corrected. This is called MSI-High. High MSI is a sign that a person may have Lynch syndrome.

Both IHC and MSI are effective methods to screen for colorectal cancer patients who are more likely to have Lynch syndrome. **If your tumor testing comes back as MSI-High or shows missing protein expression, genetic testing is recommended to confirm whether you have Lynch syndrome and the potential risks to your family.**

What's The Difference between Tumor Testing and Genetic Testing?

Genetic Testing looks for "germline" mutations that you were born with. Germline mutations will be present in every normal cell in your body and can be passed on from generation to generation.

Tumors happen when a cell develops **NEW** mutations causing the cell to grow uncontrollably. These **NEW** mutations might only be present in the tumor cell which means you were not born with them and they cannot be passed on to your children.

Genetic Testing determines if these NEW mutations are present ONLY in the tumor or if they are present in every cell in your body. This information will help guide your medical management and clarify risks for your family members.

How Is Lynch Syndrome Inherited?

Lynch syndrome is inherited in an "autosomal dominant" manner. Autosomal means that both men and women can have Lynch syndrome and pass it on to their children. Each of us has two copies of almost every gene, one from each parent, so even if one gene is altered, the other one can work normally. Dominant means that it takes only one altered copy of a gene in order to cause Lynch syndrome.

If you have an altered gene, here are the chances that other relatives might have inherited it:

- Your Children – 50% risk for each child.
- Your Mother or Father – almost a 50% risk. In most cases, you will have inherited the altered gene from either your mother or your father. In rare cases, neither of your parents will have the altered gene, because it has occurred as a new genetic event in you.

- Your Brothers and Sisters – 50% risk if one of your parents had the alteration. If neither of your parents had the alteration, then your siblings have a very low risk of having the alteration.
- More distant relatives like your aunts, uncles, cousins, nieces, and nephews may have inherited this gene alteration depending on where they are in the family tree. Please talk to your health care team about risks for specific relatives.

Otogenetics Comprehensive Inherited Cancer Panel Including Confirmation Of Lynch Syndrome

39 genes APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKn2A, CHEK2, ELAC2, EPCAM, FANCC, HRAS1, MEN1, METMLH1, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, NTRK1, PALB2, PALLD, PMS2, PTCH, PTEN, RAD50, RAD51, RAD51C, RAD51D, RET, SMAD4, STK11, TP53, VHL

Otogenetics Comprehensive Inherited Cancer Screening Panel Including Confirmation for Lynch Syndrome is designed for patients who have been diagnosed with colorectal, endometrial or ovarian cancer and demonstrated to have MMR protein deficiency by Immunohistochemistry IHC and/or Microsatellite Instability MSI.

The panel evaluates 39 genes linked to Breast, Ovarian, Endometrial, Colorectal, Lynch Syndrome, Gastric, Melanoma, Pancreatic, Polyposis, Prostate, Renal, Thyroid/Parathyroid and Uterine, and Other Major Syndromic Cancers in conjunction with confirming the presence of germline mutations in the MMR genes MLH1, MSH2, MSH6 and PMS2 and deletions in ECAMP to establish the diagnosis of Lynch Syndrome.

How Is Lynch Syndrome Managed?

Options for reducing cancer risk are available to help manage increased risks. With close monitoring, some cancers can be detected in their earliest stages when they are most amenable to treatment. Screening is testing that is done in an effort to identify and treat cancer early. Risk reduction strategies are used to try to prevent cancer. Your healthcare providers will discuss your testing options and medical management options for reducing risk such as **Increased Surveillance, Surgical Management, and Chemoprevention.**

For more information and patient advocacy groups, please visit our Patient Portal at www.otogenetics/patientportal.com

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Inherited Cancer Screening Including Lynch Syndrome Confirmation

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