# CONTINUING EDUCATION

## EDUCATIONAL OBJECTIVES

**After participating in this activity, clinicians should be better able to**

- Describe the risk profile for Lynch syndrome (hereditary nonpolyposis colorectal cancer).
- Describe the role of mismatch repair genes in this inherited autosomal dominant syndrome.
- Develop a plan for a high-risk person with Lynch syndrome

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# Lynch syndrome: Identifying patients at risk for HNPCC

Cristina Polinsky, MS, CGC; Rachael Brandt, MS, CGC; Rosemarie Tucci, RN, MSN, AOCN; Terri McHugh, DO

## STATEMENT OF NEED/PROGRAM OVERVIEW

Colorectal cancer is the third most common cancer in the United States and is the leading cause of cancer death overall. Most colorectal cancers occur sporadically; however, 5% to 10% are caused by hereditary cancer predisposition syndromes, the most common being Lynch syndrome. A thorough personal and family history can help raise the level of suspicion for Lynch syndrome. Knowing the risk factors for Lynch syndrome and the availability of genetic counseling/testing services is very important for these patients.

## CE INFORMATION

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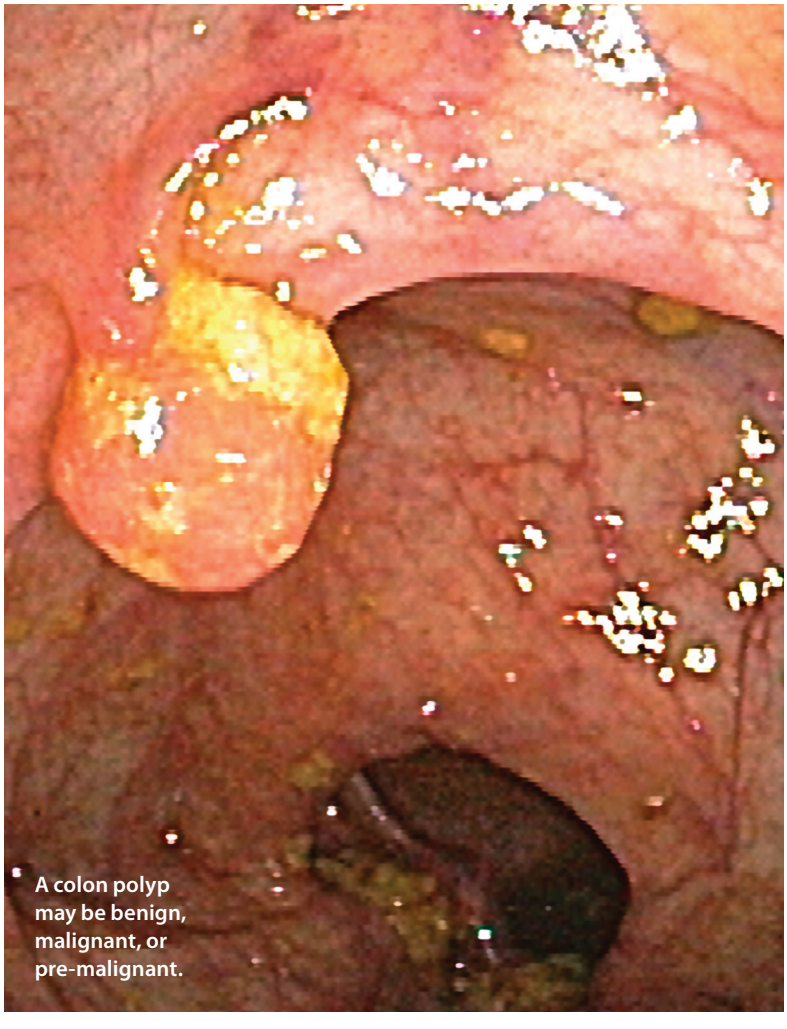
# Lynch syndrome: Identifying patients at risk for HNPCC

Hereditary nonpolyposis colorectal cancer is caused by an inherited genetic mutation. This review explains how to screen and counsel patients at risk.



A colon polyp may be benign, malignant, or pre-malignant.



**CRISTINA POLINSKY, MS, CGC; RACHAEL BRANDT, MS, CGC; ROSEMARIE TUCCI, RN, MSN, AOCN; TERRI McHUGH, DO**

Hereditary cancer predisposition syndromes account for a small percentage of all cancer diagnoses. Approximately 5% to 10% of all colorectal cancers are hereditary. The most prevalent hereditary colorectal cancer syndrome is Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC). HNPCC is caused by an inherited mutation in a DNA mismatch repair gene. Persons with Lynch syndrome have an increased lifetime risk not only for colorectal cancer, but also for endometrial, stomach, ovarian, urinary tract, and other cancers. Fortunately, established risk-management recommendations for patients with Lynch syndrome are associated with a decrease in cancer-related deaths.[1]

The first step in identifying a person at risk for Lynch syndrome is to obtain an accurate cancer history. Oncology nurses are essential in this step as they often have a close, ongoing relationship with their patients. Knowing the features of hereditary cancer syndromes can help save patients' and their family members' lives. This article provides a review of the current knowledge about Lynch syndrome, an overview of high-risk patient management, and strategies for identifying patients who are candidates for genetic evaluation.

## MISMATCH REPAIR GENES

Inherited mutations occurring in any of four DNA mismatch repair genes—*MLH1, MSH2, MSH6*, or *PMS2*—have known associations with Lynch syndrome. Mutations in *MLH1* and *MSH2* cause approximately 71% of Lynch syndrome cases; mutations in *MSH6* and *PMS2* occur less often.[2] Recently, a deletion in the gene *TACSTD1* was found in families suspicious for Lynch syndrome and accounts for a small fraction of persons without an identifiable mutation in the four known mismatch repair genes.[3]

Mismatch repair genes are necessary for fixing incorrect pairings of nucleotide bases in DNA during the replication or copying process. If the error or "mismatch" is not corrected, the risk of the cell becoming cancerous is increased. All cells, except gonadal cells, have two copies of each mismatch repair gene. Persons with Lynch syndrome are born with one functional copy and one nonfunctional copy due to an inherited mutation. A tumor can develop when a person *acquires* a mutation to the one functional copy or allele.[4] Thus, Lynch syndrome is inherited in an autosomal dominant manner, which means that a child whose parent has Lynch syndrome has a 50% chance of inheriting the mutation.

## RISK PROFILES

Persons with Lynch syndrome are at high risk for colorectal cancer as well as other cancers, most notably endometrial cancer. Lynch syndrome–related cancers often develop in multiple generations of a family, and these patients are usually younger at diagnosis than patients in the general population. The lifetime risk (up to age 70 years) for colorectal cancer is approximately 54% to 70% for men[5,6] and approximately 42% to 52% for women,[5,7] and average age of onset is 44 to 61 years.[5] Comparatively, the lifetime risk for colorectal cancer in the general population is only about 5%, and median age of onset is 70 years.[8]

Those with Lynch syndrome are also more likely to develop a second primary colorectal cancer, which could occur simultaneously or at a later time. The cumulative risk per year after diagnosis for a second primary colorectal cancer is 3%; therefore, the risk for a second colorectal cancer within 10 years is 30%.[9]

For women with Lynch syndrome, lifetime risk for endometrial cancer is up to 60%, and median age of onset is 47 to 62 years.[5,7,10] Conversely, the lifetime risk for endometrial cancer in the general population is approximately 2.5%, and median age of onset is 62 years.[8] Women with Lynch syndrome also have a lifetime risk for ovarian cancer of up to 12% compared with less than 2% in the general population.[10]

Risk for gastric cancer is higher in persons with Lynch syndrome; their lifetime risk is 6% to 13%.[10,11] In addition, risk for several other cancers, such as small bowel, hepatobiliary tract, pancreatic, renal pelvis, ureter, and brain, is higher in patients with Lynch syndrome than in the general population. Lifetime risk of each of these cancers is less than 10%.[10,12]

Because the majority of mutations are identified in *MLH1* and *MSH2*, the risk estimates discussed above are more closely related to mutations in these two genes. Persons with *MSH6* or *PMS2* mutations have different colorectal and endometrial cancer risks. For example, colorectal cancer risk ranges from 22% to 69% among men with *MSH6* mutations, whereas the risk for women is only 10% to 30%.[13,14] An *MSH6* mutation confers a lifetime risk for endometrial cancer of up to 71%; therefore, endometrial cancer develops more frequently in families with *MSH6* gene mutations.[13,14] Cancer risks in persons with a *PMS2* mutation are not as clear, as mutations in this gene are seen rarely. One recent study estimated lifetime risks in *PMS2*-mutation carriers of only 15% to 20% for colorectal cancer and 15% for endometrial cancer.[15] Other extracolonic cancer risks were also increased in persons with *MSH6* and *PMS2* mutations.[13,15]

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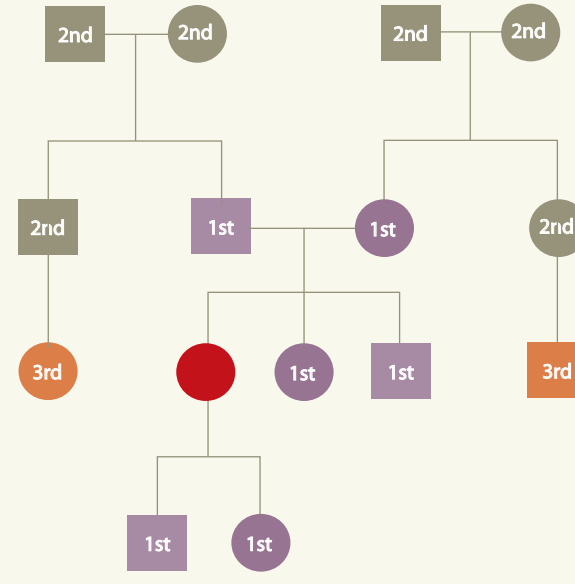


**Key:** Circles, women; squares, men.
**Note:** First-degree relatives include parents, siblings, and children; second-degree relatives include aunts and uncles, nieces and nephews, grandparents, and half siblings; third-degree relatives include cousins, great aunts, and great uncles.

**FIGURE 1.** Genetic pedigree including first-, second-, and third-degree relatives

**TABLE 1. Research criteria for identifying persons at risk for Lynch syndrome[19,21]**

| | |
|---|---|
| **Amsterdam criteria II** Revised minimum criteria for clinical definition of Lynch syndrome | • Cancer diagnosis at <50 y in at least one relative<br>• No evidence of FAP<br>• Three or more relatives with Lynch syndrome-related cancer;[a] one is a first-degree relative of the other two<br>• Two successive affected generations |
| **Revised Bethesda guidelines** Criteria for testing colorectal tumors with MSI or IHC analysis | • Colorectal cancer diagnosis at <50 y<br>• Colorectal cancer diagnosis with MSI-H histology[b] at <60 y<br>• Colorectal cancer diagnosis with one or more first-degree relatives with a Lynch syndrome-related cancer, including one cancer diagnosis at <50 y<br>• Colorectal cancer diagnosis with two or more first- or second-degree relatives with Lynch syndrome-related cancer at any age<br>• Presence of synchronous or metachronous Lynch syndrome-related cancers[c] at any age |

**Key:** FAP, familial adenomatous polyposis; MSI-H, microsatellite instability high.
[a] Amsterdam criteria limit consideration to the most common Lynch cancers: colorectal, endometrial, small bowel, renal pelvis, or ureteral cancer.
[b] MSI-H histology: Crohnlike lymphocytic reaction, medullary growth pattern, mucinous/signet-ring differentiation, or presence of tumor-infiltrating lymphocytes.
[c] Bethesda criteria account for a broader range of Lynch-related cancers: biliary tract, brain, colorectal, endometrial, gastric, ovarian, pancreas, renal pelvis, small intestinal, or ureteral cancer; sebaceous gland adenoma; and keratoacanthoma.

## CHARACTERISTICS OF COLORECTAL DISEASE

Colonoscopy screening can help differentiate Lynch syndrome from other hereditary colorectal cancer syndromes. Lynch syndrome is typically associated with fewer than 10 adenomatous (precancerous) polyps cumulatively, whereas familial adenomatous polyposis (FAP), also a hereditary colorectal cancer syndrome, is associated with hundreds to thousands of adenomas.[22] In Lynch syndrome, adenomas are commonly seen in patients younger than 40 years, are frequently found to have a villous growth pattern with moderate- to high-grade dysplasia, and tend to develop into cancer more rapidly than in the general population.[16] Both adenomas and tumors in the colon associated with Lynch syndrome occur most frequently on the right side of the colon, which is not examined with flexible sigmoidoscope.[12] Tumors often have characteristic pathologic features such as poorly differentiated medullary-type features, mucinous features, signet-ring cells, a Crohnlike lymphocytic reaction, and infiltrating T-lymphocytes.[17]

## IDENTIFYING FAMILIES WITH LYNCH SYNDROME

Assessment for Lynch syndrome begins with a thorough family cancer history that includes at least three generations of both maternal and paternal first-, second-, and third-degree relatives (**Figure 1**). All cancers in the family should be noted with the person's age at diagnosis. Research criteria were developed to identify persons at risk for Lynch syndrome (**Table 1**). The original Amsterdam Criteria are limiting in that they accounted only for colorectal cancers;[18] thus, a subsequent modification, Amsterdam Criteria II (AC II), includes extracolonic tumors.[19] For those patients who meet AC II criteria, genetic testing of the four mismatch repair genes associated with Lynch syndrome can be offered.

A broader set of criteria, the Revised Bethesda Guidelines, was developed to determine when tumors should be screened for evidence of a mismatch repair defect[21] (**Table 1**). Two commonly used screening tests for Lynch syndrome are microsatellite instability (MSI) analysis and immunohistochemistry (IHC) analysis. Because Lynch syndrome tumors often have loss of a mismatch repair protein due to mutations in the corresponding mismatch repair gene, the absence of protein can be detected through IHC analysis. Tumors caused by mutations in mismatch repair genes are frequently MSI high (MSI-H), which is an increased level of instability in tumor DNA; however, not all MSI-H colorectal tumors are due to Lynch syndrome. Ten percent to 20% of sporadic colorectal cancers are also MSI high.[20] Patients with MSI-H tumors can be offered additional tumor screening, including IHC analysis or direct testing of the genes related to Lynch syndrome. One benefit of IHC analysis is that it can define which specific mismatch repair gene may be mutated, thus decreasing total test time and cost.

Patients who meet the revised Bethesda criteria should be referred for further genetic evaluation, especially those patients with a personal history of colorectal cancer at younger than 50 years or who have had another Lynch syndrome-related cancer such as endometrial, ovarian, stomach, urinary tract, or pancreatic cancer. Other patients with a personal history of a Lynch syndrome-related cancer at any age and a family history of colorectal cancer, adenomatous polyps, or a Lynch syndrome-related cancer in at least two first- or second-degree relatives should also consider genetic evaluation. Important limitations in family histories to consider are early death, adoption, lack of cancer screening, and small family size. When in doubt, or if the patient expresses a concern for hereditary cancer, refer the patient for genetic counseling.

Genetic counseling involves confirmation of family history, evaluation of cancer risk, and psychosocial assessment. Counselors can conduct an in-depth discussion regarding the pros and cons of genetic testing, coordination of genetic

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http://www.nsgc.org

**GeneTests**
http://www.genetests.org

**The National Cancer Institute Physician Data Query**
http://www.cancer.gov/search/genetics_services/

testing, and interpretation of genetic test results. Customized risk reduction options and risk-appropriate screening recommendations, as well as resources for follow-up and support, should be reviewed. Some institutions may have a medical genetics department or cancer risk assessment program, but many do not. Helpful resources for locating a health care professional who performs genetic counseling and testing for Lynch syndrome can be found through the National Society of Genetic Counselors, GeneTests, and the National Cancer Institute Physician Data Query.

## HIGH-RISK MANAGEMENT OPTIONS

The goal for diagnosis of Lynch syndrome is to reduce the number of cancer-related deaths through cancer risk reduction and early detection of new lesions. Increasing the frequency of colonoscopies has been proven to decrease cancer mortality in Lynch syndrome families.[1] Consequently, recommendations suggest affected persons with Lynch syndrome begin colonoscopy screening at age 20 to 25 years or 2 to 5 years younger than the youngest relative at diagnosis of colon cancer, whichever is younger. Patients should undergo repeat colonoscopy screening every 1 to 2 years. If a patient is unable to adhere to colonoscopy screening or colorectal cancer is diagnosed, colectomy can be considered to reduce (subsequent) cancer risk.[22] Aspirin and celecoxib (Celebrex) are two nonsteroidal anti-inflammatory drugs (NSAIDs) associated with a possible decrease in polyp recurrence and lower number of high-grade adenomas in Lynch syndrome;[23] thus, they can be offered as chemopreventive agents for colorectal cancer.

Women with Lynch syndrome should consider screening with annual transvaginal ultrasound and endometrial sampling. Serum measurement of the tumor marker cancer antigen (CA)-125 can be included to screen for ovarian cancer; however, screening has not been associated with a reduction in ovarian cancer mortality.[24] Therefore, total abdominal hysterectomy with bilateral salpingo-oophorectomy is encouraged for women with Lynch syndrome who have completed childbearing. The procedure has been shown to reduce the risk for endometrial and ovarian cancers in women.[25]

Additional extracolonic surveillance is also recommended for patients with Lynch syndrome. Screening for gastric and small bowel cancers should occur every 2 to 3 years starting at age 30 to 35 years. Gastric cancer screening involves upper GI endoscopy. Gastric biopsies may be performed to monitor for histologic changes. Screening for small bowel cancers can be achieved using capsule endoscopy.[22] Annual urinalysis with or without urine cytology can be used to screen for urinary tract cancers. Screening is limited for other Lynch syndrome-related cancers. Currently, an annual physical examination is the only recommendation for brain tumors and other CNS cancers. Pancreatic cancer screening is available only on a research basis.[22] Patients are counseled to report any lingering symptoms or illnesses, particularly headache, bone pain, or abdominal discomfort, for prompt evaluation. Additional organ-targeted surveillance can be considered based on the specific symptoms and cancers in the patient's family.

Persons who test negative for the confirmed germline mutation in their family may follow screening guidelines similar to those for the general population.[22] Of note, family cancer histories may remain consistent with Lynch syndrome despite not identifying a germline DNA mutation. This may be due to a mutation in a region of the mismatch repair gene not being tested or in an undiscovered gene. Therefore, high risk recommendations should also be given to these families.

## CONCLUSION

Nurses and nurse practitioners (NPs) involved in the care of oncology patients serve an important role in identifying patients at risk for Lynch syndrome. Early recognition of risk factors can determine if patients have a high risk for subsequent cancers and family members at high risk. Oncology nurses have the opportunity to raise the patient's awareness of his or her risk for Lynch syndrome. Identifying high-risk families can reduce cancer mortality through early detection or prevention of cancers. ■

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