Table of Contents

Introduction .............................................................. 2
What Is Lynch Syndrome? ........................................ 3
What Causes Lynch Syndrome? ............................... 6
How Is Lynch Syndrome Inherited? ......................... 9
How Is Lynch Syndrome Diagnosed? .................... 12
What Is Involved in the Decision
to Have Genetic Testing? .................................. 15
Colon Cancer Prevention ...................................... 17
Cancer Screening Guidelines
  for Lynch Syndrome ........................................ 18
Conclusion .......................................................... 21
Word List .............................................................. 22
This material discusses a condition called Lynch syndrome. This was previously known as hereditary non-polyposis colon cancer, or HNPCC. *Lynch syndrome* (named after Henry Lynch, a physician who spent many years studying the disorder) is the term used in the rest of this material to refer to HNPCC.

This material explains:
• What Lynch syndrome is.
• The genetic nature of Lynch syndrome.
• How Lynch syndrome is diagnosed.
• What can be done to reduce the risk of cancer in families that have Lynch syndrome.

If you have questions about this information, discuss them with your health care provider.

Note: In the information that follows, “colon” or “colorectal cancer” refers to cancers of the colon and the rectum. Words that appear in bold are explained in the word list.
What Is Lynch Syndrome?

Lynch syndrome is a genetic condition that greatly increases a person’s risk of colon cancer. “Genetic” means that Lynch syndrome originates in a person’s genes and can be passed from one generation to the next.

If you have Lynch syndrome, you have a much greater chance of developing colon cancer during your lifetime than the general population. Also in people with Lynch syndrome, the average age of colon cancer diagnosis is much younger than in the general population.

In addition, people with Lynch syndrome have a high risk of developing more than one cancer in the colon. For those who have Lynch syndrome, two-thirds of colon cancers develop in the right side of the colon. In the general population, colon cancer is found more frequently on the left side of the colon (Figure 1).
Women who have Lynch syndrome are also at increased risk for endometrial cancer (a cancer affecting the lining of the uterus). More than one in three women with Lynch syndrome could develop endometrial cancer during their lifetimes. Women with Lynch syndrome also have an increased risk of ovarian cancer.
Both men and women who have Lynch syndrome have some increased risk of cancer in these locations:
• Stomach
• Small intestine
• Urinary tract/bladder
• Skin
• Liver and biliary tract
• Pancreas
• Brain

Fortunately for people who have Lynch syndrome, the risk of developing the cancers listed above is much lower than the risk of developing colon or endometrial cancer.

Some people may wonder why Lynch syndrome (hereditary non-polyposis colon cancer) is not simply called “hereditary colon cancer.” “Non-polyposis” is included in the name to highlight the difference between Lynch syndrome and another type of inherited colon cancer known as familial adenomatous polyposis or FAP. While people with Lynch syndrome probably develop more colon polyps (growths in the colon) than usual, people with FAP develop hundreds to thousands of colon polyps. This development is not seen in Lynch syndrome.
What Causes Lynch Syndrome?

Lynch syndrome is a “genetic” condition. This means the problem originates in a gene or genes. In order to understand the genetic basis of Lynch syndrome, it is important to understand some basic genetic concepts.

Each cell in a person’s body has 46 packages of genetic material called chromosomes. Chromosomes are made of genes, which are long chains of special chemicals called DNA (deoxyribonucleic acid) (Figure 2). The DNA in each gene “spells out” instructions for the body’s cells. When the DNA of a gene is changed in some way or “misspelled,” it is called a mutation.

Figure 2. Each cell contains chromosomes in its nucleus. Chromosomes consist of long chains of DNA. Genes are segments of the chains of DNA.
The job of genes that are spelled correctly, with no mutation, is to provide instructions for making specific types of **proteins**. These proteins control how your cells grow and function. If there is a gene mutation, the proteins may not be made properly, and the cells may not function correctly.

A mutation can be either **inherited** or non-inherited (**acquired**). Inherited mutations can be passed from parents to children and are present in every cell of the body. Inherited mutations are present from birth.

Normal effects of the environment, like aging, can cause acquired mutations. Normally, acquired mutations are not a problem because our bodies have extremely efficient “spell-checker” mechanisms that correct them. Specific genes provide instructions for the body to make these “spell-checker” mechanisms.

An inherited gene mutation causes Lynch syndrome. In people with Lynch syndrome, one of the spell-checker mechanisms is not working properly because of the inherited mutation. The spell-checker mechanism involved in Lynch syndrome is a group of proteins that work as a team to repair acquired misspellings in DNA. This protein team is called the DNA mismatch repair system. Usually, the proteins in the mismatch repair system are made by four genes (**MLH1, MSH2, MSH6, PMS2**).
In Lynch syndrome, one of these four genes has a mutation that causes it to make a defective spell-checker protein. This defective protein interferes with the correction of other acquired mutations and can lead to cells that acquire genetic damage. The risk of those cells becoming cancerous increases. People who have an inherited mutation in one of the Lynch syndrome spell-checker genes have a higher risk of cancer and may get cancer at an earlier age.
How Is Lynch Syndrome Inherited?

Lynch syndrome is an *autosomal dominant* genetic condition. Autosomal dominant describes how the gene alteration (mutation) is passed from parent to child (Figure 3a, b). This means:

- Males and females are equally likely to inherit a Lynch syndrome gene alteration.
- Each child of a parent affected by Lynch syndrome has a 50-50 (or 1 in 2) chance of inheriting a Lynch syndrome gene alteration.
D = dominant, altered gene

d = functioning genes

Figure 3a. Affected mother

Figures 3 a,b. Autosomal dominant form of inheritance
Figure 3b. Affected father

D = dominant, altered gene

d = functioning genes
How Is Lynch Syndrome Diagnosed?

Today, diagnosing Lynch syndrome can be a three-stage process. The three stages include:
1. Review of family cancer history
2. Tumor testing
3. Genetic testing

**Stage 1 — review of family cancer history**
To find out if you are at risk for Lynch syndrome, your health care provider will ask you whether there is cancer in your immediate and extended family. If your family has a pattern of cancer that meets all four criteria below (known as the Amsterdam Criteria), it is possible that the cancer may be due to Lynch syndrome.

- At least three family members have colon cancer. Two of the three are first-degree relatives (parent/brother/sister/child) of the third person. For example, this could be a grandmother, her son and his daughter.
- These three family members are from more than one generation.
- At least one family member with colon cancer was diagnosed under age 50.
- Your family does not have a diagnosis of familial adenomatous polyposis (FAP), an inherited disorder unrelated to Lynch syndrome.
Difficulties in diagnosing Lynch syndrome based on family cancer history alone may arise if families are small, if individuals are adopted, or if information about extended family members is not available. When the cancer history of the extended family is limited, your health care provider may use more general guidelines.

Family cancer history alone cannot identify all families with or without Lynch syndrome.

**Stage 2 — tumor testing**

If your family cancer history meets the Amsterdam Criteria or more general guidelines, additional laboratory tests can be done to help determine whether you might carry a Lynch syndrome genetic mutation. The tests are done on tumor tissue that has been removed, even if the surgery was done years before.

The tumor tests are:

- **MSI (microsatellite instability) screening** — This test looks for the presence of genetic instability associated with Lynch syndrome
- **IHC (immunohistochemistry) screening** — Samples of tumor tissue are stained to find out which spell-checker proteins are present
- **Tumor testing for acquired changes in the BRAF gene**
- **Tumor testing for methylation**
For more detailed information on tumor testing, ask your health care provider. Your health care provider can decide which of these tests should be done.

**Stage 3 — genetic testing**

If both family history and tumor testing suggest it is likely that you have a Lynch syndrome genetic mutation, you may consider having the blood test that looks for the presence or absence of a Lynch syndrome gene mutation. (If no tumor tissue was saved, genetic testing can still be done. However, a gene test that finds nothing provides less information when tumor testing was not done previously.)

The decision to go forward with genetic testing is complex. It is important to note that in some people who have Lynch syndrome, the specific Lynch syndrome genetic mutation cannot be identified.
What Is Involved in the Decision to Have Genetic Testing?

Before having genetic testing for Lynch syndrome, consult with a genetic specialist. This consultation can help you understand the following aspects of genetic testing:

• The likelihood of finding a gene mutation
• The accuracy of genetic testing
• Medical usefulness of identifying a genetic mutation
• Medical interpretation of not finding a mutation
• Costs, waiting time for a result, and implications for insurance coverage
• Possible emotional reactions to genetic testing
• Implications for cancer prevention for you and your relatives

True negative results
If you have a family member with a known Lynch syndrome gene mutation and Lynch syndrome genetic testing shows that you do not have that mutation, you can be reassured that you have not inherited the Lynch syndrome gene mutation. If you do not have the Lynch syndrome gene mutation, your risk and your children’s risk for colon cancer and other Lynch syndrome-related cancers remain the same as the general population.
Uninformative results
However, if in your family the specific gene mutation has not been identified, a negative genetic test in an at-risk family member does not mean that the person is not at risk for Lynch syndrome.

When family cancer history, tumor testing and genetic testing point toward Lynch syndrome, even if genetic testing did not identify the gene mutation, you are still considered to be at risk and should follow the cancer screening guidelines for Lynch syndrome.
 Colon Cancer Prevention

In many cases, colon cancer is preventable. Colon cancer almost always begins as a colon polyp. A **colonoscopy** is a test that can identify and remove colon polyps before they become cancers. If colon cancer has occurred and is found in its early stages, it is often curable.

In some cases, when a person has been diagnosed with Lynch syndrome, he or she may choose to have the colon removed to reduce the risk of colon cancer.
Cancer Screening
Guidelines for Lynch Syndrome

People diagnosed with Lynch syndrome
Not all physicians agree on cancer screening guidelines for Lynch syndrome — the best cancer screening tests, how often they should be used, and the ages at which testing for Lynch syndrome should begin.

In addition, your health care provider may tailor cancer-screening guidelines for you and your family. Screening may include:

• A colonoscopy every 1 to 2 years starting at an earlier age than the general population. If polyps are found, have a colonoscopy at least yearly. You also may want to consider surgical removal of the colon.

• For women — Screening for endometrial cancer and ovarian cancer may be suggested if you have or are at risk for Lynch syndrome. Any vaginal bleeding between menstrual periods or after menopause should be investigated carefully. Removal of the uterus and ovaries may be considered when childbearing is done.
• Yearly urine cytology tests to look for cancer cells in the urine.
• An upper endoscopy if there is already a family history of gastric cancer.
• Follow the American Cancer Society guidelines for all other cancer screening.

You should seek immediate evaluation of any persistent, unexplained symptoms.
Guidelines for people at risk for Lynch syndrome (close relatives of people with Lynch syndrome who have not had cancer themselves)

• Schedule a colonoscopy every 1 to 3 years, starting between ages 20 and 30. If polyps are found, have a colonoscopy every year. The presence of polyps, especially in a young person who has relatives with Lynch syndrome, may be a sign that you have inherited the Lynch syndrome genetic mutation.

• For women — Get a yearly pelvic exam starting at age 18 or with onset of sexual activity. To screen for endometrial cancer, get a yearly endometrial biopsy, ultrasound or both, starting at age 25 to 35. Vaginal bleeding between menstrual periods or after menopause should be investigated carefully. Yearly blood tests for tumor antigen CA-125 and a transvaginal ultrasound may be done to screen for ovarian cancer starting at age 30 to 35.

• Schedule urine tests yearly to check for the presence of blood. Consider regular urine cytology tests to look for cancer cells in the urine.

• Follow the American Cancer Society guidelines for all other cancer screening.

You should seek immediate evaluation of any persistent, unexplained symptoms.
Conclusion

If you know you are at risk for Lynch syndrome, regardless of whether you choose to have genetic testing, follow the cancer screening guidelines suggested by your health care provider. There is strong evidence that regular cancer screening saves lives.
Acquired — Not genetic. Produced by external influences or as a result of aging.

At risk — In this booklet “at risk” describes a person whose first-degree relative (parent, brother, sister or child) or second-degree relative (grandparent, aunt, uncle, grandchild) has a genetic condition. It is not yet known if the individual in question inherited the genetic condition.

Biopsy — A procedure in which small tissue samples are removed from the body to detect cancer or other abnormal cells.

Cancer — A general term for illnesses characterized by growth of abnormal or malignant cells. Some cancers exist quietly within the body for years without causing a problem. Others are aggressive, rapidly forming tumors that may destroy surrounding tissue and spread to other parts of the body.

Chromosomes — The threadlike structures in the nucleus of a cell that are composed of DNA and pass on genetic information.
Colonoscopy — A procedure that allows direct viewing inside the colon (large intestine). A physician uses a colonoscope — a thin, flexible tube — to visually inspect the colon and diagnose bleeding, inflammation or tumors. Colonoscopy may also be used to obtain biopsy specimens, remove polyps, or treat bleeding sites.

DNA — The abbreviation for deoxyribonucleic acid. One of two acids (the other is RNA) found in the nuclei of all cells. DNA holds genetic information on cell growth, division, and function.

Endometrial — Referring to the endometrium, the lining of the uterus or womb.

Familial adenomatous polyposis (FAP) — An inherited disorder in which affected people get multiple polyps in the colon. Abnormal growths also may occur in other parts of the body. FAP accounts for only 1 percent of colon cancers.

Gene — A segment of a DNA molecule located on a chromosome that contains genetic information. The markers that carry traits from parents to children.

Inherited — Passed from one generation to the next through genes.
**Mutation** — A change in the genetic material, usually in a single gene.

**Polyps** — Noncancerous growths protruding from a mucous membrane, such as the colon lining. Some polyps can become cancerous.

**Protein** — One of many complex chemicals that perform a wide variety of activities in cells.

**Screening** — The search for disease, such as cancer, in people without symptoms.

**Ultrasound** — An imaging exam that uses sound waves to outline a part of the body. High-frequency sound waves are transmitted through the area of the body being studied. The sound-wave echoes are picked up and displayed on a video screen. No radiation exposure occurs.

**Uterus** — The female organ in which the embryo/fetus develops. The uterus is also known as the womb.
Barbara Woodward Lips Patient Education Center

Mrs. Lips, a resident of San Antonio, Texas, was a loyal Mayo Clinic patient of more than 40 years and a self-made business leader who significantly expanded her family’s activities in oil, gas and ranching. Upon her death in 1995, Mrs. Lips paid the ultimate compliment by leaving her entire estate to Mayo Clinic. By naming the Barbara Woodward Lips Patient Education Center, Mayo honors her generosity, her love of learning, her belief in patient empowerment and her dedication to high-quality care.

This material is for your education and information only. This content does not replace medical advice, diagnosis or treatment. New medical research may change this information. If you have questions about a medical condition, always talk with your health care provider.