Lynch Syndrome [1]

What is Lynch syndrome?

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is a type of inherited cancer of the digestive tract. People who have Lynch syndrome have a significantly increased risk of developing colorectal cancer [2] and an increased risk of developing other types of cancers, such as endometrial (uterine) [3], stomach [4], breast [5], ovarian [6], small bowel (intestinal) [7], pancreatic [8], prostate [9], urinary tract [10], liver [11], kidney [12], and bile duct [13] cancers.

Lynch syndrome is a possible diagnosis when multiple people on the same side of the family diagnosed with colorectal cancer. In addition, cancer is more likely to be diagnosed at a young age. The average age for colorectal cancer to be diagnosed in someone with Lynch syndrome is 45, as compared with the average age of 72 for a new diagnosis of colorectal cancer in the general population. In Lynch syndrome, colorectal cancer is somewhat more likely to develop on the right side of the colon.

ASCO recommends tumor testing for Lynch syndrome in all patients with colorectal cancer. As an alternate option, tumor testing is recommended for people who develop colorectal cancer younger than 70, or for those who are older than 70 and meet any of the revised Bethesda guidelines (see below). There is also an increased risk of a person with Lynch syndrome to develop multiple cancers during his or her lifetime. Read more about these recommendations and the recommendations for screening listed below at www.asco.org/endorsements/HereditaryCRC [14].

What are the signs of Lynch syndrome?

One set of criteria used to identify Lynch syndrome are called the revised Bethesda guidelines, which are listed below:

- Developing colorectal cancer younger than age 50
- Developing colorectal cancer and other cancers* linked with Lynch syndrome separately or at the same time
- Developing colorectal cancer with tumor features linked to Lynch syndrome at an age younger than 60

- Colorectal cancer in one or more first-degree relatives who also has or has had another Lynch syndrome-related cancer*, with one of these cancers developing before age 50
- Colorectal cancer in two or more first- or second-degree relatives with another Lynch syndrome-related cancer.

  *(colorectal cancer, endometrial cancer, small bowel, ureter, or renal pelvis cancer; some people would also consider including ovarian cancer)

The definition of Lynch syndrome is still evolving. A family may still have Lynch syndrome even if the revised Bethesda guidelines do not fully match the family history. Therefore, meeting with a health professional who has training in genetic diseases and conditions, such as a genetic counselor or medical geneticist, is recommended for people who have a family history that suggests Lynch syndrome.

There are two variant forms of Lynch syndrome called Muir-Torre syndrome [15] and Turcot syndrome [16].

What causes Lynch syndrome?

Lynch syndrome is a genetic condition. This means that the cancer risk can be passed from generation to generation in a family. Several genes have been identified that are linked to Lynch syndrome. They include *MLH1*, *MSH2*, *MSH6*, *PMS2,* and *EPCAM*. A mutation (alteration) in any of these genes gives a person an increased lifetime risk of developing colorectal cancer and other related cancers. Women also have an increased risk of developing endometrial and ovarian cancers.

Most mutations that cause Lynch syndrome are found in the *MLH1* or *MSH*2 genes. Not all families that appear to have Lynch syndrome will have mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2,* or *EPCAM*. Research is ongoing to identify other genes associated with Lynch syndrome. Some people will develop changes in these genes that are not inherited, but are related to the aging process and other causes that are not well understood. If a tumor is found to have alterations in these genes, the person?s blood will also be tested for that abnormal gene. If the blood and tumor both have the changed gene, the condition is inherited rather than acquired, meaning other family members could be affected; testing is available (see below).

How is Lynch syndrome inherited?

Normally, every cell has two copies of each gene: one inherited from the mother and one inherited from the father. Lynch syndrome follows an autosomal dominant inheritance pattern, in which a mutation needs to happen in only one copy of the gene for the person to have an increased risk of getting that disease. This means that a parent with a gene mutation may pass along a copy of their normal gene or a copy of the gene with the mutation. Therefore, a child who has a parent with a mutation has a 50% chance of inheriting that mutation. A brother, sister, or parent of a person who has a mutation also has a 50% chance of having the same mutation.

Options exist for couples interested in having a child when they know that one of them carries a gene mutation that increases the risk for this hereditary cancer syndrome. Preimplantation

genetic diagnosis (PGD) is a medical procedure done in conjunction with in-vitro fertilization (IVF). It allows people who carry a specific known genetic mutation to have children who do not carry the mutation. A woman?s eggs are removed and fertilized in a laboratory. When the embryos reach a certain size, one cell is removed and is tested for the hereditary condition in question. The parents can then choose to transfer embryos that do not have the mutation. PGD has been in use for over a decade, and more recently has been used for several hereditary cancer predisposition syndromes. However, this is a complex procedure with financial, physical, and emotional factors for couples to consider before starting. For more information, talk with an assisted reproduction specialist at a fertility clinic.

How common is Lynch syndrome?

Most colorectal cancer is sporadic, meaning it occurs by chance with no known cause. Approximately 3% to 5% of all cases of colorectal cancer are thought to be due to Lynch syndrome.

How is Lynch syndrome diagnosed?

Lynch syndrome is likely if a family history meets the revised Bethesda guidelines listed above. Lynch syndrome can be confirmed through a blood test. The test can determine if someone has a mutation in one of the genes associated with Lynch syndrome. Currently testing is available for the *MLH1*, *MSH2*, *MSH6,* and *EPCAM* genes. The *PMS2* gene is tested for in some clinical trials [17] (research studies) as well as cancer centers that specialize in Lynch syndrome. However, not all families with Lynch syndrome will have a mutation in one of these genes.

For patients who have a family history that suggests Lynch syndrome, screening tests can be performed on tumor (cancer) tissue to help determine if Lynch syndrome is likely. The two screening tests suggested are microsatellite instability testing (MSI) and immunohistochemistry testing (IHC). The results of these tests can indicate whether more specific genetic testing should be considered.

Since most colorectal cancer is sporadic, genetic testing is only recommended for people who have a family history that suggests Lynch syndrome. Testing for mutations in the Lynch syndrome genes may not be beneficial for the average person.

What are the estimated cancer risks associated with Lynch syndrome?

General cancer risks for people with Lynch syndrome

- Colorectal cancer [2] 80%
- Stomach cancer [4] 11% to 19%
- Hepatobiliary tract cancer [13] (liver/bile duct [13]) 2% to 7%
- Urinary tract cancer [10] 4% to 5%
- Small bowel cancer [7] (intestines) 1% to 4%
- Brain [18] or central nervous system tumor [19] 1% to 3%

Cancer risks for women with Lynch syndrome

- Endometrial cancer [3] 20% to 60%
- Ovarian cancer [6] 9% to 12%

As noted above, Lynch syndrome has been linked to higher risk of other types of cancer as well, including pancreatic, prostate, kidney, and breast cancers [20].

What are the screening options for Lynch syndrome?

ASCO recommends the following screening for people with Lynch syndrome. It is important to discuss these options with your doctor, as each individual is different:

General screening guidelines

- Colonoscopy [21] every one to two years, beginning between the ages of 20 to 25 or five years younger than the earliest age at diagnosis in the family, whichever is sooner
- Testing and treatment for *Helicobacter pylori* is recommended if a person has been diagnosed with Lynch syndrome
- Screening for other cancers linked with Lynch syndrome may be recommended depending on a person?s family history. This could include:

Screening for women

- Yearly pelvic examination, pelvic ultrasound [22], endometrial biopsy [23], from age 30 to 35. Women who have finished having children may want to consider having preventive surgery to remove the uterus and ovaries.

Screening options may change over time as new technologies are developed and more is learned about Lynch syndrome. It is important to talk with your doctor about appropriate screening tests.

Learn more about what to expect with common tests and procedures [24].

Questions to ask the doctor

If you are concerned about your risk of colorectal cancer or other types of cancer, talk with your doctor. Consider asking the following questions of your doctor:

- What is my risk of developing colorectal cancer or other types of cancer?
- What can I do to reduce my risk of cancer?
- What are my options for cancer screening?

If you are concerned about your family history and think your family may have Lynch syndrome, consider asking the following questions:

- Does my family history increase my risk of colorectal cancer or other types of cancer?
- Have MSI or IHC tests been done on my tumor tissue?
- Should I meet with a genetic counselor?
- Should I consider genetic testing?

More Information

The Genetics of Cancer [25]

Genetic Testing [26]

What to Expect When You Meet With a Genetic Counselor [27]

Collecting Your Family Cancer History [28]

Sharing Genetic Test Results with Your Family [29]

Additional Resources

Lynch Syndrome International
http://www.lynchcancers.com [30]

Colon Cancer Alliance
www.ccalliance.org [31]

Colorectal Cancer Coalition (C3)
www.fightcolorectalcancer.org [32]

To find a genetic counselor in your area, ask your doctor or visit the following websites:

National Society of Genetic Counselors
www.nsgc.org [33]

National Cancer Institute: Cancer Genetics Services Directory
www.cancer.gov/cancertopics/ [34]

Links:
[1] http://www.cancer.net/cancer-types/lynch-syndrome
[2] http://www.cancer.net/node/31317
[3] http://www.cancer.net/node/31260
[4] http://www.cancer.net/node/31376
[5] http://www.cancer.net/node/31322
[6] http://www.cancer.net/node/31343
[7] http://www.cancer.net/node/31377
[8] http://www.cancer.net/node/31388
[9] http://www.cancer.net/node/31382
[10] http://www.cancer.net/node/31330
[11] http://www.cancer.net/node/31274
[12] http://www.cancer.net/node/31256
[13] http://www.cancer.net/node/31332
[14] http://www.asco.org/endorsements/HereditaryCRC
[15] http://www.cancer.net/node/19364
[16] http://www.cancer.net/node/19307
[17] http://www.cancer.net/node/24863
[18] http://www.cancer.net/node/31327

[19] http://www.cancer.net/node/31323
[20] http://www.cancer.net/node/24431
[21] http://www.cancer.net/node/24481
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[29] http://www.cancer.net/node/24906
[30] http://www.lynchcancers.com/
[31] http://www.ccalliance.org/
[32] http://www.fightcolorectalcancer.org/
[33] http://www.nsgc.org/
[34] http://www.cancer.gov/cancertopics/genetics/directory