# What the Primary Care Physician Needs to Know About Hereditary Colorectal Cancer

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## Abstract

- *Objective:* To review the clinical features, genetics, surveillance, and management of common hereditary colorectal cancer (CRC) syndromes.
- *Methods:* Review of the literature.
- *Results:* Almost 10% of all CRC patients display a hereditary pattern, and their risk of developing CRC or other related malignancies can be as high as 100%. Some features such as early age of onset (< 50 years), several family members with colorectal or other related malignancies, presence of more than 1 type of cancer or 2 primary CRCs, and more than 10 to 15 cumulative colorectal adenomatous polyps over time are highly suggestive of hereditary CRC syndromes and should prompt a thorough evaluation. The most common form of inherited CRC, hereditary nonpolyposis colorectal cancer or Lynch syndrome, is characterized by an early age of onset of CRC and an increased risk of other related cancers, most commonly endometrial, ovarian, gastric, small bowel, brain, hepatobiliary tract, pancreatic, ureteral, or renal pelvis. Affected individuals have an estimated risk of developing CRC that approaches 80% by age 70 years.
- *Conclusions:* Genetic testing is an important tool in the identification and management of hereditary CRC.


The cumulative lifetime risk for colorectal cancer (CRC) in the United States is approximately 6% [1]. In 2007, an estimated 154,000 men and women were diagnosed with CRC and 52,180 died of the disease [1]. Roughly 15% to 20% of patients with CRC present in familial clusters, with approximately 10% displaying a hereditary pattern [2]. Of these hereditary cancers, about half represent well-characterized syndromes in which the responsible genes have already been described [3]. Individuals with an inherited predisposition to CRC are at extremely high risk of developing this cancer and often other types of cancer as well [3]. Identifying the individuals and families affected with a genetic predisposition allows for implementation of tailored screening and preventive interventions that have been shown to save lives. The American Society of Clinical Oncology recommends that genetic counseling and testing be offered when (1) an individual has personal or family history features suggestive of a genetic cancer susceptibility condition, (2) the genetic test can be adequately interpreted, and (3) the test results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer [4].

This article reviews the clinical features, genetics, surveillance, and management for the most common CRC syndromes.

## GENERAL GUIDANCE

### Identifying Patients at Risk

Some hereditary CRC syndromes, such as classical familial adenomatous polyposis, are often easily recognized due to the presence of family members with history of polyps and cancer, prompting the performance of colonoscopy with the subsequent finding of large numbers of polyps at an early age. Polyposis syndromes also present as attenuated forms, such as attenuated familial adenomatous polyposis or the more recently identified *MYH*-associated polyposis syndrome. In these cases, the number of polyps may be limited to 15 to 100 over time and present at a later age. These cases are often missed, as the clinician tends to expect a more spectacular syndrome with hundreds or thousands of polyps presenting at very early ages. The presence of more than 10 adenomas or more than 15 cumulative adenomas in 10 years should raise suspicion for an attenuated polyposis form [5].

While family history is determinant in identifying patients at risk, the lack of family history does not rule out a hereditary syndrome as inherited CRC can be the result of *de novo* mutations. At any time, a new family can be affected. This is particularly common in familial adenomatous polyposis, where up to 30% of affected families result from new mutations [3].

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**Table 1.** Red-Flag System for Suspicion of Hereditary Colorectal Cancer Syndrome

Questions that can be used for a quick prescreen of patients who may have hereditary colorectal cancer:

- Has the patient or any relatives had colorectal cancer at an age younger than than 50 years?
- Are there 2 or more relatives affected with colorectal cancer or other types of cancer, predominantly endometrial, ovarian, or gastric?
- Has the patient had more than 10 to 15 cumulative adenomatous polyps in the colon over time?
- Has the patient had more than 1 type of cancer or 2 primary colorectal cancers?
- Does the patient have any relatives with polyposis?

The most common form of inherited CRC, hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome, may present with a small number of polyps or none at all before cancer is diagnosed.

A "red flag" system can be used to identify patients who may have hereditary CRC (**Table 1**) [5].

## Obtaining a Family History

Obtaining a family history in the primary care physician's office is often challenging, as time is limited and urgent issues may take precedence. Options for facilitating a family history assessment include adding a few questions to the patient's initial intake form addressing family history; asking patients to complete a questionnaire at home prior to their appointment or in the waiting room the day of the appointment; and training nurses and medical assistants to ask patients about family history prior to seeing the physician. In addition, the American Medical Association has created an adult family history form as a means to initiate a family history (available online at www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/family-history.shtml) [6]. By increasing the opportunities for a patient to share family history information, the more likely it is that a physician will recognize at-risk families.

## Family Cancer Units

When any of the features associated with HNPCC is present or there is a family history of cancer and multiple adenomas, a timely referral to a specialized unit is often the most sensible approach. Familial cancer units or services specialize in caring for families with inherited cancer syndromes. These units usually include genetic counselors and clinical geneticists that identify families at risk, provide genetic counseling, select tumors for pregenetic screening tests, and choose the appropriate genetic tests according to the suspected genetic mutation. These units are also responsible for advising on the appropriate surveillance tests for early cancer detection and provide risk information so patients can decide about prophylactic interventions.

## SPECIFIC SYNDROMES

### Lynch Syndrome

#### Clinical Features

Lynch syndrome is an autosomal dominant disorder and the most common form of hereditary CRC. It accounts for 2% to 3% of all CRC. Penetrance is approximately 80%. Lynch syndrome is challenging to diagnose because there is no distinctive premalignant phenotype. Usually the diagnosis is suspected on the basis of strong family history of CRC and other associated malignancies. Patients with Lynch syndrome may present with a small number of polyps early in life, usually in the third or fourth decades. Cancers develop from a discrete number of adenomas through an accelerated carcinogenic process [7]. They tend to present in the proximal colon (up to 70%) and often are multiple, either presenting synchronously (~18%) or metachronously (~24%) [8]. Lynch tumors more commonly present with certain histological features (*see* Diagnostic Strategies, below) [9].

Lynch syndrome is characterized by an early age of onset of CRC and an increased risk of other related cancers, most commonly endometrial, ovarian, gastric, small bowel, brain, hepatobiliary tract, pancreatic, ureteral, or renal pelvis. Affected individuals have an estimated risk of developing CRC that approaches 80% by age 70 years. The mean age at diagnosis is the mid 40s [10,11]; however, there is a wide range of ages at presentation, ranging from 16 to 90 years [12].

Less frequently, patients with Lynch syndrome can also present with sebaceous gland adenomas and carcinomas and multiple keratoacanthomas, constituting a variant named Muir-Torre syndrome [13]. Furthermore, approximately 30% of patients identified as having Turcot syndrome (polyposis and central nervous system tumors, usually glioblastomas) have the mutations usually responsible for Lynch syndrome tumors [13].

#### Genetics and Genetic Testing

Lynch syndrome is caused by mutations in the main genes of the DNA mismatch repair (MMR) system: *MLH1, MSH2, MSH6*, and *PMS2*. Mutations in these genes result in malfunctioning of the DNA repair activity and ultimately in a widespread presence of errors all over the genome. These types of errors can usually be detected in microsatellite segments of DNA. Microsatellites are short sequences, commonly of mononucleotide or dinucleotide repeats, present throughout the genome. When the MMR system is compromised, the integrity of these repeats cannot be maintained. This phenomenon, called microsatellite instability (MSI), is

**Table 2.** Amsterdam Criteria for Clinical Definition of Lynch Syndrome

| |
|---|
| Amsterdam I criteria* |
| 3 or more relatives with colorectal cancer, 1 of whom is a first-degree relative of the other 2 |
| Cancer in at least 2 generations of the same family |
| At least 1 colorectal cancer case diagnosed before age 50 |
| Amsterdam II criteria* |
| 3 or more relatives with a Lynch-associated cancer (ie, colorectal, endometrial, ureter or renal pelvis, small-bowel), 1 of whom is a first-degree relative of the other 2 |
| Cancer in at least 2 generations of the same family |
| At least 1 cancer case diagnosed before age 50 |

Adapted from references 20 and 21.

*The presence of all 3 features is necessary to fulfill either set of criteria.

**Table 3.** Revised Bethesda Guidelines for Testing Colorectal Cancer Tumors for Microsatellite Instability

| |
|---|
| The presence of any 1 of these features should prompt testing for microsatellite instability and/or immunohistochemistry testing |
| CRC diagnosed at age < 50 years |
| Presence of synchronous or metachronous CRC or other HNPCC-associated tumors,* regardless of age |
| CRC that exhibits MSI-H histology (presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in a patient age < 60 years |
| CRC diagnosed in a patient with 1 or more first-degree relatives with an HNPCC-related tumor,* with 1 of the cancers being diagnosed age < 50 years |
| CRC diagnosed in a patient with 2 or more first- or second-degree relatives with HNPCC-related tumors,* regardless of age |

HNPCC = hereditary nonpolyposis colon cancer. (Adapted from reference 26.)

*Endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, glioblastoma, sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel.

one of the hallmarks of tumors from patients with Lynch syndrome. It is important to bear in mind that 10% to 15% of sporadic CRC tumors also display MSI, and these cases are almost always due to loss of *MLH1* protein expression caused by gene silencing through promoter hypermethylation [14]. These patients with sporadic colorectal cancer with MSI tumors are older and mostly female [15].

Recently, it has been shown that sporadic MSI tumors usually present a *BRAF* mutation (V600E) [16]. The fact that this *BRAF* mutation is commonly absent in Lynch syndrome tumors makes its study a good molecular tool to distinguish hereditary MSI tumors from their sporadic counterparts [17,18]. When a tumor shows an MSI phenotype, immunohistochemical analysis of *MLH1, MSH2, MSH6* and *PMS2* commonly results in one of these proteins not being expressed. In Lynch syndrome cases, this lack of expression is due to a pathogenic mutation in the corresponding gene [19].

## Diagnostic Strategies

Several diagnostic approaches have been suggested in order to identify Lynch syndrome–causing mutations. In 1991, an international panel drafted the Amsterdam criteria, a set of clinical conditions that would suggest the presence of this syndrome in a given family and therefore would prompt MMR gene testing (**Table 2**) [20]. These criteria were later revised in order to take into account the extracolonic tumors associated with this syndrome (Amsterdam II criteria) (Table 2) [21]. Soon after, it became apparent that these criteria are so strict that a majority of families with Lynch syndrome do not fulfill them [22,23]. The sensitivity of genetic testing in patients meeting the criteria is between 40% and 60% [15,24].

To improve the detection rate of Lynch syndrome families, a set of looser criteria, the Bethesda guidelines, were proposed and recently revised (**Table 3**) [25–27]. These criteria take into account not only personal and familial history of cancer but also histology features commonly associated with this syndrome [9]. Patients who meet any of the Bethesda criteria should undergo genetic counseling and MSI analysis and/or immunohistochemistry (IHC) testing for MMR protein expression [28]. A suggested algorithm of pregenetic and genetic testing is provided in the **Figure**.

Finally, some authors have proposed various algorithms that combine family history information and tumoral features in order to predict the likelihood of carrying a germline mutation in any of the MMR genes [29–31]. Recently, one algorithm, the PREMM 1,2 model (www.dfci.org/pat/cancer/gastrointestinal/crc-calculator/default.asp) has been shown to be highly useful in identifying MMR gene mutations in a large group of unselected colorectal cancers [32]. Genetic testing and counseling in Lynch syndrome has been shown to reduce morbidity and mortality in affected families [33].

## Surveillance and Management

Actions are directed towards detection of polyps (and subsequent polypectomy) or early CRC and the other associated malignancies (**Table 4**). While these interventions have been shown to prevent CRC and CRC deaths [7], there is no definitive data about reduction of other associated cancers with the proposed strategies. In patients carrying a Lynch syndrome mutation and presenting with CRC, a subtotal colectomy should be performed given the very high risk of

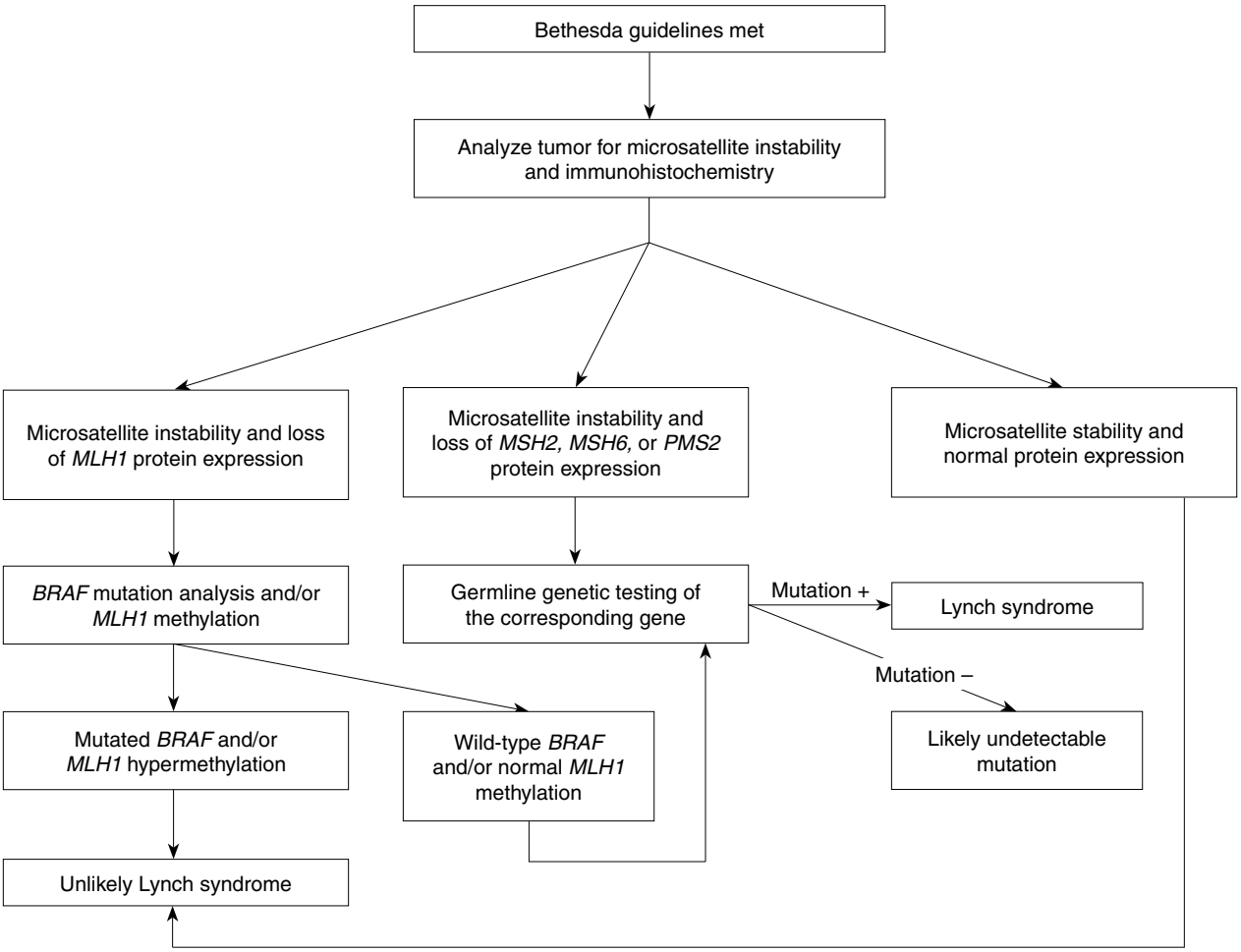


**Figure.** Algorithm for evaluation of a patient with possible Lynch syndrome.

developing metachronous cancers. Regarding prophylactic surgery in mutation carriers, colectomy should be evaluated taking into consideration the unique circumstances of each patient, such as potential screening compliance. Hysterectomy and oophorectomy should also be considered after completion of childbearing age in mutation carriers.

These recommendations apply to all family members who carry a cancer-causing mutation. If a mutation is identified in the family, all family members can be tested, and the ones who did not inherit the mutation do not need to undergo the mentioned surveillance and management measures as they did not inherit a high risk of cancer development. If families do clinically have Lynch syndrome, the recommendations stand for all family members as we do not have a way to individually assess who is at risk.

## Non–Lynch Syndrome HNPCC

When MMR gene mutations were identified as the cause of hereditary HNPCC, it was thought that they would be responsible for the great majority of cases fulfilling clinical criteria for HNPCC. The reality is more complex, and we now know that at least half of families fulfilling Amsterdam criteria of HNPCC actually do not have alterations in the MMR system [15]; therefore, it is likely that other genes are responsible for this syndrome. Thus, HNPCC includes Lynch syndrome (caused by inherited MMR genes) and at least 1 other group of inherited cancers of a yet unknown cause. The latter group, as a whole, also presents clinical features distinct from Lynch syndrome tumors: patients present with mostly left-sided tumors without lymphocytic infiltrate; cancers usually present at a later age, though still much earlier than sporadic colorectal cancers; penetrance is lower; and patients more often fulfill Amsterdam II criteria [15]. Other authors have reported a subset of families fulfilling Amsterdam I clinical criteria for HNPCC but without MMR deficiency. This group had a lower incidence of CRC

**Table 4.** Recommended Surveillance for Lynch Syndrome

| Type of Screening | Intervention |
|---|---|
| Colon cancer | Colonoscopy every 1–2 years beginning at age 20–25 (or 10 years before the youngest diagnosis of colon cancer in the family) |
| Endometrial/ ovarian cancer | Annual transvaginal ultrasound, endometrial biopsy every year beginning at age 25–30 |
| Gastric cancer | Upper endoscopy every 2–3 years starting at age 25 |
| Genitourinary cancer (renal pelvis, ureter, bladder) | Annual renal ultrasound, urinalysis with cytology starting at age 25 |

Data from reference 5.

**Table 5.** Recommended Surveillance for Familial Adenomatous Polyposis Syndrome

| Type of Screening | Intervention |
|---|---|
| Colon cancer | Annual flexible sigmoidoscopy beginning at age 10–12. Total colectomy (or subtotal colectomy if relative rectal sparing of polyps) once polyposis is established. |
| Gastric/ duodenal/ ampullary cancer | Upper endoscopy with side-viewing scope every 1–3 years beginning at age 25–30 |
| Thyroid cancer | Annual thyroid exam or ultrasound beginning age 12 |
| Hepato-blastoma | Liver palpation, $\alpha$-fetoprotein test, and hepatic ultrasound annually during the first decade of life |

Data from reference 5.

than the group with Lynch syndrome but no increased incidence of other cancers. The authors named this group familial CRC type X [34].

While it has not been well established, these patients should have CRC surveillance as Lynch syndrome patients. The onset of surveillance tests may be at a later age but always taking into consideration the age of onset of the different family members affected with cancer. It is unclear if they need surveillance for other cancers, as data about the risk of these cancers are limited.

## Familial Adenomatous Polyposis

### Clinical Features

Familial adenomatous polyposis (FAP) is an autosomal dominant disease that accounts for less than 1% of all CRC [35]. Affected patients, if not treated, have a CRC risk close to 100%, with a mean age of diagnosis of 39 years [36].

FAP is clinically characterized by the presence of hundreds to thousands of adenomatous colon polyps. The average age at polyp appearance is 16 years, but polyps can present at a much younger age. FAP patients are also at higher risk for upper gastrointestinal tract tumors [37], desmoid tumors [38], and thyroid cancer [39]. The presence of congenital hypertrophy of the retinal pigment epithelium is often seen associated with mutations in specific areas of the *APC* gene.

In addition to classical FAP, 3 variants of the syndrome have been described: Gardner syndrome, Turcot syndrome, and attenuated FAP (AFAP). Gardner syndrome is characterized by all the manifestations of FAP plus benign extracolonic tumors, such as desmoid or soft-tissue tumors, osteomas, and dental abnormalities [40]. Turcot syndrome is characterized by the development of central nervous system malignancies such as medulloblastomas, astrocytomas, and ependymomas. Most patients also commonly present with typical FAP features. A small subset of patients with Turcot have MMR gene mutations instead of *APC* mutations [41].

### Genetics and Genetic Testing

FAP is caused by germline mutations in the *APC* gene. One mutated allele is inherited from the affected parent, and the subsequent development of an acquired (or somatic) mutation in the other *APC* allele results in development of adenomas and eventually carcinomas. When a patient has clinical evidence of FAP, genetic analysis can be performed. This involves mutation testing of *APC*. Approximately 30% of FAP cases arise *de novo*. In these cases, there is no warning from the family history data, and this can lead to a delay in diagnosis. Referral for genetic evaluation and *APC* testing is recommended for all individuals with clinical symptoms of FAP even in the absence of a family history.

If a mutation is identified in a proband, family members can be unequivocally tested for that specific mutation. This would allow appropriate management with prophylactic colectomy, or alternatively, a subtotal colectomy if there were relative rectal sparing of polyps and upper gastrointestinal tract screening for patients who have inherited the familial mutation. Family members who had not inherited the mutation could be spared unnecessary procedures and the anxiety about potential development of the disease. In a small percentage of cases, *APC* testing does not yield an identifiable mutation. In this case, all family members need to be screened as if they had inherited the mutation and in fact had FAP.

### Surveillance and Management

Patients with FAP need intense surveillance for gastrointestinal cancers as well as thyroid cancer (**Table 5**). These

recommendations apply to all family members who carry a cancer-causing mutation. If a mutation is identified in the family, all family members can be tested and the ones who did not inherit the mutation do not need to undergo the mentioned surveillance and management measures, as they did not inherit a high risk of cancer development. If families do clinically have FAP, the recommendations stand for all family members as we do not have a way to individually assess who is at risk.

## Attenuated FAP

### Clinical Features

AFAP-affected patients develop a much lower number of polyps, commonly less than 100. The risk of cancer development is very high (~80%) but not reaching the almost 100% risk in FAP [42]. Polyps and cancer appear 10 to 15 years later on average than in FAP [43]. Polyps tend to present in the proximal colon and rectal sparing is not uncommon [43]. Duodenal adenomas and fundic gland polyps are also frequently described in AFAP patients [43].

### Genetics and Genetic Testing

Most cases of AFAP are caused by germline mutations in the *APC* gene, often at the proximal and distal extremes of the gene or in certain areas of exon 9 [44], but a significant number are caused by biallelic mutations in the base excision repair gene *MYH*. Genetic testing involves *APC* gene mutation analysis and *MYH* mutations analysis if *APC* is not mutated.

### Surveillance and Management

Screening for AFAP is tailored to the individual's family history. A flexible sigmoidoscopy is not sufficient for screening purposes due to the common proximal location of the polyps. Therefore, a full colonoscopy should be performed. Surveillance should start at age 25 or 10 years earlier than the youngest age of diagnosis in the family and continue yearly or at intervals according to the individual's disease expression. Upper endoscopy with side-viewing scope every 2 to 3 years starting at age 25 should be performed for screening of gastric, duodenal, or ampullary cancer. Colectomy should be recommended when polyps become difficult to manage endoscopically [40]. If colectomy needs to be performed, a subtotal modality sparing the rectum is often a sensible approach.

These recommendations apply to all family members who carry a cancer-causing mutation. If a mutation is identified in the family, all family members can be tested and the ones who did not inherit the mutation do not need to undergo the mentioned surveillance and management measures, as they did not inherit a high risk of cancer development. If families do clinically have AFAP, the recommendations stand for all family members as we do not have a way to individually assess who is at risk.

## *MYH*-Associated Polyposis Syndrome

### Clinical Features

Recently, the base excision repair gene *MYH* has been identified as being responsible for an autosomal recessive inherited syndrome associated with multiple adenomas and carcinoma. This constitutes a new paradigm in hereditary CRC, as the other CRC syndromes have an autosomal dominant pattern of inheritance. The syndrome has been called MAP for *MYH*-associated polyposis syndrome [45]. This syndrome represents 0.7% of all CRC [46]. Patients with this syndrome have more than a 90-fold increased risk of CRC [47]. The presence of more than 15 synchronous colorectal adenomas and a colorectal adenocarcinoma diagnosis before 50 years of age have been described recently as factors independently associated with the syndrome [46].

### Genetics and Genetic Testing

As with all autosomal recessive inherited syndromes, the mutation has to be inherited from both paternal and maternal alleles. Biallelic *MYH* mutations account for 7% of FAP cases without an identified germline mutation in the *APC* gene and for 29% of patients with 15 to 100 adenomas [48]. Therefore, in those cases with a clinical phenotype characteristic of FAP or AFAP in which a mutation in the *APC* gene is not identified, it is recommended to proceed with sequencing of *MYH*.

### Surveillance and Management

Surveillance and management in MAP is not well established, although it is reasonable to proceed as in AFAP.

## Hamartomatous Polyposis Syndromes

The hamartomatous polyposis syndromes are characterized by the development of multiple polyps at a very young age, representing an overgrowth of cells native to the area in which they normally occur (ie, mesenchymal, stromal, endodermal, ectodermal elements) [49]. Although altogether the hamartomatous polyposis syndromes represent less than 1% of all CRC, their identification is important due to their predisposition to colorectal and other extraintestinal malignancies. All hamartomatous polyposis syndromes are autosomal dominant.

### Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) affects 1 in 100,000 individuals. Unlike the sporadic juvenile polyps, polyps in JPS are more numerous and may affect the proximal gastrointestinal tract [50]. The clinical diagnosis of JPS is made when a patient presents with at least 3 to 10 colonic hamartomatous polyps, any extracolonic hamartomatous polyps, or any hamartomatous polyps in a person with a known family history of JPS [51]. CRC risk is approximately 60% [52].

JPS is caused by germline mutations in *BMPR1A* (10q22.3), *SMAD4* (18q21.1), and *PTEN* [53,54]. Approximately 25% are *de novo* mutations [24]. Surveillance involves upper endoscopy and colonoscopy beginning in the late teens, or earlier if symptoms are present. Repeat annually if polyps are present or every 3 years if no polyps are found.

### Cowden Syndrome

Cowden syndrome affects 1 in 200,000 patients [55]. Patients have a high risk of benign and malignant tumors. Up to 80% present dermatologic manifestations (trichellemomas or oral papillomas) [56]. Breast cancer is the most serious complication (≥ 50% of male and female patients) [56]. *PTEN* mutations are responsible for 80% of Cowden cases. No special screening recommendations are given for CRC due to at most a slight increased risk [57], but screening for breast and thyroid tumors is often recommended.

### Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) affects 1 in 10,000 to 100,000 patients [40]. There is a highly variable penetrance, even within families [55]. These patients present with typical freckling mucocutaneous hyperpigmentation in lips, buccal mucosa, vulva, fingers, and toes [58]. Gastrointestinal polyps occur in almost all individuals. They start developing during the first decade with symptoms usually presenting in the second or third decades due to polyp growth and subsequent obstruction or intussuception. Patients have an increased risk of developing gastrointestinal cancers, such as colon (40%), stomach (30%–60%), small intestine (15%–30%), and esophagus (0.5%–30%) [40]. Other commonly seen cancers are breast, endometrial, pancreatic, and lung [59]. PJS is diagnosed when hamartomatous polyps are present and at least 2 of the following are present: family history, hyperpigmentation, and small bowel polyposis [60].

PJS is caused in 50% to 75% of familial cases by germline mutations in *STK11* or *LKB1* [61]. In 25% they are *de novo* mutations [59]. Patients with PJS should have cancer surveillance for different intestinal and extraintestinal cancers (**Table 6**). Colectomy may be necessary if polyps are difficult to control endoscopically [57]. An attempt should be made to locate and remove all polyps larger than 1 cm in diameter, preferably by endoscopic techniques [58].

**Table 6.** Recommended Surveillance for Peutz-Jeghers Syndrome

| Age, yr | Intervention |
|---|---|
| Birth to 12 | History and physical exam (with attention to testicles in males) and routine blood tests |
| 8 | Upper endoscopy and small bowel series. If positive, repeat every 2–3 years |
| 18 | Colonoscopy, upper endoscopy, and small bowel series or capsule endoscopy every 2–3 years. Monthly breast self-exam in females. |
| 21 | Pelvic exam with Pap smear annually |
| 25 | Endoscopic ultrasound of the pancreas every 1–2 years. For females, clinical breast exam semi-annually and mammography or MRI annually, transvaginal ultrasound and serum CA-125 annually. |

Data from reference 57.

## CONCLUSION

The field of hereditary CRC has seen great development over the last few years, and striking advances have been achieved in the areas of diagnosis, surveillance, and prophylaxis. For the primary care provider, being aware of a few red flags can help identify cases that have a significant chance of being a hereditary type of CRC. Prompt referral of these cases to teams that specialize in these cancers and incorporate genetic counseling and testing can improve the survival and well being of families affected by these syndromes.

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*Funding/support: Support for this work was provided by the Sirazi Foundation, Raymond Cole Memorial Foundation, and an internal grant from the Department of Medicine and Cancer Center of the University of Illinois at Chicago.*

*Financial disclosures: None.*

## References

1. Cancer facts & figures 2007. Atlanta: American Cancer Society; 2007.
2. Lynch HT, Boland CR, Gong G, et al. Phenotypic and genotypic heterogeneity in the Lynch syndrome: diagnostic, surveillance, and management implications. Eur J Hum Genet 2006;14:390–402.
3. Xicola RM, Llor X. Hereditary colorectal cancer. In: Kim K, editor. Colorectal cancer: early detection and prevention. Thorofare (NJ): Slack; 2009. In press.
4. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol 2003;21:2397–406. Epub 2003 Apr 23.
5. National Comprehensive Cancer Network (NCCN). Colorectal cancer screening. Clinical Practice Guidelines in Oncology—v.1.2009. Available at www.nccn.org.
6. American Medical Association. Genetics and molecular medicine—family history. Available at www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-

molecular-medicine/family-history.shtml.
7. Jarvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 1995;108:1405–11.
8. Jass JR, Stewart SM. Evolution of hereditary non-polyposis colorectal cancer. Gut 1992;33:783–6.
9. Lynch HT, de la Chapelle A. Genetic susceptibility to non-polyposis colorectal cancer. J Med Genet 1999;36:801–18.
10. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919–32.
11. Gruber SB. New developments in Lynch syndrome (hereditary nonpolyposis colorectal cancer) and mismatch repair gene testing. Gastroenterology 2006;130:577–87.
12. Vasen HF, Stormorken A, Menko FH, et al. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. J Clin Oncol 2001;19:4074–80.
13. Kruse R, Rutten A, Lamberti C, et al. Muir-Torre phenotype has a frequency of DNA mismatch-repair-gene mutations similar to that in hereditary nonpolyposis colorectal cancer families defined by the Amsterdam criteria. Am J Hum Genet 1998;63:63–70.
14. Fishel R. Signaling mismatch repair in cancer. Nature Medicine 1999;5:1239–41.
15. Llor X, Pons E, Xicola RM, et al. Differential features of colorectal cancers fulfilling Amsterdam criteria without involvement of the mutator pathway. Clin Cancer Res 2005;11:7304–10.
16. Kambara T, Simms LA, Whitehall VL, et al. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. Gut 2004;53:1137–44.
17. Domingo E, Laiho P, Ollikainen M, et al. BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. J Med Genet 2004;41:664–8.
18. Bessa X, Balleste B, Andreu M, et al. A prospective, multicenter, population-based study of BRAF mutational analysis for Lynch syndrome screening. Clin Gastroenterol Hepatol 2008;6:206–14.
19. Marcus VA, Madlensky L, Gryfe R, et al. Immunohistochemistry for hMLH1 and hMSH2: a practical test for DNA mismatch repair-decicient tumors. Am J Surg Pathol 1999;23:1248–55.
20. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 1991;34:424–5.
21. Vasen HFA, Watson P, Mecklin J-P, Lynch HT, HNPCC I-. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch Syndrome) Proposed by the International Collaborative Group on HNPCC. Gastroenterology 1999;116:1453–6.
22. Pinol V, Castells A, Andreu M, et al. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA 2005;293:1986–94.
23. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2005;352:1851–60.
24. Burt R, Neklason DW. Genetic testing for inherited colon cancer. Gastroenterology 2005;128:1696–716.
25. Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al. A National Cancer Institute workshop on hereditary nonpolyposis colorectal cancer syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997;89:1578–762.
26. 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;96:261–8.
27. Rodriguez-Moranta F, Castells A, Andreu M, et al. Clinical performance of original and revised Bethesda guidelines for the identification of MSH2/MLH1 gene carriers in patients with newly diagnosed colorectal cancer: proposal of a new and simpler set of recommendations. Am J Gastroenterol 2006; 101:1104–11.
28. 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: 1507–17.
29. Barnetson RA, Tenesa A, Farrington SM, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med 2006;354:2751–63.
30. Balmana J, Stockwell DH, Steyerberg EW, et al. Prediction of MLH1 and MSH2 mutations in Lynch syndrome. JAMA 2006;296:1469–78.
31. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA 2006;296:1479–87.
32. Balaguer F, Balmana J, Castellvi-Bel S, et al. Validation and extension of the PREMM1,2 model in a population-based cohort of colorectal cancer patients. Gastroenterology 2008;134:39–46.
33. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009;11:35–41.
34. 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: 1979–85.
35. Burt RW, Bishop DT, Lynch HT, et al. Risk and surveillance of individuals with heritable factors for colorectal cancer. WHO Collaborating Centre for the Prevention of Colorectal Cancer. Bull World Health Org 1990;68:655–65.
36. Bisgaard ML, Fenger K, Bulow S, et al. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. Hum Mutat 1994;3:121–5.
37. Bulow S, Bjork J, Christensen IJ, et al. Duodenal adenomatosis in familial adenomatous polyposis. Gut 2004;53:381–6.
38. Arvanitis ML, Jagelman DG, Fazio VW, et al. Mortality in patients with familial adenomatous polyposis. Dis Colon Rectum 1990;33:639–42.
39. Truta B, Allen BA, Conrad PG, et al. Genotype and phenotype of patients with both familial adenomatous polyposis and thyroid carcinoma. Fam Cancer 2003;2:95–9.
40. Strate LL, Syngal S. Hereditary colorectal cancer syndromes. Cancer Causes Control 2005;16:201–13.
41. Hamilton SR, Liu B, Parsons RE, et al. The molecular basis of Turcot's syndrome. N Engl J Med 1995;332:839–47.

42. Brensinger JD, Laken SJ, Luce MC, et al. Variable phenotype of familial adenomatous polyposis in pedigrees with 3' mutation in the APC gene. Gut 1998;43:548–52.
43. Soravia C, Berk T, Madlensky L, et al. Genotype-phenotype correlations in attenuated adenomatous polyposis coli. Am J Hum Genet Jun 1998;62:1290–301.
44. Knudsen AL, Bisgaard ML, Bulow S. Attenuated familial adenomatous polyposis (AFAP). A review of the literature. Fam Cancer 2003;2:43–55.
45. Sampson JR, Dolwani S, Jones S, et al. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. Lancet 2003;362:39–41.
46. Balaguer F, Castellvi-Bel S, Castells A, et al. Identification of MYH mutation carriers in colorectal cancer: a multicenter, case-control, population-based study. Clin Gastroenterol Hepatol 2007;5:379–87.
47. Farrington SM, Tenesa A, Barnetson R, et al. Germline susceptibility to colorectal cancer due to base-excision repair gene defects. Am J Hum Genet 2005;77:112–9.
48. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med 2003;348:791–9.
49. Schreibman IR, Baker M, Amos C, McGarrity TJ. The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol 2005;100:476–90.
50. Kapetanakis AM, Vini D, Plitsis G. Solitary juvenile polyps in children and colon cancer. Hepatogastroenterol 1996;43:1530–1.
51. Giardiello FM, Hamilton SR, Kern SE, et al. Colorectal neoplasia in juvenile polyposis or juvenile polyps. Arch Dis Child 1991;66:971–5.
52. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol 1998;5:751–6.
53. Sayed MG, Ahmed AF, Ringold JR, et al. Germline SMAD4 or BMPR1A mutations and phenotype of juvenile polyposis. Ann Surg Oncol 2002;9:901–6.
54. Olschwang S, Serova-Sinilnikova OM, Lenoir GM, Thomas G. PTEN germ-line mutations in juvenile polyposis coli. Nat Genet 1998;18:12–4.
55. Boardman LA. Heritable colorectal cancer syndromes: recognition and preventive management. Gastroenterol Clin North Am 2002;31:1107–31.
56. Salem OS, Steck WD. Cowden's disease (multiple hamartoma and neoplasia syndrome). A case report and review of the English literature. J Am Acad Dermatol 1983;8:686–96.
57. Burt RW, Jacoby RF. Polyposis syndromes. In: Yamada T, editor. Textbook of gastroenterology. Vol 2. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:1914–39.
58. Tomlinson IP, Houlston RS. Peutz-Jeghers syndrome. J Med Genet 1997;34:1007–11.
59. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000;119:1447–53.
60. Giardiello FM, Welsh SB, Hamilton SR, et al. Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med 1987;316:1511–14.
61. Hemminki A, Markie D, Tomlinson I, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature 1998;391:184–7.

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