Diagnostic Approach to Hereditary Colorectal Cancer Syndromes

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Clin Colon Rectal Surg 2015;28:205–214.

Abstract

Keywords

- hereditary colorectal cancer syndromes
- familial adenomatous polyposis
- genetic testing
- Lynch syndrome
- hereditary nonpolyposis colorectal cancer
- MYH-associated polyposis

Approximately 5 to 10% of colorectal cancers develop within a known hereditary syndrome. Specific underlying genetic mutations drive the clinical phenotype and it is imperative to determine the genetic etiology to provide meaningful surveillance and intervention. Recognizing potential patients and families with a hereditary predisposition is the first step in management. Syndromes can be categorized according to polyp burden as polyposis or nonpolyposis. Clinical assessment should start with a personal and family medical history, physical examination, and evaluation for the presence and type of colorectal polyps or cancers. Key information is gained from these simple steps and should guide the specific genetic analysis for diagnosis. Genetic counseling is a critical component to any hereditary colorectal cancer program and should be conducted before genetic testing to provide education about the implications of test results. This review focuses on the thought process that drives initial clinical evaluation and guides genetic testing for patients with suspected hereditary colorectal cancer syndromes.

The genetic and molecular basis of disease continues to be unraveled at an exponential rate. We have entered the era of “precision medicine” or “personalized care” where the clinical management of a patient is tailored to that specific patient based on any number of factors, but mainly driven by genetics. This is particularly relevant in the field of hereditary colorectal cancer (CRC) syndromes. As opposed to most personalized care approaches in CRC that offer or withhold a particular chemotherapy based on tumor genetics, personalized care in hereditary CRC syndromes draws its strength on prevention. Programs are based on risk assessment and subsequent cancer prevention and detection. Over the past 20 years, there have been sentinel discoveries regarding heritable gene mutations at the root of hereditary CRC syndromes. Through the use of registries and collaboration, researchers and clinicians have been able to delineate risk of various cancers associated with an underlying mutation.

Approximately 30% of CRCs are believed to have a familial component and approximately one-third (10% of all CRC) are hereditary. Approximately 5% of all CRCs occur within a hereditary syndrome with a known highly penetrant gene mutation. The management of hereditary CRC syndromes requires a multidisciplinary team, but colorectal surgeons are often the point of contact for the initial presentation. Clinicians must be aware of these syndromes and be able to identify patients who are potentially at risk. For example, the surgeon must think beyond the single encounter of dealing with a cecal cancer in a 42-year-old, but dive deeper into the potential cause and implications. Diagnosing a hereditary cancer syndrome impacts the care and management for both current and future generations. The specific gene mutation identified allows for risk assignment and stratification, which then leads to specialized surveillance regimens and even prophylactic interventions to reduce cancer risk. This article

Issue Theme Colon Cancer; Guest Editor: Garrett M. Nash, MD, MPH, FACS, FASCRS

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Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0035-1564432>.
ISSN 1531-0043.

focuses on a practical approach to identifying, evaluating, and testing patients with a suspected hereditary CRC syndrome. The approach requires suspicion, application of knowledge, and some investigation.

Classification of Syndromes

Hereditary CRC syndromes may be broadly classified as those associated with or without colorectal polyposis. The polyposis syndromes are further subdivided according to polyp histology: adenomas, hamartomas, or serrated polyps. The main adenomatous polyposis syndromes include familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP). Peutz-Jeghers syndrome (PJS), Juvenile polyposis syndrome (JPS), and Cowden syndrome are the more common hamartomatous polyp syndromes. A predominance of serrated polyps or large serrated polyps is characteristic of serrated polyposis syndrome (SPS) that is defined by clinical criteria. Nonpolyposis syndromes are generically referred to as *hereditary nonpolyposis colorectal cancer* (HNPCC) and are defined by patterns of cancer within the family. HNPCC is a clinical definition based on Amsterdam criteria within a family.^{1,2} Lynch syndrome is defined by a genetic predisposition to developing colorectal and extracolonic cancers.^{1,2} Importantly, Lynch syndrome is a genetic diagnosis and is not based on meeting Amsterdam criteria. In fact, approximately 50% of patients with Lynch syndrome do not meet Amsterdam criteria.³ Conversely, patients who are diagnosed with HNPCC via meeting Amsterdam criteria but whose tumors are microsatellite stable are termed *familial colorectal cancer type X* (FCC X).^{2,4} The classification is represented in ►Table 1. Individual syndromes are discussed later in this manuscript.

Initial Clinical Evaluation

Determining whether a patient has a hereditary CRC syndrome starts with the basics of medicine: history and physical examination. Information obtained should be used to guide further diagnostic evaluation and potential referral for genetic counseling and testing.

Personal and Family History

Every patient encounter provides an opportunity to ask patients about personal and family history. Taking a history is free, physically noninvasive, does not require special equipment, and does not need insurance preauthorization. There are rare excuses to omit exploring history with all patients, but obtaining this history is particularly important for those with CRC or polyps. A thorough family history will include at least three generations. The authors prefer to construct a family pedigree to allow for a visual representation of the cancers within a family. This also creates a structure that can be easily updated as new information becomes available. There are multiple software applications commercially available for drawing pedigrees and maintaining a database. Constructing the pedigree always starts with the proband, or the patient through whom the family history

is uncovered. The pedigree typically is developed around first-degree relatives and expands to second- and third-degree relatives. For each family member, the presence of colorectal polyps, CRC, and any extracolonic cancers should be documented. Key information for each family member includes the phenotype and the age at which each component of the phenotype was diagnosed. For example, if a woman had both uterine and colon cancer, each of these would be noted on the pedigree along with the age at diagnosis. The pedigree can then be analyzed for the presence of particular cancers within the family, age of onset, and inheritance patterns. For example, multiple family members affected across successive generations suggests a dominant inheritance pattern. On the other hand, a pedigree with less penetrant cancers that skip generations suggests a recessively inheritance pattern.

The information in the pedigree depends on the quality of the source. There is great variability among patient accuracy in reported family history. Patients often are not aware of their family medical history. When they do report, it may be compromised by the use of a generic term like “stomach cancer” to refer to any time of gastrointestinal cancer. A history should always be followed by obtaining medical records and pathology reports to validate the accuracy. Verification is essential so that any decisions regarding clinical management are appropriate. In our institution, we approach all suspected patients for consent into the Jagelman Hereditary Colorectal Cancer Registries, which facilitates obtaining records for clinical care and research.

Physical Examination

Although somewhat of a lost art in surgery, a thorough physical examination can provide clues to diagnosing a hereditary CRC syndrome. Some of the more prominent findings exist with FAP such as the presence of supernumerary teeth, jaw osteomas, and epidermoid cysts. Abdominal wall desmoids or larger intra-abdominal desmoids can be detected on physical examination and may be an initial presentation of FAP. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is a sensitive physical examination finding although in reality most surgeons do not perform an ophthalmologic examination. However, if there is suspicion for FAP, this finding supports the diagnosis of FAP. Thyroid pathology including nodules and hyperplasia may be present in 36% of patients with FAP.⁵ Sebaceous adenomas and adenocarcinomas are associated with Lynch syndrome and can be detected on routine skin examinations. These findings may be the sentinel finding that leads to further investigation and eventual detection of a syndrome.

Colorectal Neoplasia Phenotype and Histology

The next clue in deciphering which syndrome may be present is provided by the number and histologic type of polyps, as outlined in ►Table 1. Multiple polyps or polyps detected at a young age should raise suspicion for a hereditary syndrome. Adenomas are the precursor polyps in FAP, MAP, and Lynch syndrome. The presentation varies even within syndromes. FAP may present with profuse (> 1,000 adenomas), classic (100–1,000 adenomas), or attenuated (< 100 adenomas)

Table 1 Classification and overview of hereditary colorectal cancer syndromes

Polypoid syndromes					
Syndrome	Gene(s)	Main polyp type	Inheritance	Predominant clinical findings	Approximate CRC risk (%)
FAP					
Classic	APC	Adenoma	AD	100–1,000 adenomas; duodenal adenomas and carcinomas; gastric fundic gland polyps desmoid tumors, epidermoid cysts, extra teeth, osteomas	100
Profuse	APC	Adenoma	AD	> 1,000 adenomas; duodenal adenomas and carcinomas; gastric fundic gland polyps desmoid tumors, epidermoid cysts, extra teeth, osteomas	100
Attenuated	APC	Adenoma	AD	< 100 adenomas; gastric fundic gland polyps desmoid tumors, epidermoid cysts, extra teeth, osteomas	80
MAP	MYH	Adenoma	AR	0–1,000 adenomas, CRC < 50 years; gastric fundic gland polyps, duodenal adenomas, and carcinomas	80
JPS	BMPRT1A SMAD4	Hamartoma	AD	≥ 5 juvenile polyps any juvenile polyp and JPS family history; HHT	40
PJP	STK11	Hamartoma	AD	PJPs orcutaneous pigmentation family history of PJP; cancer of small bowel, colon, stomach, pancreas, breast, ovary, testis	40
PHTS	PTEN	Hamartoma	AD	Colorectal adenomas, lipomas, fibromas, ganglioneuromas, juvenile hamartomas; colorectal cancer; macrocephaly, trichilemmomas	10 (Cowden syndrome)
SPS	Unknown	Serrated polyps	Unknown	> 20 serrated polyps Any serrated polyp and family history of SPS > 5 serrated polyps proximal to the sigmoid, 2 are > 1 cm diameter	25–40
Nonpolypoid syndromes					
Syndrome	Gene(s)	Main polyp type	Inheritance	Predominant clinical findings	Approximate CRC risk
Lynch syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Adenoma	AD	Microsatellite unstable CRC, advanced adenomas; gastric, duodenal, small bowel, transitional cell, gallbladder, pancreas, endometrial, ovarian	60–80
Familial CRC type X	Unknown	Adenoma	AD	Amsterdam criteria positive, microsatellite stable tumors	12

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CRC, colorectal cancer; FAP, familial adenomatous polyposis; HHT, hereditary hemorrhagic telangiectasia; JPS, juvenile polyposis syndrome; MAP, MUTYH-associated polyposis; PHTS, PTEN hamartoma tumor syndromes; PJP, Peutz-Jeghers polyposis; SPS, serrated polyposis syndrome.

disease. MAP is the imitator in that it can present with hundreds of adenomas or the initial diagnosis may be made with a single CRC without any other polyps.⁶ Although Lynch syndrome is considered a nonpolyposis condition, an increased number of adenomas does not preclude Lynch syndrome and attention must be paid to the family history. Recent data from Cleveland Clinic reported that the most common number of adenomas per patient seen in Lynch syndrome patients was 2 to 5, but 13% (9 of 70) of patients had more than 10 adenomas and one presented with 22 synchronous adenomas.⁷

Nonadenomatous polyps provide a clue to other syndromes. Hamartomatous polyps are the tell-tale sign of the hamartomatous syndromes. Peutz-Jeghers polyps and juvenile polyps are the pathognomic polyps in PJS and JPS, respectively. Hamartomatous polyps, including ganglioneuromas, are also seen in the PTEN-hamartoma syndromes that can have a variety of polyp types.⁸ The presence of multiple or large serrated polyps suggests SPS, which is a clinical diagnosis. Although no genetic defect has been identified to explain the underlying etiology of SPS, it is believed to be a heritable condition with possible environmental modifiers that bring about its phenotype.

It is important to note that any polyp type can be seen in any syndrome. There can be overlap between the various syndromes and patients can develop sporadic polyps that are not necessarily related to the underlying syndrome. Serrated polyps can also be seen in Lynch syndrome, MAP, and FAP.⁹⁻¹¹ Hereditary mixed polyposis syndrome and PTEN may all have multiple types of polyps. Patients with SPS also commonly may have adenomas.¹² Clinicians should be aware of the different types of polyps that are associated with each syndrome so as to guide further genetic evaluation and counseling. The National Society of Genetic Councilors recommends referral to a genetic counselor for consultation and possible testing for anyone who has 10 or more cumulative adenomas during their lifetime.^{13,14}

Tumor Testing: Is This Lynch Syndrome?

Genetic and molecular changes within the tumor may provide critical information regarding the syndrome and guide additional evaluation and diagnostic confirmation. This approach is used in suspected Lynch syndrome cases. The underlying genetic mutations in Lynch syndrome results in mismatch repair deficiency (discussed in the following text). Impaired DNA mismatch repair results in a tumor phenotype called *microsatellite instability* (MSI). MSI studies are conducted on neoplastic tissue, such as a cancer, using a standardized panel of five DNA markers. If two or more of the five microsatellite markers show instability, the target lesion is considered to be MSI-high (MSI-H). Among Lynch syndrome-associated CRCs, up to 91% will display (MSI-H).¹³ Immunohistochemistry (IHC) for the mismatch repair proteins can also be utilized to screen cancers for Lynch syndrome. Approximately 83% of Lynch syndrome-associated CRCs will have an abnormal IHC staining pattern.¹³ Lack of

expression of one or more proteins can help direct germline testing to the impair mismatch repair gene.

Because tumor screening serves as a surrogate to guide genetic testing, the main question is which tumors should be tested? A family history of colorectal and Lynch-related cancers has been the initial trigger to evaluate tumors for Lynch syndrome. The Amsterdam criteria were initially developed to identify families for hereditary CRC research, and subsequently to recognize potential patients with HNPCC. The Amsterdam II criteria are listed in ►Table 2.¹⁵ Other guidelines that incorporate histologic findings have also been used to guide tumor testing. The revised Bethesda guidelines were developed to identify patients with CRCs appropriate for MSI testing or IHC analysis. The revised Bethesda guidelines are provided in ►Table 3.¹⁶ Both the Amsterdam criteria and revised Bethesda guidelines have

Table 2 Amsterdam II criteria¹⁵

1.	≥ 3 family members affected, one of whom is a first-degree relative of the other two, with HNPCC-related cancers ^a
2.	2 successively affected generations
3.	≥ 1 of the HNPCC-related cancers diagnosed before age 50 years
4.	Familial adenomatous polyposis is excluded

Abbreviations: HNPCC, hereditary nonpolyposis colorectal cancer.
^aHNPCC-related cancers: colorectal, endometrial, stomach, small bowel, hepatobiliary, renal pelvis, ureteral, pancreatic.

Table 3 Revised Bethesda criteria¹⁶

1.	Colorectal cancer diagnosed in patient aged < 50 years.
2.	Presence of synchronous, metachronous colorectal cancer, or other HNPCC-associated tumors, ^a regardless of age
3.	Colorectal cancer with the MSI-H histology, ^b diagnosed in a patient aged < 60 years
4.	Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years
5.	Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

Abbreviations: HNPCC, hereditary nonpolyposis colorectal cancer; MSI-H, microsatellite instability-high.
^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.

been shown to have reduced sensitivity for identifying patients with Lynch syndrome. Therefore, in 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommended that all newly diagnosed CRCs undergo MSI and/or IHC.¹³ These guidelines are endorsed by the Collaborative Group of the Americas on Inherited Colorectal Cancer.¹⁷ The NCCN has recently recommended universal screening of all CRCs younger than 70 and those older than 70 who meet Bethesda guidelines.¹⁴ The current practice at Cleveland Clinic includes universal screening of all CRCs, regardless of age. A recent analysis of our own data showed a mismatch repair deficiency rate of 16%.¹⁸ Approximately 25% of mismatch repair deficient tumors had a putative diagnosis of Lynch syndrome and 18% of Lynch syndrome cases were diagnosed at age greater than 70 years.¹⁹ Our approach to universal tumor testing is summarized in ►Fig. 1.

A pattern of MSI-H and/or abnormal IHC is not specific for Lynch syndrome. About 10 to 15% of CRCs are MSI-H, most of which can be attributed to acquired methylation of the MLH1 promoter.^{20,21} The next step in evaluation depends on which mismatch repair protein is lost. If MSH2, MSH6, or PMS2 are lost, germline confirmation is pursued for those genes. If MSI-H is caused by loss of MLH1, results should be taken within context of age and family history. In our universal screening protocol, additional tumor tests are done to evaluate MLH1 results. As most non-Lynch MLH1-deficient tumors harbor BRAF mutations and are methylated at the MLH1 promoter,² these patients undergo BRAF mutation and MLH1 methylation testing. This approach is represented as an algorithm in ►Fig. 1. Involvement of genetic counseling and testing to drive this process has increased the detection of Lynch syndrome cancers.¹⁸

Ideally, preoperative testing is done on the tumor biopsy before surgery, which would provide an opportunity for definitive diagnosis and guide surgical management. We recognize that this is not always practical as some patients do not wish to delay surgery to wait for genetic testing results. This is often an emotional decision for patients and education should be provided. In general, it takes approximately 3 to 10 days for return of in-house tumor testing and 2 to 4 weeks for performance and interpretation of germline testing.

The Importance of Genetic Counseling

Genetic testing should generally be initiated at the time of cancer or polyp diagnosis. For unaffected patients, testing should be considered around the age when cancer surveillance would commence, should the patient test positive. Because of the complexity and implications of the results, genetic testing should only occur in the context of pre- and posttest genetic counseling. Genetic counseling is a process of risk stratification, education, and, when appropriate, facilitation of genetic testing for a patient and his or her family members.²² In addition to educating and empowering patients to make informed decisions about genetic testing, genetic counseling involves assessment of psychosocial issues that may arise for patients or their families while going

Table 4 Indications for referral to genetic counseling

Detection of ≥ 10 cumulative colorectal adenomas
Colorectal or endometrial cancer diagnosed before age 50
Synchronous or metachronous primary cancers
Satisfy Amsterdam criteria or Bethesda guidelines
Mismatch repair deficient cancer not explained by MLH1 promoter hypermethylation
Family member with a known colorectal cancer hereditary syndrome
Multiple relatives, successive generations affected with the same or related cancers
Presence of ≥ 3 hamartomas

through this process. These services are most appropriately provided by a medical geneticist or genetic counselor. The process of genetic counseling should include collection of a thorough personal medical history and three- to four-generation family history; a risk assessment to determine whether the history could be hereditary; selection of what genetic test to offer and who in the family is most appropriate for testing; an overview of the suspect syndrome(s), inheritance, possible test results, technical aspects and accuracy of the test, economic considerations, possibility of genetic discrimination, confidentiality, psychosocial concerns, utilization of test results, and alternatives to genetic testing; a psychosocial assessment; and plans for disclosure of the results.^{22,23}

Genetic counseling and genetic testing should be considered whether the patient's presentation, such as family history or disease phenotype, is suggestive of an inherited syndrome. General features of a hereditary CRC syndrome that may prompt a referral to a genetic counselor are listed in ►Table 4. Ideally, genetic testing should be initiated on a member of the family who has been diagnosed with cancer or polyps. Germline genetic testing is most commonly conducted on a blood sample but may also be done on a buccal sample.

Genetics and Diagnostic Approach for Individual Syndromes

There are multiple implications of a genetic diagnosis for both the patients and their families. Each syndrome has defined cancer risks that warrant surveillance and occasionally prophylactic measures. Furthermore, all of the hereditary syndromes, with the exception of MAP, are inherited in an autosomal dominant fashion. Thus, every first-degree relative of a confirmed carrier is at 50% risk of carrying the mutant gene also. Those relatives should be encouraged to seek genetic counseling and testing also. Detailed clinical and surgical management of each individual syndrome is beyond the scope of this article and the reader is referred to other reviews.^{6,24–27} An overview of the genetics and key points to the clinical approach to the syndromes follow.

Adenomatous Polyposis

Familial Adenomatous Polyposis

FAP is the second most common hereditary CRC syndrome and accounts for approximately 1% of all CRCs, with nearly 100% of patients developing CRC. It is caused by mutations in the *APC* gene that is located on chromosome 5 and is dominantly inherited. Approximately 25% of FAP cases arise from de novo *APC* mutations.²⁸ It is recommended that individuals who have 10 or more adenomas detected on a single colonoscopy or who are first-degree relatives of patients with FAP undergo a genetic evaluation and testing for mutations in the *APC* gene.²⁹ It is also appropriate to refer patients with desmoid tumors, duodenal adenomas, and bilateral and/or multifocal CHRPE for a genetic evaluation. The clinical presentation varies from attenuated to severe or profuse. Classic FAP refers to an adenoma burden between

100 and 1,000. In classic and severe forms, adenomas tend to start to develop in late teen and early twenties. The CRC risk approaches 100% with an average age of cancer at 39 years. In the attenuated form, the polyps burden is less severe, tends to spare the rectum, and the lifetime CRC risk is slightly decreased compared with classic FAP to approximately 70%. Among patients with more than 1,000 adenomas, *APC* mutations are identified in 80%.³⁰ The mutation detection rate drops to 56, 10, and 5% for those with 100–99, 20–99, and 10–19 adenomas, respectively.³⁰ Once a mutation is detected in the family, genetic counseling and testing should be offered to at risk family members between ages 8 and 10 for classic FAP and 16 and 18 for attenuated FAP.

MUTYH-Associated Polyposis

A characteristic autosomal recessive inheritance pattern of CRC provides a useful clue to detecting MAP during clinical evaluation. MAP is caused by germline mutations in the base excision repair gene, *MUTYH*. The mutations Y179C (previously referred to as Y165C) and G396D (previously referred to as G382D) account for up to 80% of cases of MAP among individuals who are of Northern European background.³¹ An estimated 1 to 2% of the general population carries a *MUTYH* mutation. Germline *MUTYH* testing should be offered to patients who test negative for an *APC* mutation but have clinical features of FAP or attenuated FAP, have a personal history of more than 10 colorectal adenomas, or a recessive family history of polyposis.²⁹ It has been shown that up to 29% of FAP patients who are *APC* negative will have biallelic *MUTYH* mutations.^{32,33} *MUTYH* mutations are rare among patients with profuse adenomatous polyposis.³⁰ Biallelic *MUTYH* mutations are found in 7% of patients with 20 to 999 adenomas and 4% of those with 10 to 19 adenomas.³⁰ Siblings of individuals with MAP should be offered predictive *MUTYH* testing after the age of 18. The children of an individual with MAP will be carriers. The most common phenotype is moderate polyposis, with 11 to 42% of cases reported to have fewer than 100 adenomas.^{34–36} It is important to note that nearly 20% of patients may present with CRC without any history of colorectal polyps or synchronous polyps.³⁷ The lack of polyposis has led some authors to consider changing to the syndrome from MAP to MAN, *MUTYH*-associated neoplasia.⁶

Hamartomatous Polyp Syndromes

Juvenile Polyposis Syndrome

Approximately 40 to 50% of individuals who satisfy clinical criteria for JPS will have a mutation in *SMAD4* or *BMPRI1A*.^{38–40} In the other approximately 50% of cases, the genetic etiology remains unknown. Mutations are autosomal dominantly inherited. Most cases of JPS are familial and 40% of cases are sporadic. Once a mutation is known in the family, predictive testing should be offered to first-degree relatives in the mid teenage years for *BMPRI1A* and at birth for *SMAD4*. Important genotype-phenotype observations occur in patients with JPS. When compared with those with *BMPRI1A* mutation, patients with *SMAD4* have a higher prevalence of massive gastric polyps.⁴¹

Additionally, patients with *SMAD4* mutations have a risk of developing hereditary hemorrhagic telangiectasia (HHT).^{42,43} HHT is characterized by epistaxis, dermatologic and mucosal telangiectasias, and cerebral, pulmonary, and gastrointestinal arteriovenous malformations.

Peutz-Jeghers Syndrome

The tumor suppressor gene, *STK11/LKB1*, has been associated with PJS. About 50% of individuals are due to a de novo mutations and the remainder of the cases will be inherited. PJS is autosomal dominantly inherited. Mutations are detected in 39 to 99% of patients who have a clinical diagnosis.^{44–46} Predictive genetic testing is generally offered around ages 8 to 10 years.

PTEN-Hamartoma Tumor Syndrome

PTEN-hamartoma tumor syndrome (PHTS) describes the conditions that have been associated with germline *PTEN* mutations: Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (BRRS). *PTEN* mutations are inherited in a dominant manner. An estimated 10 to 46% of cases are de novo.⁴⁷ In addition, 30–35% of patients meeting consortium criteria of Cowden syndrome have mutation and 55% of those with a clinical diagnosis of BRRS.^{48,49}

Serrated Polyposis Syndrome

SPS is defined by clinical criteria according to World Health Organization as follows⁵⁰: (1) at least five serrated polyps proximal to the sigmoid colon with two or more sized greater than 10 mm; or (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; or (3) more than 20 serrated polyps of any size distributed throughout the colon. The clinical presentation varies and there is overlap between the phenotypes.¹² Although SPS is believed to be caused by an inherited genetic defect, one has not been clearly identi-

fied. It is likely a combination of genetic and environmental factors that contribute to the SPS and CRC risk. There is no genetic testing available.

Other Rare Polyposis Conditions

There are several other rare hereditary CRC syndromes that have been reported within the last few years. These syndromes have limited clinical data and information continues to evolve. They are mentioned here purely to raise awareness as they may need to be considered in a patient's differential diagnoses. Likewise, testing for many of these syndromes has become included as part of more comprehensive next-generation sequencing cancer gene panels and incidental cases may be diagnosed. These syndromes are hereditary mixed polyposis syndrome, polymerase proofreading polyposis, constitutional mismatch repair deficiency, Li-Fraumeni syndrome, and hereditary diffuse gastric cancer. They are briefly outlined in ►Table 5.

Nonpolyposis Syndromes

HNPCC

As discussed previously, HNPCC is defined by clinical criteria (Amsterdam) and is not a genetic diagnosis. Patients with HNPCC have Lynch syndrome if they have a germline defect in one of the Lynch genes. Patients with HNPCC who have microsatellite stable tumors are diagnosed with FCC X.

Lynch Syndrome

Lynch syndrome is an autosomal dominantly inherited condition caused by defective DNA mismatch repair. The DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* have been associated with Lynch syndrome. Additionally, there are cases of Lynch syndrome caused by germline deletions of *EPCAM* and germline *MLH1* promoter hypermethylation.^{51,52} The diagnostic approach starting with tumor testing is described in detail previously in this

Table 5 Other rare hereditary colorectal cancer syndromes

Syndrome	Gene	Inheritance	Phenotype
Polymerase proofreading polyposis ⁶¹	<i>POLE</i>	AD	Oligopolyposis (adenomas), early-onset colorectal cancer
Polymerase proofreading polyposis ⁶¹	<i>POLD1</i>	AD	Oligopolyposis (adenomas), early-onset colorectal cancer, endometrial cancer, brain tumors
Hereditary mixed polyposis ⁶²	<i>SCG5/GREM1</i>	AD	Multiple adenomas, “atypical” juvenile polyps and serrated polyps, colorectal cancer, Ashkenazi Jewish ancestry
Constitutional mismatch repair deficiency ⁶³	<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i>	AR	Brain tumors, childhood gastrointestinal cancers, lymphoma, polyposis (adenomas), café au lait spots
Li-Fraumeni syndrome ⁶⁴	<i>TP53</i>	AD	Early-onset colorectal cancer, breast cancer, brain tumors, sarcomas, adrenal cortical carcinomas
Hereditary diffuse gastric cancer ⁶⁵	<i>CDH1</i>	AD	Diffuse gastric cancer, lobular breast cancer, signet-ring cell colorectal cancer

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

manuscript. Germline testing should be guided by the results of the tumor testing. Once a definitive germline mutation has been identified in a clinically affected individual, at-risk individuals should be offered genetic counseling and testing for the same gene mutation at the age of 18. Surveillance and surgical management of Lynch syndrome is detailed elsewhere.²⁵

Familial Colorectal Cancer Type X

FCC X is a clinical diagnosis with a genetic diagnosis of exclusion of sorts. Patients from families who meet Amsterdam Criteria but have a microsatellite stable tumor are diagnosed with FCC X.^{2,4,53} Although these patients have an increased risk of CRC compared with the general population, there is neither increased risk of extracolonic cancers nor genetic test to evaluate the patient or family members.^{4,53}

Clinical Challenges: Variants of Unknown Significance and Negative Germline Test Results

Genetic testing is the gold standard for confirmation of a hereditary CRC syndrome. In addition to confirming the diagnosis and clarifying cancer risks for that patient, it allows for predictive testing for his or her at-risk relatives. However, when genetic testing fails to identify a deleterious mutation (in the absence of a known mutation in a family), this can create a clinical conundrum. There are no hereditary cancer syndromes with a 100% mutation detection rate, which means a negative genetic test does not definitively eliminate the existence of a hereditary syndrome. A negative result could be explained by any of the following: (1) the patient does not have the disease in question; (2) there is an mutation, large rearrangement, or epigenetic alteration present in the gene that is not detected with current testing technology; (3) there is another gene causing the phenotype in question (such as a known gene that was not tested for or a gene that is yet to be discovered); and (4) the gene expression is impaired through an entirely different mechanism. Therefore, when no mutation is identified, the clinician must defer to the patient's phenotype and family history to determine whether he/she could still have the syndrome in question.

Genetic testing can also yield variants of uncertain significance (VUS). VUS are mutations within a gene with unclear functional consequences. As the functional consequence is unknown, these results should not be used for determining the patient's cancer management or screening. Eventually, most VUS will be reclassified as deleterious or polymorphic based on advancements in research. In the interim, however, clinicians should defer to the patient's personal and family history to determine cancer risk and management.

In either situation of negative testing or a VUS, it may still be reasonable to survey and treat that patient with the syndrome showing strong clinical suspicion. This is often the case in polyposis patients who have the clinical phenotype, but in whom a mutation is not found. They are still treated as if they have the syndrome clinically in question. Notably, first-degree relatives are also screened as if they are at risk.

Future Diagnostic Directions: Gene Panel Testing

The field of hereditary cancer genetics is expanding to include multigene next-generation sequencing panels. Next-generation sequencing allows for analysis of multiple genes on one platform at a reduced cost per nucleotide compared with traditional Sanger sequencing.^{54–58} There are several hereditary cancer gene panels commercially available that range from disease-specific panels (e.g., hereditary CRC) to pan-cancer panels. These panels offer many advantages over traditional single gene/syndrome testing, such as reduced cost, elimination of testing fatigue, and increased mutation detection rate. However, panel testing has not become completely mainstream as there are still barriers to overcome and knowledge to be gained. Presently, there are no professional society guidelines advocating the use of panels for hereditary CRC syndromes. Likewise, insurance coverage for these tests is completely variable and not yet endorsed by the Center for Medicare and Medicaid Services. Many of these tests include high-risk genes as well as more recently discovered moderate-risk genes, for which the clinical utility is unknown. The VUS rate increases dramatically, with early studies showing a 10 to 93% VUS rate.^{57,59,60} Though these tests hold promise, there is still much research to be done in this area.

Concluding Remarks

Identification and diagnosis of a hereditary CRC syndrome has broad implications for the patient and their extended families. Clinicians must be aware of the potential syndromes and identify those at risk, so as to guide toward the appropriate diagnosis. Continued technological advances will further uncover the underlying genetic mechanisms. This will further refine personalized care as we are able to more precisely predict the natural history of disease, assign risk, and intervene to prevent cancer development.

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