



PATIENT EDUCATION

*Immunohistochemistry
(IHC) and
Microsatellite
Instability (MSI)
Testing*

EDUCATION
Learning CARING
EXCELLENCE INTERACTION
**HEALTHY
LIVING**

BARBARA WOODWARD LIPS
PATIENT EDUCATION CENTER

Immunohistochemistry (IHC) and microsatellite instability (MSI) are two screening tests that may be done to help find out if your or your family member's cancer may have been caused by an inherited **gene mutation**. If a cancer is caused by a gene mutation, then it may be passed from one generation of your family to another.

These tests (IHC and MSI) look at whether you or your family members have an increased risk of having one specific inherited form of colon cancer called hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome.

Lynch syndrome is the term used in the rest of this booklet. [For more information about HNPCC/Lynch syndrome, see Mayo Clinic publication *Hereditary Non-Polyposis Colon Cancer (HNPCC)/Lynch Syndrome*, (MC2484).

If you have questions about whether these tests may be useful to you, ask a member of your health care team. They will decide whether one or both tests are appropriate for you.

Words in bold are defined in a word list beginning on page 10.

How are the tests done?

Both IHC and MSI tests are done using a sample of tumor tissue that was removed from the body during a biopsy or surgery. This tissue may be from a colon cancer, precancerous colon polyp, endometrial (uterine) cancer, or sometimes, other types of tumors. Usually, this tissue is kept for at least 10 years after a biopsy or surgery is done.

IHC and MSI tests are different from general tissue studies. General **pathology** studies do not tell you about the causes of the tumor. IHC and MSI tests can be used to look at the tumor in another way and can give more information about the possible *cause* of the tumor.

What do the results mean?

To understand how these screening tests work and what the results mean, it may help you to understand some basic information about Lynch syndrome and your genes.

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 1). 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.

The job of genes that are spelled correctly, with no mutation, is to make specific types of **proteins** that control how your cells grow and function. If there is a gene mutation, the protein may not be made, and the cells may not function correctly.

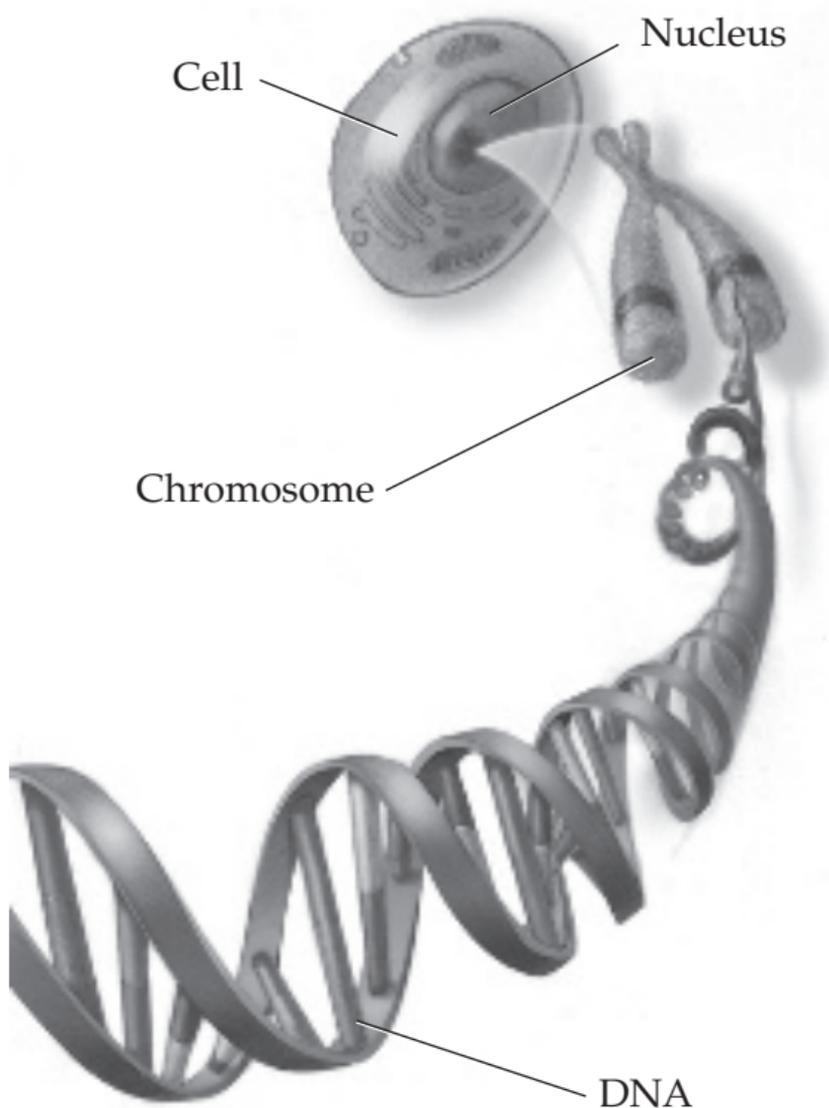


Figure 1. Each cell has chromosomes in its nucleus. Chromosomes are made of genes, long chains of special chemicals called DNA.

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, this is not a problem because our bodies have extremely efficient “spell-checker” mechanisms that correct the acquired mutations (figure 2).

Lynch syndrome is caused by an inherited gene mutation. In most people with Lynch syndrome, one of the spell-checker mechanisms is not working properly because of an 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 interferes with the correction of other acquired mutations and can lead to cells that accumulate 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.

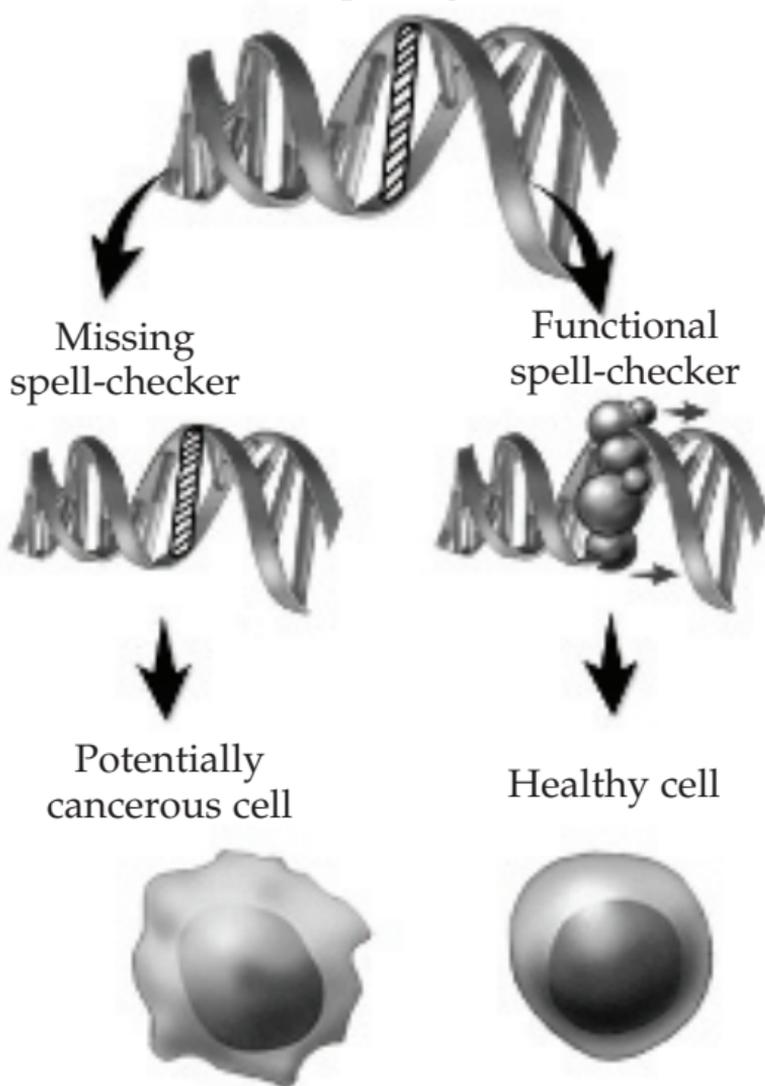


Figure 2. How “spell-checkers” work

IHC and MSI testing gives us information about whether or not the “spell-checker” system is working. This tells us if a person is at risk for Lynch syndrome.

However, most people who get cancer do not have Lynch syndrome and do not have a problem with their spell-checker proteins.

IHC testing

In IHC testing, the tissue is exposed to special stains that are made to color the tissue only if the specific “spell-checker” proteins are present. If a specific protein is missing, the stain will not color the tissue.

For IHC testing to give more information about Lynch syndrome, four specific stains are used. At minimum, these stains are used to detect the MLH1, MSH2, MSH6 and PMS2 proteins.

The IHC results will tell you whether or not MLH1, MSH2, MSH6 and PMS2 are present in your tumor tissue. If one or more of these proteins are missing, there may be an increased risk for Lynch syndrome. Studies show that loss of MSH2 and MSH6 are usually related to Lynch syndrome. Loss of MLH1 and PMS2 also can be related to Lynch syndrome but could also be **sporadic** or due to an acquired gene mutation, not hereditary.

MSI testing

To do MSI testing, the DNA is removed from the tissue so it can be studied. In your DNA, you have certain regions called **microsatellites** that tend to acquire gene mutations frequently when the “spell-checker” system does not work. MSI testing

looks at these microsatellite regions to see whether or not they have gene mutations. If many gene mutations are found, the tumor is said to show microsatellite instability (also called MSI-high). If gene mutations are not found in the microsatellites, the tumor is said to be microsatellite stable (MSI-stable or MSI-low).

The MSI test will tell you if the microsatellites in your tumor appear stable or unstable. People who have MSI-high results have a higher risk of having Lynch syndrome. On the other hand, not all people with MSI-high tumors have Lynch syndrome. About 10 to 15 percent of tumors may show microsatellite instability because of sporadic changes in the “spellchecker” genes.

It is also important to know that when people are diagnosed with colon cancer when they are older (for example, over age 60), there is a greater chance that a tumor will be MSI-high. Most older people with an MSI-high tumor will not have Lynch syndrome.

Your health care professional can help you interpret the results of your IHC and MSI testing in the context of your personal and family history.

Why should I have IHC and/or MSI testing?

Most colon cancer is not inherited and happens because everyone has a risk of developing a colon cancer. This is called sporadic colon cancer.

On the other hand, 5 percent of people who have colon cancer may have an inherited risk for this disease. About half of these people may have Lynch syndrome. If they have Lynch syndrome, they may have a much higher risk of developing a second colon cancer, as well as other types of cancers. Some of their family members also may have this increased risk for cancer. Finding the level of risk for a family may help to determine the best cancer screening guidelines and risk-reduction interventions. Therefore, it is important to figure out who may be at risk for Lynch syndrome. IHC and MSI testing can help do this.

Who might consider IHC and/or MSI testing?

People who might benefit from IHC and/or MSI testing include:

- Someone younger than the usual age when colon or endometrial cancer is diagnosed (typically less than 50 years is considered “younger”)
- Someone with more than one cancer diagnosis (two separate colon cancers or colon and endometrial cancer, for example)
- Someone with a personal and family history of colon cancer

What happens if IHC and MSI show an increased risk for Lynch syndrome?

Discuss specific recommendations for you and your family with your health care provider.

When the results of these tumor tests show that Lynch syndrome may be present in a family, gene testing from a blood sample is available. Sometimes, when IHC shows that a certain protein is missing, there may be no **hereditary** cause. Additional tests on the tumor tissue (tests called “BRAF” or “MLH1 hypermethylation”) are available to help determine whether the tumor is inherited or sporadic.

Gene testing looks for a gene mutation. This is usually a blood test. If a mutation is found, a genetic predisposition to cancer associated with Lynch syndrome is confirmed. If no mutation is found, the person may or may not have Lynch syndrome. Some mutations cannot be detected with current testing methods. Talk to a specialist in genetics to discuss the risks, benefits and limitations to this kind of testing. See Mayo publication *Genetic Testing A Fact Sheet* (MC2862) for more information about gene testing.

What does it mean if IHC and MSI do NOT show an increased risk for Lynch syndrome?

This does not rule out all types of hereditary colon cancer risk. In this case, it is possible that there is another genetic cause of cancer risk in the family, or in very rare cases, Lynch syndrome may be present but with a very unusual presentation. Or the cancer may be sporadic. Further evaluation and screening recommendations are suggested based on your personal and family history.

If you have any questions about this information, or wish to discuss IHC and MSI testing further, contact your health care professional.

Word list

Acquired — Not genetic. Produced by external influences or as a result of aging.

Chromosome — One of the threadlike structures in the nucleus of a cell that carries genes and passes on genetic information, such as eye color, blood type and tissue type.

DNA — Abbreviation for deoxyribonucleic acid. DNA holds genetic information on cell growth, division and function.

Genes — “Markers” that carry traits from parents to children. A gene is a segment of DNA on one of the chromosomes.

Genetic — Related to genes.

Hereditary — Related to transmission of genetic traits from a parent to child.

Inherited — Passed from one generation to the next through the genes.

Microsatellites — Short segments of DNA.

Mutation — Permanent change in the genetic material, usually in a single gene.

Pathology — Study of the cause and nature of a disease.

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

Sporadic — Occurring occasionally in a random or isolated manner.

BARBARA WOODWARD LIPS PATIENT EDUCATION CENTER

Mrs. Lips, a resident of San Antonio, Texas, was a loyal patient of Mayo Clinic for more than 40 years. She was a self-made business leader who significantly expanded her family's activities in oil, gas and ranching, even as she assembled a museum-quality collection of antiques and fine art. She was best known by Mayo staff for her patient advocacy and support.

Upon her death in 1995, Mrs. Lips paid the ultimate compliment by leaving her entire estate to Mayo Clinic. Mrs. Lips had a profound appreciation for the care she received at 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.



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