

CME **EDUCATIONAL OBJECTIVE:** Readers will assess their patients' personal and family histories and suspect hereditary colorectal cancer syndromes if red flags are present

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Detecting and managing hereditary colorectal cancer syndromes in your practice

ABSTRACT

Hereditary syndromes account for 5% to 10% of cases of colorectal cancer. In clinical practice, patients with these syndromes need to be identified to ensure that they and their families receive genetic counseling and testing and appropriate risk-reducing treatment. Genetic testing can offer a precise diagnosis. It allows for risk stratification and focused management and surveillance.

KEY POINTS

Hereditary colorectal cancer syndromes carry a substantial risk of intestinal and extraintestinal tumors.

Affected patients need increased cancer surveillance and may benefit from prophylactic surgery.

Identifying these patients in clinical practice begins by assessing a patient's personal and family health history.

Patients suspected of having hereditary colorectal cancer syndromes should be referred for genetic counseling and, if appropriate, for genetic testing.

HEREDITARY COLORECTAL CANCER SYNDROMES account for 5% to 10% of cases of colorectal cancer.

Identifying these patients in clinical practice begins by assessing a patient's personal and family health history. An accurate and comprehensive family history should cover three generations and include ethnic background, ages and causes of death of relatives, and any diagnosis of cancer, including age at onset and history of polyps.

Red flags for a hereditary colorectal cancer syndrome in the personal or family history are:

- Early age of onset of cancer (eg, colorectal cancer before age 50)
- More than 10 colorectal adenomas
- Synchronous (ie, occurring at the same time) or metachronous (occurring at different times) primary cancers
- Multiple relatives in successive generations with the same or related cancers (eg, colon or endometrial cancer)
- A family member with a known hereditary colorectal cancer syndrome (TABLE 1).

Any of these red flags should prompt a referral for genetic counseling.

SYNDROMES ARE CLASSIFIED AS WITH OR WITHOUT POLYPOSIS

Many hereditary syndromes are associated with a higher risk of colorectal cancer. Generally, they can be divided into two categories (TABLE 2): polyposis syndromes (in which patients have numerous colorectal polyps) and nonpolyposis syndromes (with few or no polyps).

TABLE 1

Red flags for hereditary colorectal cancer syndromes in the personal or family history

- Early age of onset of cancer (eg, colorectal cancer before age 50)
- More than 10 colorectal adenomas
- Synchronous or metachronous primary cancers
- Multiple relatives in successive generations with the same or related cancers
- Family member with a known hereditary colorectal cancer syndrome

TABLE 2

Classification of hereditary colorectal cancer syndromes

Nonpolyposis syndrome

- Lynch syndrome
- Hereditary nonpolyposis colorectal cancer
- Familial colorectal cancer type X

Polyposis syndromes

- With adenomatous polyps
 - Familial adenomatous polyposis
 - MYH*-associated polyposis
- With serrated polyps
 - Serrated polyposis syndrome
- With hamartomatous polyps
 - Juvenile polyposis syndrome
 - Peutz-Jeghers syndrome
 - PTEN-hamartoma tumor syndrome

Patients with Lynch syndrome have a 42% risk of colorectal cancer by age 80

These two main types are subclassified on the basis of the histology of most of the polyps detected: adenomatous, hamartomatous, serrated, or mixed types.

In this review, we will address the three most common of these syndromes: Lynch syndrome (hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis, and *MYH*-associated polyposis. However, as noted in **TABLE 2**, other hereditary colorectal cancer syndromes exist, and suspicion of these conditions should prompt a referral for further evaluation.

■ LYNCH SYNDROME (HEREDITARY NONPOLYPOSIS COLORECTAL CANCER)

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, predisposes people to a variety of cancers.

Colorectal cancer is the most common type of cancer associated with Lynch syndrome. Recent research suggests that the cumulative risk of developing colorectal cancer by age 80 is 42% for all patients with Lynch syndrome.¹ The median age at onset is 45 years.¹ For patients who undergo segmental resection of their initial cancer, the cumulative risk of metachronous colorectal cancer (ie, a new tumor arising later) is 16% at 10 years, 41% at 20 years, and up to 62% after 30 years.²

Endometrial cancer occurs in 17% to 57% of women with Lynch syndrome by age 70, with a median age at onset of 49 years.¹

Other extracolonic cancers in Lynch syndrome include cancers of the:

- Stomach (1%–10% risk by age 70 years)

- Ovaries (1%–20% risk)
- Hepatobiliary tract (1%–2% risk)
- Urinary tract (1%–12% risk)
- Small bowel (1%–2% risk)
- Brain (1%–8% risk)
- Skin (sebaceous adenomas, adenocarcinomas, and keratoacanthomas).^{1,3,4}

Earlier studies reported higher rates of associated cancer than those shown here. However, their data were largely derived from registries and may be overestimates. The numbers shown above are from population-based studies.

Genetics of Lynch syndrome

Lynch syndrome is caused by a germline mutation in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* genes.⁵ These genes code for proteins that are responsible DNA mismatch repair—one of the cell’s proofreading mechanisms during DNA replication.

These mutations are inherited in an autosomal dominant manner. Though de novo mutations in these genes have been reported, they are rare and the exact frequency with which they occur is unknown.⁶

In whom should Lynch syndrome be suspected?

Lynch syndrome can be suspected on the basis of family history and clinical criteria.

In 1991, the same group of experts who coined the term “hereditary nonpolyposis colorectal cancer” developed family history criteria for it¹:

- At least three relatives with histologically confirmed colorectal cancer, one of whom is a first-degree relative of the other two
- At least two successive generations involved
- At least one of the cancers diagnosed before age 50
- Familial adenomatous polyposis is excluded.

Known as the Amsterdam criteria, these were to be used in collaborative studies of families with hereditary colorectal cancer.⁷ In 1999, these criteria were broadened to include extracolonic cancers and became known as the Amsterdam II criteria (TABLE 3).⁸

Patients whose families meet the Amsterdam II criteria or who have molecular pathologic evidence of Lynch syndrome (see below) are appropriate candidates for genetic counseling and testing.

Diagnosis of Lynch syndrome

The diagnosis of Lynch syndrome is based on molecular pathologic analysis (performed on tumor samples) and confirmed by genetic testing.

Molecular pathologic evidence of Lynch syndrome includes microsatellite instability and loss of expression of one or more of the DNA mismatch repair proteins (detected using immunohistochemistry) (more on these below). The revised Bethesda guidelines (TABLE 3) were intended to identify individuals whose tumors should be tested for one or both of these phenomena.⁹

In 2009, the Evaluation of Genomic Applications in Practice and Prevention working group recommended that all patients with newly diagnosed colorectal cancer undergo microsatellite instability analysis, immunohistochemistry testing, or both, regardless of whether they meet the Amsterdam II or the Bethesda guideline criteria.¹⁰

Microsatellite instability analysis. Microsatellites are short sequences of repeated DNA. The tumor cells of patients who carry defective mismatch repair genes have microsatellites that are longer or shorter than in normal cells, a condition called microsatellite instability (ie, “MSI-high”).

TABLE 3

The Amsterdam II criteria and revised Bethesda guidelines for Lynch syndrome

Amsterdam II criteria

Three or more family members, one of whom is a first-degree relative of the other two, with Lynch syndrome-related cancers (colorectal, endometrial, stomach, small bowel, hepatobiliary, renal pelvic, or ureteral)

Two successive affected generations

One or more of the Lynch syndrome-related cancers diagnosed before age 50 years

Familial adenomatous polyposis is excluded

ADAPTED FROM VASEN HF, WATSON P, MECKLIN JP, LYNCH HT. NEW CLINICAL CRITERIA FOR HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC, LYNCH SYNDROME) PROPOSED BY THE INTERNATIONAL COLLABORATIVE GROUP ON HNPCC. *GASTROENTEROLOGY* 1999; 116:1453–1456. COPYRIGHT 1999, WITH PERMISSION FROM ELSEVIER. [HTTP://WWW.JOURNALS.ELSEVIER.COM/GASTROENTEROLOGY](http://www.journals.elsevier.com/gastroenterology).

Revised Bethesda guidelines

Colorectal cancer diagnosed in a patient less than 50 years of age

Synchronous or metachronous colorectal cancer or other Lynch syndrome-associated tumors,^a regardless of age

Colorectal cancer with a high level of microsatellite instability,^b diagnosed in a patient who is less than 60 years of age

Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch syndrome-related tumor, with one of the cancers being diagnosed before age 50 years

Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors, regardless of age

ADAPTED FROM UMAR A, BOLAND CR, TERDIMAN JP, ET AL. REVISED BETHESDA GUIDELINES FOR HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (LYNCH SYNDROME) AND MICROSATELLITE INSTABILITY. *J NATL CANCER INST* 2004; 96:261–268. BY PERMISSION OF OXFORD UNIVERSITY PRESS.

^aColorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain, sebaceous gland adenomas and keratoacanthomas, and small bowel

^bPresence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern on histologic study

Microsatellite instability testing, using a standardized panel of five DNA markers, is performed on normal and tumor tissue. If more than two of the five microsatellite markers in the tumor show instability, the lesion is considered to have a high level of microsatellite instability. About 15% of colorectal cancers have this high level, although most are not associated with Lynch syndrome and lose *MLH1* expression by promoter methylation.^{11,12}

Invasive colonic adenocarcinoma in Lynch syndrome

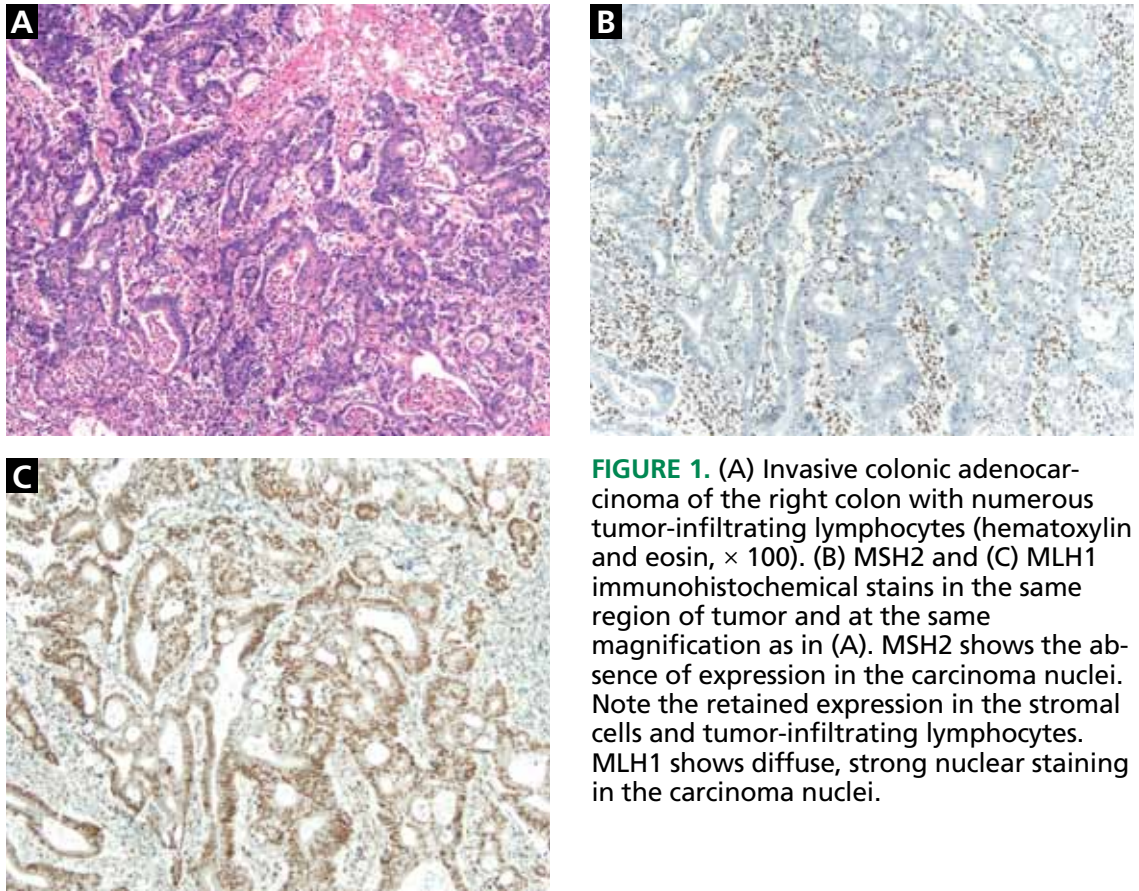


FIGURE 1. (A) Invasive colonic adenocarcinoma of the right colon with numerous tumor-infiltrating lymphocytes (hematoxylin and eosin, $\times 100$). (B) MSH2 and (C) MLH1 immunohistochemical stains in the same region of tumor and at the same magnification as in (A). MSH2 shows the absence of expression in the carcinoma nuclei. Note the retained expression in the stromal cells and tumor-infiltrating lymphocytes. MLH1 shows diffuse, strong nuclear staining in the carcinoma nuclei.

The diagnosis of Lynch syndrome is based on molecular pathology and confirmed by genetic testing

While only 2% of patients with colorectal cancer have Lynch syndrome, from 90% to 95% of colorectal cancers from patients with Lynch syndrome have high levels of microsatellite instability.¹⁰ The presence of *MLH1* promoter hypermethylation, the *BRAF* mutation V600E, or both within the tumor suggests that the cancer is not associated with Lynch syndrome.

Some families that meet the Amsterdam I criteria have microsatellite-stable tumors: their condition has been called familial colorectal cancer type X.¹³ This condition is associated with a higher risk of colorectal cancer but not the other malignancies observed in Lynch syndrome.

Immunohistochemistry is performed to assess for expression of the mismatch repair proteins MSH2, MSH6, MLH1, and PMS2. Absence of expression of the specific protein within tumor cells compared with normal cells within the specimen suggests dysfunction

of the specific gene and guides germline mutation testing (FIGURE 1). For example, a patient who lacks expression of the MSH2 protein in his or her colon cancer most likely has a mutation in the *MSH2* gene. Therefore, germline genetic testing should initially target the *MSH2* gene. Approximately 88% of Lynch syndrome-associated colorectal cancers have abnormal immunohistochemical staining.¹⁰

Testing for microsatellite instability and mismatch repair gene expression ideally precedes germline genetic testing and helps to guide which gene or genes should be tested.^{9,14}

Genetic testing for Lynch syndrome is routinely performed on a blood or saliva sample, using DNA from white blood cells and sequencing the gene or genes involved to look for mutations. Positive results from a germline genetic test confirm the diagnosis of Lynch syndrome and allow for predictive testing for relatives at risk. The term Lynch syndrome is used exclusively to describe individuals with

evidence of a mutation in one of the mismatch repair genes.¹⁵

If a patient's results are positive, genetic counseling and genetic testing should be offered to at-risk relatives age 18 and over.

Management of Lynch syndrome

Aggressive cancer surveillance is essential for people with Lynch syndrome and for those who are considered at risk but have not pursued genetic testing, such as a sibling of a person with Lynch syndrome.

Colorectal cancer. Colonoscopy is recommended every 1 to 2 years beginning at the age of 20 to 25 years, or 2 to 5 years earlier than the age of the youngest relative affected with colorectal cancer if the initial diagnosis was before age 25. When patients turn 40 years old, colonoscopy is done annually.¹⁶⁻¹⁸ A significant reduction in cancer incidence and in the mortality rate has been shown with colonoscopic surveillance.¹⁹⁻²¹

Chemoprevention may also have a role. Patients with Lynch syndrome who took aspirin 600 mg per day for an average of 25 months had a significantly lower incidence of colorectal cancer during a 55-month follow-up period compared with patients randomized to placebo.²²

For patients with Lynch syndrome who are diagnosed with colorectal cancer, the high risk of metachronous cancers after standard segmental colectomy calls for a more extended resection. Retrospective analysis of 382 Lynch syndrome patients found that none of the 50 who underwent total or subtotal colectomy were diagnosed with metachronous colorectal cancer, whereas a metachronous cancer developed in 74 (22%) of the 332 patients who had had segmented resection.² Annual surveillance of the remaining colon, rectum, or both is indicated postoperatively.

Gynecologic cancers. Women with Lynch syndrome should also consider gynecologic surveillance and risk-reducing surgery. This includes annual gynecologic examination, transvaginal ultrasonography, and endometrial aspiration, beginning at age 30 to 35 years. Although this surveillance does detect premalignant lesions and early symptomatic cancers, its effect on the mortality rate is unknown. Hysterectomy with bilateral salpingo-

oophorectomy has been shown to significantly reduce endometrial and ovarian cancers in women with Lynch syndrome.^{23,24}

Urothelial cancers. Carriers of *MSH2* mutations have a significantly higher risk of urothelial cancers.⁴ Therefore, *MSH2* carriers should consider ultrasonography of the urinary tract, urinary cytology, and urinalysis every 1 to 2 years beginning at age 40.⁴

Other extracolonic cancers. Poor evidence exists for systematic screening for the other extracolonic tumors associated with Lynch syndrome. However, the National Comprehensive Cancer Network advises considering esophagogastroduodenoscopy with extended duodenoscopy as well as capsule endoscopy every 2 to 3 years beginning at age 30 to 35.¹⁴

■ ADENOMATOUS POLYPOSIS SYNDROMES

Familial adenomatous polyposis and *MYH*-associated polyposis are the next most common hereditary colorectal cancer syndromes. Each of these accounts for about 1% of cases of colorectal cancer. Clinically, these two syndromes can be challenging to distinguish because they overlap phenotypically to a significant degree.

■ FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis is caused by mutations in the *APC* gene. Its prevalence is 2.29 to 3.2 per 100,000 individuals.^{25,26}

Genetics of familial adenomatous polyposis

APC is the only gene known to cause familial adenomatous polyposis. Mutations in *APC* are inherited in an autosomal dominant manner. Approximately 25% of cases of familial adenomatous polyposis are due to a de novo mutation in *APC*.²⁷

Clinical presentation of familial adenomatous polyposis

Familial adenomatous polyposis is classified by the burden of colorectal adenomas.

Patients who have fewer than 100 adenomas have an attenuated form of the disease. In this group, polyps usually begin to form in the late teenage years or early 20s and tend to develop in the proximal colon. The attenuated

Aggressive cancer surveillance is essential for people with Lynch syndrome and for those at risk who have not been tested

Familial adenomatous polyposis



FIGURE 2. Endoscopic picture of the colon of a patient with familial adenomatous polyposis who has numerous adenomatous polyps.

form is associated with an approximately 70% lifetime risk of colorectal cancer.²⁸

Patients who have more than 100 polyps are considered to have the classic form of the disease, and those with more than 1,000 polyps have profuse familial adenomatous polyposis (FIGURE 2). In these groups, polyps typically begin to develop in the preteenage to mid-teenage years. Without surgery, there is nearly a 100% risk of colorectal cancer. The average age at diagnosis of colorectal cancer is 39 years for patients with classic disease.

Upper gastrointestinal polyps are common in familial adenomatous polyposis. Nearly 90% of patients develop duodenal adenomas by a mean age of 44, with a cumulative lifetime risk of nearly 100%.²⁹ Fundic gland polyposis occurs in nearly 90% of patients,³⁰ while gastric adenomas are reported in fewer than 15% of patients.

Duodenal and periampullary cancer is the second most common malignancy in familial adenomatous polyposis. The lifetime risk ranges from 2% to 36%, depending on the Spigelman stage. People with Spigelman stage I, II, or III have a 2.5% risk of duodenal cancer, while those with stage IV disease have up to a 36% lifetime risk.

Gastric cancer, arising from fundic gland polyps, has been reported but is rare in Western populations.

In familial adenomatous polyposis, the incidence of jejunal adenomas and cancer is less than 10%, and the risk of ileal adenomas and cancer is less than 1%.³¹

Familial adenomatous polyposis is also associated with a higher risk of other malignancies, including:

- Pancreatic cancer (2% lifetime risk)
- Thyroid cancer (2% to 3% lifetime risk, typically papillary carcinoma)³²
- Hepatoblastoma (1% to 2% lifetime risk)
- Brain tumors (< 1% lifetime risk)
- Biliary cancer (higher risk than in the general population).³³

Benign extracolonic manifestations that have been observed include osteomas, dental abnormalities (supernumerary teeth, unerupted or absent teeth, odontomas), congenital hypertrophy of the retinal pigment epithelium, benign cutaneous lesions (epidermoid cysts and fibromas), and desmoid tumors.³³ The term “Gardner syndrome” has been used to describe patients who have familial adenomatous polyposis but also have osteomas and soft-tissue tumors.³⁴ These patients carry the same risk of colorectal cancer as other patients with familial adenomatous polyposis.

Diagnosing familial adenomatous polyposis

The diagnosis of familial adenomatous polyposis is suspected when a patient has more than 10 adenomatous polyps.

Seventy-five percent of patients with familial adenomatous polyposis have a family history of the condition. Therefore, most cases are identified at a young age on screening sigmoidoscopy or colonoscopy or by predictive gene testing. Patients rarely have cancer at the time of diagnosis.

The other 25% of patients typically are diagnosed when symptoms develop from the polyps or cancer. Over 50% of these symptomatic patients have cancer at the time of diagnosis.

It is recommended that people who have more than 10 adenomas detected on a single colonoscopy or who are first-degree relatives of patients with familial adenomatous polyposis undergo a genetic evaluation and testing for mutations in the *APC* gene.¹⁴ Once an *APC* mutation is identified in the family, at-risk relatives should be offered testing around age 10 years for families with classic familial

Classic familial adenomatous polyposis carries a 100% risk of colorectal cancer

adenomatous polyposis or in the mid to late teenage years for those with the attenuated form. It also appropriate to refer patients with desmoid tumors, duodenal adenomas, and bilateral or multifocal congenital hypertrophy of the retinal pigment epithelium for a genetic evaluation.

Management of familial adenomatous polyposis

Flexible sigmoidoscopy every 1 to 2 years beginning at age 10 to 12 years is recommended for individuals and families who have been phenotypically or genetically diagnosed with familial adenomatous polyposis.³⁵⁻³⁷ If colorectal adenomas are found, surgical options should be discussed and annual colonoscopic surveillance should commence.

For people with the attenuated form, because of the later age of disease onset and the tendency for right-sided disease, colonoscopy every 1 to 2 years should commence at about age 18.³⁵⁻³⁷ If polyps are found, colonoscopy should be performed every year.

The decision of when to offer colectomy is based on polyp burden (taking into account the number, pathologic appearance, and size of the polyps) and psychosocial factors such as patient maturity. Surgical options include total colectomy and ileorectal anastomosis or total proctocolectomy and ileal pouch anal anastomosis.³⁸ Colonic and extracolonic phenotype as well as genotype should factor into the type of operation recommended. After colectomy, annual endoscopic surveillance of the rectum or ileal pouch is indicated to screen for recurrent polyposis and cancer.

Chemoprevention with sulindac (Clinoril) 150 mg or celecoxib (Celebrex) 400 mg twice a day causes regression of colorectal adenomas in familial adenomatous polyposis and may be useful as an adjunct to endoscopy in managing the colorectal polyp burden.^{39,40}

Forward and side-viewing upper endoscopy should commence at age 20. This should include visualization and biopsy of the papilla and periampullary region.²⁹ The frequency of endoscopic surveillance depends on the Spigelman stage, which reflects the duodenal polyp burden. It is recommended that patients with Spigelman stage IV duodenal polyposis be seen in consultation with an experienced

gastrointestinal surgeon for consideration of a prophylactic, pylorus-preserving, pancreas-sparing duodenectomy. This procedure has been shown to be more effective in polyp control and cancer prevention than endoscopic polyp ablation and local surgical resection.⁴¹

Some evidence for the utility of celecoxib 400 mg twice daily for the regression of duodenal polyposis was noted in a 6-month placebo-controlled trial.⁴² Some experts recommend removal of large duodenal adenomas, with adjunctive celecoxib therapy to control polyposis burden.³⁰

People with familial adenomatous polyposis have been shown to have a 2.6% risk of thyroid cancer, and ultrasonography of the neck with attention to the thyroid is recommended for them.³²

■ MYH-ASSOCIATED POLYPOSIS

Biallelic mutations in the *MYH* gene result in an adenomatous polyposis syndrome that may be indistinguishable from the attenuated or classic forms of familial adenomatous polyposis. A characteristic autosomal recessive pattern of inheritance in the family can be useful for identifying these patients in the clinic.

Genetics of *MYH*-associated polyposis

MYH-associated polyposis is the only known autosomal recessive hereditary colorectal cancer syndrome. In white populations, the most commonly reported mutations in *MYH* are Y179C (previously called Y165C) and G396D (previously called G382D), which account for up to 80% of cases.⁴³ These two mutations are estimated to occur in 1% to 2% of the general population.⁴⁴

Clinical presentation of *MYH*-associated polyposis

MYH-associated polyposis typically presents as multiple adenomatous polyps and is diagnosed at a mean age of 47 years. Eleven percent to 42% of affected individuals are reported to have fewer than 100 adenomas, while a minority (7.5% to 29%) of patients present with classic polyposis.⁴⁵⁻⁴⁷ In one study, an estimated 19% of patients presented with colorectal cancer and reported no history of colorectal polyps.⁴⁸ Synchronous colorectal

The diagnosis of familial adenomatous polyposis is suspected when a patient has more than 10 adenomatous polyps

cancer is seen in more than 60% of patients with biallelic *MYH* mutations.⁴⁹ Patients with monoallelic (heterozygous) *MYH* mutations appear to have the same risk of developing colorectal adenomas and cancer as the general population.⁴⁹

Upper-gastrointestinal polyps have been reported in *MYH*-associated polyposis; as many as 17% to 25% of patients have duodenal adenomas.^{50,51}

Diagnosis of *MYH*-associated polyposis

Genetic testing for biallelic *MYH* mutations should be performed in patients who test negative for an *APC* mutation but who have clinical features of familial adenomatous polyposis, a personal history of more than 10 colorectal adenomas, or a recessive family history of polyposis.¹⁴ It has been shown that up to 29% of patients with familial adenomatous polyposis who are *APC*-negative will have biallelic mutations in the *MYH* gene.⁵² The siblings of a patient with biallelic *MYH* mutations should be offered genetic counseling and testing in their late teens or early 20s. All children of an individual with *MYH*-associated polyposis will carry one *MYH* mutation and are only at risk of having the syndrome if the other parent is also a *MYH* carrier and passed on his or her mutation.

Management of *MYH*-associated polyposis

The management of patients with *MYH*-associated polyposis is similar to that recommended for attenuated and classic familial adenomatous polyposis.¹⁴ Genetic counseling and testing and colonic and extracolonic surveillance are warranted. There are no data on the use of chemoprevention in *MYH*-associated polyposis. Surgery should be considered early because of the high risk of colorectal cancer, even in individuals with very few adenomas. Patients with monoallelic *MYH* mutations should follow the general population screening guidelines for colorectal cancer.⁴⁹

■ GENETIC COUNSELING AND GENETIC TESTING

The American College of Gastroenterology advises that patients suspected of having hereditary colorectal cancer syndromes

be advised to pursue genetic counseling and, if appropriate, genetic testing.¹⁶ They further recommend genetic counseling and informed consent before genetic testing.¹⁶

Genetic counseling is a process of working with patients and families whereby:

- A detailed medical and family history is obtained
- A formal risk assessment is performed
- Education about the disease in question and about genetic testing is provided
- Psychosocial concerns are assessed
- Informed consent is obtained when genetic testing is recommended.⁵³

This process is important for helping patients better understand their cancer risks, the benefits and limitations of genetic testing, and the protections that are in place for people who undergo genetic testing, including the Genetic Information Non-Discrimination Act.

In 1996 the American Society of Clinical Oncology issued a policy statement highlighting the essential elements of informed consent for genetic testing for cancer susceptibility, and this was updated in 2003.⁵⁴ In particular, it notes that patients should be informed of the implications of positive and negative results and of the possibility that the test may be uninformative.

When a hereditary colorectal cancer syndrome is suspected, a positive genetic test result confirms the diagnosis and allows for predictive testing of the patient's relatives. However, no genetic test for a hereditary colorectal cancer syndrome is 100% sensitive. Therefore, a negative result does not rule out the syndrome in question.

Further, all cancer susceptibility genes have variants of uncertain significance, which are genetic alterations for which there are insufficient data to determine if the mutation is disease-causing or polymorphic (benign). Both negative and uninformative results can be confusing for patients and providers and can lead to false reassurance or undue worry when patients are not properly educated about these potential outcomes of testing.

Genetic testing is an evolving field, and with additional research and improved testing technologies, appropriate diagnoses can be made over time. That is why it is important for the genetic counseling relationship to continue over time. ■

For individuals and families with familial adenomatous polyposis, flexible sigmoidoscopy every 1 to 2 years beginning at age 10 to 12 is advised

REFERENCES

- Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in *MLH1*, *MSH2*, and *MSH6* genes in Lynch syndrome. *JAMA* 2011; 305:2304–2310.
- Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. *Gut* 2011; 60:950–957.
- Barrow E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. *Clin Genet* 2009; 75:141–149.
- van der Post RS, Kiemeneij LA, Ligtenberg MJ, et al. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among *MSH2* mutation carriers. *J Med Genet* 2010; 47:464–470.
- Wijnen JT, Vasen HF, Khan PM, et al. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. *N Engl J Med* 1998; 339:511–518.
- Bisgaard ML, Bernstein I. HNPCC mutation rate. *Familial Cancer* 2003; 2:20–22.
- Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 1991; 34:424–425.
- Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 1999; 116:1453–1456.
- Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004; 96:261–268.
- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? *Genet Med* 2009; 11:15–20.
- Aaltonen LA, Peltomäki P, Leach FS, et al. Clues to the pathogenesis of familial colorectal cancer. *Science* 1993; 260:812–816.
- Kim H, Jen J, Vogelstein B, Hamilton SR. Clinical and pathological characteristics of sporadic colorectal carcinomas with DNA replication errors in microsatellite sequences. *Am J Pathol* 1994; 145:148–156.
- Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA* 2005; 293:1979–1985.
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines) colorectal cancer screening version 2.2011. www.nccn.org. Accessed October 2, 2012.
- Jass JR. Hereditary non-polyposis colorectal cancer: the rise and fall of a confusing term. *World J Gastroenterol* 2006; 12:4943–4950.
- Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM; American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol* 2009; 104:739–750.
- Winawer S, Fletcher R, Rex D, et al; Gastrointestinal Consortium Panel. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. *Gastroenterology* 2003; 124:544–560.
- Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA* 2006; 296:1507–1517.
- de Jong AE, Hendriks YM, Kleibeuker JH, et al. Decrease in mortality in Lynch syndrome families because of surveillance. *Gastroenterology* 2006; 130:665–671.
- Mecklin JP, Aarnio M, Läärä E, et al. Development of colorectal tumors in colonoscopic surveillance in Lynch syndrome. *Gastroenterology* 2007; 133:1093–1098.
- Engel C, Rahner N, Schulmann K, et al; German HNPCC Consortium. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. *Clin Gastroenterol Hepatol* 2010; 8:174–182.
- Burn J, Gerdes AM, Macrae F, et al; CAPP2 Investigators. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 2011; 378:2081–2087.
- Vasen HF, Möslein G, Alonso A, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). *J Med Genet* 2007; 44:353–362.
- Manchanda R, Menon U, Michaelson-Cohen R, Beller U, Jacobs I. Hereditary non-polyposis colorectal cancer or Lynch syndrome: the gynaecological perspective. *Curr Opin Obstet Gynecol* 2009; 21:31–38.
- Burn J, Chapman P, Delhanty J, et al. The UK Northern region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium, and DNA markers in risk calculations. *J Med Genet* 1991; 28:289–296.
- Järvinen HJ. Epidemiology of familial adenomatous polyposis in Finland: impact of family screening on the colorectal cancer rate and survival. *Gut* 1992; 33:357–360.
- Bisgaard ML, Fenger K, Bülow S, Niebuhr E, Mohr J. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. *Hum Mutat* 1994; 3:121–125.
- Neklason DW, Stevens J, Boucher KM, et al. American founder mutation for attenuated familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008; 6:46–52.
- Burke CA, Beck GJ, Church JM, van Stolk RU. The natural history of untreated duodenal and ampullary adenomas in patients with familial adenomatous polyposis followed in an endoscopic surveillance program. *Gastrointest Endosc* 1999; 49:358–364.
- Bianchi LK, Burke CA, Bennett AE, Lopez R, Hasson H, Church JM. Fundic gland polyp dysplasia is common in familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008; 6:180–185.
- Kadmon M, Tandara A, Herfarth C. Duodenal adenomatosis in familial adenomatous polyposis coli. A review of the literature and results from the Heidelberg Polyposis Register. *Int J Colorectal Dis* 2001; 16:63–75.
- Jarrar AM, Milas M, Mitchell J, et al. Screening for thyroid cancer in patients with familial adenomatous polyposis. *Ann Surg* 2011; 253:515–521.
- Jasperson KW, Burt RW. APC-associated polyposis conditions. In: Pagon RA, Bird TD, Dolan CR, et al, eds. *GeneReviews* (Internet). Seattle, WA: University of Washington; 2011.
- Gardner EJ, Richards RC. Multiple cutaneous and subcutaneous lesions occurring simultaneously with hereditary polyposis and osteomatosis. *Am J Hum Genet* 1953; 5:139–147.
- Dunlop MG; British Society for Gastroenterology; Association of Coloproctology for Great Britain and Ireland. Guidance on gastrointestinal surveillance for hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, juvenile polyposis, and Peutz-Jeghers syndrome. *Gut* 2002; 51(suppl 5):V21–V27.
- Burke W, Petersen G, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. *Cancer Genetics Studies Consortium*. *JAMA* 1997; 277:915–919.
- Vasen HF, Möslein G, Alonso A, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 2008; 57:704–713.
- Church J. Familial adenomatous polyposis. *Surg Oncol Clin N Am* 2009; 18:585–598.
- Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993; 328:1313–1316.
- Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000; 342:1946–1952.
- Johnson MD, Mackey R, Brown N, Church J, Burke C, Walsh RM. Outcome based on management for duodenal adenomas: sporadic versus familial disease. *J Gastrointest Surg* 2010; 14:229–235.
- Phillips RK, Wallace MH, Lynch PM, et al; FAP Study Group. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002; 50:857–860.

43. **Tenesa A, Campbell H, Barnetson R, Porteous M, Dunlop M, Farrington SM.** Association of MUTYH and colorectal cancer. *Br J Cancer* 2006; 95:239–242.
 44. **Croitoru ME, Cleary SP, Di Nicola N, et al.** Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. *J Natl Cancer Inst* 2004; 96:1631–1634.
 45. **Croitoru ME, Cleary SP, Berk T, et al.** Germline MYH mutations in a clinic-based series of Canadian multiple colorectal adenoma patients. *J Surg Oncol* 2007; 95:499–506.
 46. **Sampson JR, Dolwani S, Jones S, et al.** Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. *Lancet* 2003; 362:39–41.
 47. **Nielsen M, Franken PF, Reinards TH, et al.** Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with MYH associated polyposis coli (MAP). *J Med Genet* 2005; 42:e54.
 48. **Cleary SP, Cotterchio M, Jenkins MA, et al.** Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. *Gastroenterology* 2009; 136:1251–1260.
 49. **Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS.** Clinical implications of the colorectal cancer risk associated with MUTYH mutation. *J Clin Oncol* 2009; 27:3975–3980.
 50. **Aretz S, Uhlhaas S, Goergens H, et al.** MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. *Int J Cancer* 2006; 119:807–814.
 51. **Vogt S, Jones N, Christian D, et al.** Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. *Gastroenterology* 2009; 137:1976–1985.e1–e10.
 52. **Gismondi V, Meta M, Bonelli L, et al.** Prevalence of the Y165C, G382D and 1395delGGA germline mutations of the MYH gene in Italian patients with adenomatous polyposis coli and colorectal adenomas. *Int J Cancer* 2004; 109:680–684.
 53. **Trepanier A, Ahrens M, McKinnon W, et al; National Society of Genetic Counselors.** Genetic cancer risk assessment and counseling: recommendations of the national society of genetic counselors. *J Genet Couns* 2004; 13:83–114.
 54. **American Society of Clinical Oncology.** American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 2003; 21:2397–2406.
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