Familial Colorectal Cancer: Understanding the Alphabet Soup

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Abstract

While most colorectal cancers (CRCs) originate from nonhereditary spontaneous mutations, one-third of cases are familial or hereditary. Hereditary CRCs, which account for < 5% of all CRCs, have identifiable germline mutations and phenotypes, such as Lynch syndrome and familial adenomatous polyposis (FAP). Familial CRCs, which account for up to 30% of CRCs, have no identifiable germline mutation or specific pattern of inheritance, but higher-than-expected incidence within a family. Since the discovery that certain genotypes can lead to development of CRC, thousands of mutations have now been implicated in CRC. These new findings have enhanced our ability to identify at-risk patients, initiate better surveillance, and take preventative measures. Given the large number of genes now associated with hereditary and familial CRCs, clinicians should be familiar with the alphabet soup of genes to provide the highest quality of care for patients and families.

Keywords

- colorectal cancer
- hereditary
- familial
- genetic

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States with over 132,000 new cases diagnosed each year.¹ The majority of CRCs are sporadic (i.e., arise from nonhereditary, spontaneous mutations) but up to one-third of cases are familial or hereditary (► **Fig. 1**). While the terms “familial” and “hereditary” are often used interchangeably, “hereditary” CRCs are technically a subset of familial CRCs that describe cases (< 5%) with identifiable genetic signatures, penetrance, and transmission. Prototypical examples include the two most common and well-described hereditary syndromes: Lynch syndrome and familial adenomatous polyposis (FAP). “Familial” CRCs describe the remainder of cases (range, 10–30%) that have no specific patterns of inheritance or gene mutations but higher-than-expected incidence within a family. Familial CRCs are particularly challenging to manage because the genotype-to-phenotype pathway is not completely understood and likely driven by complex gene–gene and gene–environment interactions.

Since the discovery of the adenomatous polyposis coli (APC) gene in 1987,² the alphabet soup of genes implicated

in familial and hereditary CRCs has increased exponentially with rapidly advancing techniques that include genome-wide association studies (GWAS). Understanding the role of genetic mutations in familial and hereditary CRCs is critically important because it allows for more precise (1) identification, (2) surveillance, and (3) prevention of CRC in at-risk individuals and family members. This article will review our current understanding of genetic mutations in familial and hereditary CRC under this framework.

Hereditary Colorectal Cancer

Hereditary CRCs have identifiable genetic mutations and are traditionally classified as nonpolyposis or polyposis syndromes, based on the number of polyps found in the colon and rectum. Nonpolyposis syndrome includes hereditary nonpolyposis CRC (HNPCC or Lynch syndrome). Polyposis syndromes include FAP, attenuated FAP (aFAP), MUTYH-associated polyposis (MAP), polymerase proofreading-associated polyposis (PPAP), juvenile polyposis syndrome (JPS), Peutz–Jehgers syndrome (PJS), phosphatase and tensin homolog (PTEN)-hamartoma tumor

Fig. 1 Distribution of sporadic, familial, and hereditary colorectal cancers.

syndrome, and hyperplastic polyposis (HPP) (► **Table 1**). Each of these syndromes exhibits a significantly increased risk of developing CRC and extracolonic carcinomas.

Nonpolyposis Syndromes

Hereditary Nonpolyposis CRC

HNPCC, or Lynch syndrome, is the most common hereditary CRC and an autosomal-dominant disorder with 90% penetrance caused by germline mutations in DNA mismatch repair genes (MMR).³ The disease is named after Dr. Henry Lynch, who first suspected an inheritable mutation after studying two families afflicted with many cancers, including CRC, in 1966.⁴ In 1993, a germline mutation in the *MMR* gene *hMSH2* was identified and linked to Lynch syndrome.⁵ Lynch patients

have an approximately 80% lifetime risk of developing CRC at a median age of 42 years and are at high-risk for extracolonic cancers, including ovarian, gastric, endometrial, hepatobiliary, and small bowel carcinomas.⁶

Genetics: Lynch syndrome is characterized by specific mutations in DNA MMR genes, including *hMLH1*, *hPMS1*, *hPMS2*, *hMSH2*, *hMSH3*, and *hMSH6*. The MMR system is designed to correct errors in base pairing that inevitably occur during normal DNA replication. These base substitutions and small insertion-deletion mismatches tend to occur in regions of repetitive nucleotide sequences called DNA microsatellites. Mutations within these regions generate microsatellite instability (MSI), which can affect cell growth and apoptosis pathways that lead to carcinogenesis.^{7,8} MSI is not specific, however, for Lynch syndrome and as many as 15% of sporadic CRC have MSI. In these cases, MSI results from secondary alterations, such as aberrant DNA methylation of *MMR* gene promoters resulting in loss of gene expression.

Identification, surveillance, and preventative measures: Current strategies to identify patients with Lynch syndrome include (1) family history-based screening tools (Amsterdam and Bethesda criteria), (2) tumor-based testing (MSI and immunohistochemistry [IHC]), and (3) prediction models (MMRpredict, MMRpro, and PREMM). The Amsterdam and Bethesda criteria are well-described and use family history of cancers to determine whether further genetic testing for Lynch syndrome should be pursued.^{9–11} Tumor-based techniques require tissue samples and use IHC and polymerase chain reaction to test for MMR protein deficiency or MSI, respectively.¹² If these tumor-based tests are suggestive for Lynch syndrome, then the patient's germline DNA isolated from white blood cells can be further sequenced for specific

Table 1 Summary of hereditary colorectal cancers

Condition		Inheritance	Gene	Identification	Surveillance	Prevention
Nonpolyposis	Lynch	Autosomal dominant	<i>hMLH1</i> , <i>hPMS1</i> , <i>hPMS2</i> , <i>hMSH2</i> , <i>hMSH3</i> , <i>hMSH6</i>	Individuals with positive family history (Amsterdam/Bethesda criteria), tumor-based testing or prediction for MMR mutations using prediction models	Colonoscopy yearly, beginning at age 20–25 y	Prophylactic surgery may be offered for high polyp burden, inability to provide surveillance or endoscopic treatment, or patient preference
Polyposis: Adenomatous polyps	FAP	Autosomal dominant	<i>APC</i>	Individuals with > 10 polyps, first-degree relative with FAP/aFAP, presence of adenomas with extracolonic features of FAP	Colonoscopy yearly, beginning at age 12 y	Prophylactic surgery advised by age 20 y
	aFAP	Autosomal dominant	<i>APC</i>		Colonoscopy yearly, beginning in late teenage years	Prophylactic surgery may be offered for high-polyp burden, inability to provide surveillance or endoscopic treatment, or patient preference
	MAP	Autosomal recessive	<i>MUTYH</i>	Individuals with > 10 polyps, presence of adenomas with extracolonic features of MAP,	Colonoscopy yearly, beginning at age 25 y	Prophylactic surgery may be offered for high-polyp burden, inability to provide

Table 1 (Continued)

Condition		Inheritance	Gene	Identification	Surveillance	Prevention
				features of FAP but lack APC germline mutation or dominant inheritance pattern		surveillance or endoscopic treatment, or patient preference
	PPAP	Autosomal dominant	<i>POLE</i> <i>POLD1</i>	Individuals with < 100 adenomatous polyps who do not fulfill criteria for other syndrome	To be determined	To be determined
Polyposis: Hamartomatous polyps	PJS	Autosomal dominant	<i>LKB1</i> (<i>STK11</i>)	Individuals with early-onset pigmented lesions, first-degree relative with PJS or upper/lower GI tract hamartomatous polyps consistent with PJS pathology	Colonoscopy every 2–3 y, beginning with onset of symptoms or in late teens	Prophylactic surgery may be offered for high-polyp burden, inability to provide surveillance or endoscopic treatment, or patient preference
	JPS	Autosomal dominant	<i>SMAD4</i> , <i>BMPR1A</i>	Juvenile individual with > 10 juvenile polyps or any patient with juvenile polyps with a first-degree relative diagnosed with JPS	Colonoscopy every 2–3 y, beginning with onset of symptoms or in late teens	
	CS	Autosomal dominant	<i>PTEN</i>	Individuals with a first-degree relative with CS or a variety of colonic polyps and extracolonic manifestations	Colonoscopy every 2–3 y, beginning at age 30 y	
Polyposis: Hyperplastic polyps	HPP	Unknown	Unknown	Usually found incidentally	Colonoscopy yearly after diagnosis	

Abbreviations: aFAP, attenuated FAP; CS, Cowden syndrome; FAP, familial adenomatous polyposis; GI, gastrointestinal; HPP, hyperplastic polyposis; JPS, juvenile polyposis syndrome; MAP, MUTYH-associated polyposis; MMR, mismatch repair genes; PJS, Peutz–Jehgers syndrome; PPAP, polymerase proofreading associated polyposis.

MMR mutations. Prediction models were developed to provide even better estimates of the likelihood of MMR mutations. MMRpredict and PREMM, developed in 1996 and 2011, respectively, use clinical information such as sex, age, and family history to determine the risk of an MMR mutation.^{13–15} MMRpro, developed in 2006, is the only model that includes genetic information from tumor-based MMR and germline testing.¹⁴ All of these models, particularly MMRpredict, predict MMR mutations more accurately than family history-based models.¹⁶ Ultimately, germline testing for mutations in the MMR genes is required to establish the final diagnosis.

CRC in Lynch syndrome is aggressive and can develop within 2 years of a negative colonoscopy.^{17,18} Screening colonoscopies are therefore recommended to start by age 25 or 2 to 5 years earlier than the youngest affected relative's age at diagnosis. Screening frequency continues every 2 years until age 40 and then annually.¹⁹ If an adenoma is found on colonoscopy before the age of 40, then the frequency is increased to annually.

Prophylactic surgery by either total abdominal colectomy or proctocolectomy can be offered to patients, although not

absolutely indicated as with FAP. If CRC were to develop, surgical options include segmental colectomy, total abdominal colectomy with ileorectal anastomosis (IRA), or proctocolectomy with ileal pouch-anal anastomosis (IPAA). If the colon and rectum are left, surveillance colonoscopies are imperative as patients with HNPCC have a 40% chance of developing metachronous CRC within 10 years of segmental colectomy.²⁰

Polyposis Syndromes

Adenomatous Polyps (FAP, aFAP, MAP, and PPAP)

Familial Adenomatous Polyposis and Attenuated FAP

FAP is the second most common hereditary CRC and accounts for less than 1% of all CRC.²¹ FAP is an autosomal dominant, 100% penetrant disorder caused by a germline mutation of the *APC* gene.²² Patients have a 100% lifetime chance of CRC development.²³ The classic phenotype is the presence of numerous colorectal adenomatous polyps (> 100) by adolescence and CRC by an average age of 40.²⁴ FAP is also associated

with extracolonic disorders, including upper gastrointestinal carcinomas, desmoid tumors, epidermoid cysts, osteomas, congenital hypertrophy of the retinal pigmented epithelium (CHRPE), and papillary thyroid cancers. aFAP is a less severe form of FAP, characterized by fewer polyps (< 100) and onset of CRC at an average age of 59 years.²⁵

Genetics: FAP results from a mutation in the tumor-suppressing *APC* gene, which is located on chromosome 5q21. Over 1,000 different germline mutations of *APC* have been identified that result in truncation of the *APC* protein and thus its inactivation or dysfunction.²⁶ The *APC* protein normally binds to cytoplasmic B-catenin and prevents its translocation to the nucleus. When *APC* is inactivated, the accumulation of B-catenin leads to transcriptional activation of several genes that promote cell growth, which leads to adenomatous polyp formation and eventual transformation to carcinoma.²⁷

Genetic studies have linked specific mutations in the *APC* gene to clinical phenotypes. For example, mutations between codons 169 and 1,393 have been associated with classic FAP while aberrations on the tail ends (5' to codon 158 and 3' to codon 1,596) are linked to aFAP.²⁸ Mutations between codons 1445 and 1,578 and 463 and 1,444 are observed with desmoid tumors and CHRPE, respectively. Interestingly, somatic *APC* mutations are found in up to 80% of sporadic CRCs, which highlights the carcinogenic role of *APC*.²⁹

Identification, surveillance, and preventative measures: At-risk patients include individuals with 10 or more polyps found on colonoscopy, a first-degree relative diagnosed with FAP or aFAP, and history of extracolonic FAP-associated features, such as duodenal adenomas and desmoids. Genetic testing for germline mutations in the *APC* gene is the definitive method to diagnose FAP. Once a mutation is identified, further genetic testing can then be offered to family members of the patient, starting at puberty or age 12, to determine if they also carry the specific genetic mutation. Identifying affected individuals allows for implementation of appropriate surveillance and preventative measures for the patient, family, and future generations.

Surveillance for patients diagnosed with FAP begins with colonoscopies at puberty or age 12 and EGD at age 20.³⁰ Esophagogastroduodenoscopy (EGD) screening is essential, as studies have shown over 95% of patients with FAP develop duodenal adenomas³¹ and duodenal cancer is the second most common cause of death in FAP patients.³⁰ Patients with aFAP should be screened with annual colonoscopies starting in the late teenage years.¹⁹

Prophylactic surgery is recommended for all patients with FAP by the age of 20. Patients with severe polyposis (> 1,000 colonic polyps), obstruction or CRC should have surgery as soon as possible. Surgical options include total abdominal colectomy with IRA, proctocolectomy with IPAA, and proctocolectomy with end ileostomy.¹⁹ If the IRA is performed, then the remaining rectum must undergo surveillance with at least yearly flexible endoscopy.¹⁹ If IPAA is performed, the ileal pouch should undergo pouchoscopy every 3 years or more frequently if polyp burden was extensive¹⁹ since neoplasia can occur in the pouch and in the anal transition

zone.³² At this time, aFAP patients do not absolutely require prophylactic colectomy as most patients can be managed with endoscopic surveillance and polypectomies. However, up to two-thirds of aFAP patient eventually require colectomy.³³

MUTYH-Associated Polyposis

MAP is an autosomal recessive form of FAP with an incidence of 1:10,000³⁴ and near 100% penetrance³⁵ caused by mutations in the MutY homolog (*hMUTYH*) gene.³⁶ MAP is also associated with extracolonic disease, including duodenal adenomas, desmoid tumors, fundic gland polyps, and other extracolonic cancers such as ovarian, bladder, and endometrial cancers.^{37,38}

Genetics: MAP results from biallelic mutations in the *MUTYH* gene, which is a base excision repair gene that normally ensures proper coupling during DNA replication. Mutations in the *MUTYH* gene result in transversion of G:C to T:A coupling in the *APC* gene or the *KRAS* gene.³⁹ The two most common *MUTYH* gene mutations are Y179C and G396D with the former genotype associated with a more severe form of the disease.⁴⁰ These genetic mutations lead to the adenomatous polyposis with *APC* mutations and serrated polyposis with *KRAS* mutations.³⁹ Increased risk of CRC has also been reported in carriers of *MutY* gene mutations.³³

Identification, surveillance, and preventative measures: At-risk patients include individuals with 10 or more colorectal adenomas on colonoscopy, adenomas with concurrent extracolonic features associated with MAP, or clinical features of FAP but no identifiable *APC* germline mutation or autosomal dominant mode of inheritance. If a patient is considered at-risk, the patient's serum should undergo DNA sequencing for MutY homolog gene mutations. If the diagnosis of MAP is confirmed, the patient should be referred for genetic counseling and screening colonoscopy. At-risk family members can be offered genetic testing for MutY mutations, including siblings of the index patient and their offspring, as carriers of MutY mutations are at higher-risk for CRC development.

Surveillance colonoscopy for MAP patients should commence by age 25 and be repeated every 1 to 2 years. If colonic adenomas are found and endoscopically removable, surgical resection is not necessary.¹⁹ For family members who test positive for biallelic *MUTYH* mutations or siblings of a known MAP patient, colonoscopy should begin at age 25 and be repeated every 2 to 3 years.¹⁹

Prophylactic surgery is not absolutely indicated, but may be offered based on patient preferences, surveillance capability, and polyp burden. Surgical resection is recommended if polyp burden cannot be managed endoscopically or carcinoma is found. Surgical options include segmental resection, total abdominal colectomy with the IRA, and proctocolectomy with IPAA. Surveillance following resection is similar to FAP and dependent on reconstruction technique.¹⁹

Polymerase Proofreading-Associated Polyposis

PPAP is a highly penetrant, autosomal-dominant disorder characterized by less than 100 adenomatous polyps.³⁵ The syndrome is linked to germline mutations in DNA polymerase

ϵ and δ with the latter mutation also accounting for an increased risk of endometrial cancer. These mutations disrupt the function of the proofreading exonuclease of DNA polymerase, which repairs mismatched nucleotides during replication.⁴¹ Loss of proofreading may result in secondary mutations in the *APC* and *KRAS* genes that lead to adenomatous polyposis. The majority of CRC cases are diagnosed in the 4th and 5th decades of life.⁴¹ PPAP is a recently discovered syndrome and no formal screening or surveillance guidelines have been established.

Hamartomatous Polyps (JPS, PJS, and PTEN)

Juvenile Polyposis Syndrome

JPS is a sporadic and inherited disorder (autosomal dominant) with a 1:100,000 incidence and 90% penetrance.³⁵ JPS is characterized by the presence of at least five juvenile polyps in the colon or any number of juvenile polyps in a patient with a family history of JPS.¹⁹ JPS often presents with rectal bleeding, anemia, or polyp prolapse before the age of 10. Histologically, juvenile polyps are hamartomas with hyperplastic stroma, lamina propria, and cystic glands but without smooth muscle that anchor poorly to the colonic wall. Up to half of juvenile polyps in JPS have some degree of dysplasia, which can transform to adenocarcinoma.

Genetics: JPS has been linked to mutations in *SMAD4* and *BMPR1A*. *SMAD4* and *BMPR1A* are located on chromosomes 18q21 and 10q22, respectively, and both are involved in the TGF- β signaling pathway which regulates cell proliferation. Mutations in either gene can lead to polyposis, dysplasia, and eventually adenocarcinoma. Up to 60% and 15% of JPS patients in the United States have germline mutations in *SMAD4* and *BMPR1A*, respectively.^{42,43}

Identification, surveillance, and preventative measures: At-risk patients include any pediatric patient found to have greater than five juvenile polyps on colonoscopy or any patient with juvenile polyps with a first-degree relative diagnosed with JPS. Family members, especially offspring, of known patients with *SMAD4* mutations should undergo genetic testing within the first 6 months of life due to the early onset risk of hereditary hemorrhagic telangiectasias.¹⁹

Patients with JPS have a lifetime risk of up to 50 and 20% of developing CRC or upper gastrointestinal cancer, respectively.^{44,45} Surveillance with EGD and colonoscopy are recommended from the time of diagnosis or starting at the age of 15 (whichever is earliest) and repeated every 2 years.¹⁹ Polyps should be managed endoscopically. However, in cases where polyps are too numerous/large or severe symptoms are present (anemia, rectal bleeding, or diarrhea), total colectomy with IRA is the procedure of choice. Currently, there are no data that supports the role for prophylactic surgery based upon germline mutation.

Peutz-Jeghers Syndrome

PJS is an autosomal-dominant disorder with an incidence of 1:200,000 and 95% penetrance,³ characterized by multiple gastrointestinal hamartomatous polyps, mucocutaneous pigmentation, and extracolonic cancers. Diagnosis of PJS

requires two of three criteria: (1) perioral, buccal, or genital melanin pigmentation, (2) gastrointestinal hamartomatous polyposis, and (3) family history of PJS.¹⁹ Polyps are found predominantly in the small intestine, although also present in the colon in half of cases.⁴⁶ The polyps are hamartomas with smooth muscle in the submucosa but may develop adenomatous changes, dysplasia, and malignant transformation.⁴⁷

Genetics: PJS is caused by germline mutations of *LKB1* (also known as *STK11*) on chromosome 19. *LKB1* is a tumor suppressor gene and its mutation results in an absent or dysfunctional serine-threonine kinase enzyme that leads to unregulated cell proliferation and hamartomatous polyposis. There is a 40% lifetime risk of CRC in PJS patients.¹⁹

Identification, surveillance, and preventative measures: At-risk individuals for PJS include patients with early-onset pigmented lesions, PJS-related hamartomatous polyps, and a first-degree relative with PJS. For suspected patients, genetic testing should be performed to evaluate for *LKB1* gene mutations.

PJS patients should begin endoscopic surveillance in the late teen years with EGD, capsule endoscopy and colonoscopy, and be repeated every 2 to 3 years.¹⁹ Intraoperative enteroscopy was previously recommended when laparotomy was required to reduce polyp burden and to minimize future bowel resections and major laparotomies.⁴⁸ Intraoperative enteroscopy has more recently been replaced by double balloon enteroscopy, which is an effective and less-invasive technique for surveillance and endoscopic resection of small bowel polyps.⁴⁹

PTEN Hamartoma Tumor Syndrome

PTEN-hamartoma tumor syndrome, also known as Cowden syndrome (CS), is an autosomal-dominant syndrome with an incidence of 1:200,000 and a penetrance of > 90%³ characterized by a colonic polyps, macrocephaly, and extracolonic neoplasms involving the thyroid, breast, uterine, and skin. Trichilemmomas, which is a benign cutaneous skin neoplasm, is pathognomonic for this disease. CS confers a lifetime 9 to 18% risk of developing CRC.¹⁹ Colonic polyps range in morphology and include adenomas, hamartomas, fibromas, lipomas, neurofibromas, and ganglioneuromas.

Genetics: CS is associated with germline mutations of the *PTEN* gene. *PTEN* is a tumor suppressor gene on chromosome 10q23 that codes for a phosphatase that inhibits the mTOR/AKT signaling pathway.⁵⁰ AKT and mTOR signaling pathways are critical for cell proliferation, cell cycle progression and apoptosis.⁵¹ *PTEN* mutations lead to increased mTOR/AKT signaling, cellular proliferation, and eventually polyposis in the large bowel. Other non-*PTEN* gene mutations implicated in CS include the p53 tumor suppressor genes *SDH* and *KLLN*, which are also located on chromosome 10q23.⁵²

Identification, surveillance, and preventative measures. At-risk patients for CS include individuals that have colonic polyps and extracolonic disorders characteristic for CS or a first-degree relative with CS. For patients with CS, surveillance colonoscopy is initiated in the third decade of life and continued every 3 years.⁵³ Polyps are managed endoscopically. Surgical resection is recommended for high-polyp

burden or if limited endoscopic options. Currently, prophylactic surgery is not recommended on the basis of CS diagnosis alone.

Hyperplastic Polyps

Hyperplastic Polyposis

HPP is a rare condition characterized by multiple, large hyperplastic polyps found throughout the colon. Diagnostic criteria for HPP include at least 30 cumulative and synchronous hyperplastic polyps of any size throughout the colon.³³ Recently, sessile serrated polyps have been added to the histologic type included in this syndrome. HPP is usually diagnosed incidentally during screening colonoscopy and studies have observed a 35% risk of CRC.⁵⁴ The genetic

etiology is unknown and no mutations have been identified to aid in diagnosis. No definitive surveillance strategy has been agreed upon but colonoscopy every 1 to 2 years after diagnosis has been recommended.³³

Familial CRC

Familial CRCs encompass a larger proportion of CRC cases than hereditary CRCs and significantly less is known about their genetic etiologies (► **Table 2**). In contrast to hereditary CRCs with discrete genotype–phenotype relationships (i.e., FAP and Lynch), familial CRCs represent an as-yet poorly defined disorder that likely involve complex gene–gene and gene–environment interactions. The optimal strategies for identification, surveillance, and preventative measures for

Table 2 Summary of familial colorectal cancer-associated genes

Gene	Symbol	Location	Risk for development of CRC
Adenomatous polyposis coli	<i>APC</i>	5q21	Increases risk for adenomas and FAP
Colorectal-associated cancer 1	<i>CRAC1/HMPS</i>	15q13.3	Associated with hyperplastic polyposis
Cyclin D1	<i>CCND1</i>	11q13.3	Causes younger onset of Lynch syndrome; protective effect from sporadic cancer with exposure to estrogen
Cytochrome P450 family 24 subfamily A	<i>CYP24A1</i>	20q13.2	Associated with increase in site-specific CRC risk
Cytochrome P450 family 24 subfamily B	<i>CYP24B1</i>	20q13.2	Alters proximal CRC risk when associated with UV-spectrum sun exposure
Glutathione S-transferase mu 1	<i>GSTM1</i>	1p13.3	Modifies presentation of Lynch syndrome, ethnic and smoking factors modulate population risk in null allele carriers
Glutathione S-transferase theta 1	<i>GSTT1</i>	22q11.23	
Hemochromatosis protein	<i>HFE</i>	6p22.2	Modifies presentation of Lynch syndrome
Insulin-like growth factor 1A	<i>IGF-1</i>	12q23.2	Modifies presentation of Lynch syndrome, possibly interacting with diabetes
Insulin-like growth factor binding protein-3	<i>IGFBP-3</i>	7p12.3	Modifies colon cancer risk interacting with diabetes
N-acetyltransferase 1	<i>NAT1</i>	8p22	Modifies presentation of FAP and affects sporadic cancer risk in association with environmental factors
N-acetyltransferase 2	<i>NAT2</i>	8p22	
Ornithine decarboxylase 1	<i>ODC</i>	2p16.3	Modifies adenoma risk interacting with NSAID use
Selenoprotein P	<i>SEPP1</i>	5p12	Modifies adenoma risk interacting with certain dietary factors and smoking
Thioredoxin reductase 1	<i>TXNRD1</i>	12q23.3	
Transcription factor 7-like 2 isoform 2	<i>TCF7L2</i>	10q25	Modifies CRC risk, possibly in association with diabetes
Transforming growth factor, β receptor 1	<i>TGFBRI</i>	9q22.33	Modifies CRC risk in high-risk families
Tumor protein 53	<i>TP53</i>	17p13.1	Causes Li–Fraumeni syndrome; certain alleles also modify sporadic site-specific colon cancer risk in gender-dependent manner

Abbreviations: CRC, colorectal cancer; FAP, familial adenomatous polyposis; NSAID, nonsteroidal anti-inflammatory drug; UV, ultraviolet.
Source: Adapted from Jasperson et al.³³

at-risk patients with familial CRC are currently subject for debate. Recent studies on these variably penetrant but more common cases of CRC, however, have yielded more data to better inform our strategies in caring for patients with familial CRC.

High-Risk Familial, Nonsyndromic CRC

Familial CRC Type X

Familial CRC type X is an autosomal-dominant disorder that closely resembles the Lynch syndrome. These patients fulfill the Amsterdam criteria for Lynch syndrome, but lack many of the typical clinical and genetic features of a traditional Lynch patient. First, type X patients do not carry a DNA MMR deficiency and therefore do not exhibit MSI.⁵⁵ Second, type X patients demonstrate a lower lifetime risk of developing CRC compared with Lynch syndrome (2.3 vs. 6.1 incidence ratio compared with the general population) and have an average 10-year later onset of CRC.^{55,56} Third, type X patients have no additional risk of extracolonic malignancies such as Lynch patients.³³ The classification of type X patients will likely differentiate when the gene(s) responsible for this disease are identified. Recent studies have discovered several genetic mutations in type X families that may be responsible, including RSP20, SEMA4A, HNRNPA0, and WIF1.⁵⁶ The diverse nature of these genes and lack of a consistent mutation suggest that type X is likely a heterogeneous condition.⁵⁶

Common Familial Risk CR

Patients with CRC and a family history of CRC, but without an identifiable germline mutation causing a high-penetrance syndrome, are currently classified as having common familial risk CRC. Studies have shown that having a first-degree relative over the age of 50 with CRC increases the risk of developing CRC by two to threefold.³³ Additionally, having a first-degree relative under the age of 45 or two first-degree relatives with CRC increases an individual's CRC risk by three to sixfold.⁵⁷

Genetics: In contrast to hereditary CRCs syndromes which are usually highly penetrant autosomal-dominant disorders, common familial risk CRCs likely arise from less-penetrating genetic mutations and polymorphisms with significant gene–

gene and gene–environment interactions. Genome wide-association studies (GWAS) have become integral in the genetic analysis of familial CRC. GWAS compare affected and nonaffected individuals by entire genomes using micro-array technology. Variations in single nucleotide polymorphisms (SNPs)⁵⁸ may be more frequent in affected individuals and therefore associated with the disease.⁵⁹ GWAS have recently identified between 10 and 170 common SNPs that increase the risk of CRC. The specific SNPs identified in these studies did not confer a large increase in CRC risk individually, but were found to have additive risk when found together in certain individuals. For example, the odds ratio of developing CRC might be 1.10 in an individual with one SNP but coinheritance of multiple SNPs increased the odds ratio to > 2.0.³³ SNPs may not directly change a protein product, but through gene–gene interactions may alter noncoding regions of the genome, which then disrupt other genes that increase CRC risk. Gene–environment interactions also play an important role and SNPs may be modified by a patient's age, sex, medication intake, smoking, and environmental factors.³³

Identification, surveillance, and preventative measures: At-risk patients include any individual with a first-degree relative with CRC who does not fulfill criteria for a hereditary syndrome. Currently, no specific genetic markers are available to test for common familial risk CRC. Screening and surveillance are based completely on family history (► Table 3).

Predicting Risk for Future Cancer-Based Mutation

Several prediction models have been developed to identify high-risk individuals for familial and hereditary CRC (► Table 4). Many of these models focus on Lynch syndrome and use clinical information and family history to predict the likelihood of MMR mutations in patients who might benefit from further genetic testing. Only one model (MMRpro) includes both clinical and genetic information from tumor-based testing.

Though many risk prediction models have been created for CRC, none have been found to adequately assess the risk

Table 3 Screening recommendations for familial colorectal cancer

Risk factor	Screening recommendation
Single first-degree relative > 60 y of age at time of CRC or advanced adenoma diagnosis	Continue with average risk screening for CRC with colonoscopy every 10 y starting at age 50 y
Single or multiple second- or third-degree relatives with CRC or advanced adenoma diagnosis	
Single first-degree relative < 60 y of age at time of CRC or advanced adenoma diagnosis or two first-degree relatives of any age with CRC or advanced adenomas	Start screening colonoscopy every 5 y beginning at age 40 or 10 y prior to age at youngest diagnosis of affected relative (whichever is earliest)

Abbreviations: CRC, colorectal cancer.

Source: Adapted from Rex DK, Johnson DA, Anderson JC, et al; American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009;104(3):739–750.

Table 4 Summary of colorectal cancer prediction models

Model	Model components			Outcome	Strengths	Limitations
	Family history	Clinical and environmental factors	Genetics			
MMRpredict (1996)	First-degree relative with endometrial cancer, age at CRC diagnosis of first-degree relative	Sex, age at CRC diagnosis, tumor location, presence of multiple CRCs	None	Predicts risk of having MMR mutation	User friendly, web version available	Does not consider family history outside of first degree; does not accurately predict individuals with strong family history or high-risk genetic mutation; only applies to Lynch syndrome
Harvard cancer risk index (2000)	First-degree relative with colon CA (yes/no)	BMI, FOBT, and sigmoidoscopy, aspirin, IBD, folate, vegetables, alcohol, height, physical activity, estrogen replacement, OC, red meat, fruits, fiber, saturated fat, cigarette smoking	None	Predicts 10 y risk of CRC	User friendly	Not applicable to rectal cancer. Does not consider family history beyond first-degree relatives and not useful for people with high-risk genetic mutation
Imperiale et al (2003)	None	Age, sex, most advanced distal nonmalignant neoplasm (no polyps; hyperplasia; tubular adenoma < 1 cm; advanced lesions: tubular adenoma > 1 cm, any polyp with villous histology or severe dysplasia)	None	Predicts risk of proximal CRC	Improves efficiency of CRC screening	Limited to those undergoing sigmoidoscopy; not applicable to those under 50 y; not applicable to individuals with strong family history or high-risk genetic mutation
Chen et al, MMRpro (2006)	First- and second-degree relatives: relationship to first affected family member; history of CRC or endometrial cancer (yes/no); age at diagnosis	Age, race/ethnicity	MSI status, MLH1, MSH2, MSH6	Predicts risk of MLH1, MSH2, or MSH6 mutation	Includes family history to second degree; uses genetic markers	Does not consider family history beyond second degree; not applicable to PMS2 mutation carriers; does not estimate risk of metachronous CRC; only applies to Lynch and not applicable to MUTYH mutation carriers
Driver et al (2007)	None	Age, smoking, alcohol, BMI	None	Predicts 20 y CRC risk for men	User friendly, based on large sample	Limited to males only; not applicable to individuals with strong family history or with high-risk genetic mutation
Freedman et al (2009)	First-degree relative with CRC (yes/no), number of first-degree	Age, sex, sigmoidoscopy, and colonoscopy, current leisure time activity, aspirin, NSAIDs,	None	Predicts 5-, 10-, 20 y, and lifetime risk of CRC for individuals > 50 y	User friendly, web version available; based on large sample	Not applicable to those under 50 y; does not consider family history beyond first degree; not applicable to people with

Table 4 (Continued)

Model	Model components			Outcome	Strengths	Limitations
	Family history	Clinical and environmental factors	Genetics			
	relatives with CRC (0, 1, ≥ 2)	cigarette smoking, vegetables, BMI, and hormone replacement				strong family history or with high-risk genetic mutation
Wei et al (2009)	First-degree relative with CRC (yes/no)	Age, sigmoidoscopy, and colonoscopy, physical activity, aspirin, cigarette smoking, processed meat or red meat consumption, folate, height, BMI, and hormone replacement	None	Predicts CRC risk for women 30–70 y	User friendly; based on large sample	Not applicable to men or any women older than 70 y; does not consider family history outside of first degree; not applicable to people with strong family history or with high-risk genetic mutation
Ma et al (2010)	None	Age, BMI, physical activity, smoking, alcohol use	None	Predicts 10-y CRC risk for Japanese men	User friendly	Not applicable to non-Japanese patients or Japanese females; not applicable to people with strong family history or high-risk genetic mutation
Cleveland clinic tool (2010)	First- and second-degree relatives; relationship to first affected family member; history of CRC and polyps (yes/no); age at CRC dx; age at poly-dx	Age, sex, ethnicity, weight, height, CRC screening, fruit, vegetables, smoking, exercise, personal history of CRC and polyps	None	Provides CRC risk scores	User friendly, web version available	Does not predict cumulative risk over a specified period
PREMM (2011)	Sex of the first family member ever diagnosed with CRC; family history of CRC, endometrial, and other Lynch-associated carcinomas	Patient history of CRC, endometrial, and other Lynch-associated carcinomas	None	Estimates likelihood of having MMR mutation	User friendly, web version available	Does not accurately predict people with strong family history or high-risk genetic mutation; only applies to Lynch syndrome

Abbreviations: BMI, body mass index; CA, cancer; CRC, colorectal cancer; FOBT, fecal occult blood test; IBD, inflammatory; MMR, mismatch repair genes; MSI, microsatellite instability; NSAID, nonsteroidal anti-inflammatory drug; OC, oral contraceptives.
Source: Adapted from Win et al.⁶⁰

across the entire population or be accepted for generalized use. Win et al demonstrated that these predictive models overestimated or underestimated CRC risk for key demographic groups.⁶⁰ For example, the Harvard cancer risk index was not applicable to patients with high-risk genetic mutations and the model created by Freedman et al applies only to individuals over 50 years of age. Even more concerning is that only one model (MMRpro) incorporates genetic information into risk calculations. Future prediction models for CRC will undoubtedly begin including more genetic data as more genes are identified.

Absolute Indication for Prophylactic Surgery

Prophylactic surgery is absolutely indicated in classic FAP with germline APC mutations due to the 100% lifetime risk of developing CRC. At this time, prophylactic surgery is relatively indicated in Lynch syndrome. Lynch patients have an 80% lifetime risk of CRC⁶ but can be offered prophylactic surgery if there is concern for endoscopic screening adherence or due to patient preference.⁶¹ For Lynch patients, prophylactic surgery would include total abdominal colectomy with IRA or proctocolectomy with IPAA. If rectum is left, continued surveillance is mandated. Diagnosis of CRC would necessitate therapeutic surgery and these options include segmental colectomy, total abdominal colectomy with IRA and proctocolectomy with IPAA.

Currently, there is no evidence to justify prophylactic surgery for any other hereditary or familial disorders based upon the presence of a genetic mutation alone; however, prophylactic surgery should be considered for patients with non-FAP and non-Lynch hereditary CRCs if there is concern for an aggressive family cancer history, poor endoscopic screening adherence, or even patient fears. These cases must be determined on an individual basis.

Conclusion

The management of familial and hereditary CRC has improved significantly with the identification of specific gene mutations and genotype-phenotype pathways. The discovery of the genes behind Lynch and FAP are model examples of how recognition of genetic mechanisms can enhance strategies in identifying at-risk patients, providing effective surveillance, and implementing preventative measures. Unraveling the genetic framework of familial CRCs will be a much-anticipated area of research that will improve our overall understanding of CRC pathogenesis and ability to provide the best, individualized care for patients and families with CRC.

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