Colorectal Cancer Genetics and Hereditary Colorectal Cancer Syndromes for the Practicing General Surgeon

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KEYWORDS

• Colorectal cancer • Genetics • Hereditary colorectal cancer syndromes

KEY POINTS

- All colorectal cancers should undergo universal tumor screening for mismatch repair deficiency and patients with early-onset CRC or suggestive family history should undergo germline testing.
- Cascade testing (targeted relative testing) is recommended for at-risk family members of patients diagnosed with a hereditary CRC syndrome to identify germline pathogenic variants.
- Lynch syndrome patients with CRC may undergo an extended or segmental colonic resection after shared decision-making discussions, although immunotherapy is changing surgical management.
- Familial adenomatous polyposis patients require colorectal surgery to reduce the risk of CRC, with timing and surgery type individualized based on disease and patient factors.
- Management of all hereditary CRC syndromes requires lifelong surveillance and multidisciplinary care to minimize death from cancer and to maximize quality of life preservation.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and is the second most common cause of cancer-related death in the United States.[1] Most CRCs arise sporadically (60%–70%), although CRC can also be familial or hereditary. Familial CRC is defined as CRC that clusters in families without a known hereditary cancer syndrome or identifiable germline pathogenic variant (PV, 25%–30%). Hereditary CRC is

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Surg Clin N Am 106 (2026) 481–500
https://doi.org/10.1016/j.suc.2026.03.005 **surgical.theclinics.com**

Abbreviations	
APC	adenomatous polyposis coli
cCR	complete clinical response
CIMP	CpG island methylator phenotype
CIMP-H	CIMP-high
CIN	chromosomal instability
CRC	colorectal cancer
dMMR	MMR deficiency
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
ER	extended resection
FAP	familial adenomatous polyposis
GI	gastrointestinal
JPS	juvenile polyposis syndrome
LARCs	locally advanced rectal cancers
LS	Lynch syndrome
MAP	MUTYH-associated polyposis
MMR	mismatch repair
MMR IHC	mismatch repair immunohistochemistry
MSI	microsatellite instability
MSI PCR	microsatellite instability polymerase chain reaction
MSI-H	MSI-high
MSI-L	MSI-low
PJS	Peutz-Jeghers syndrome
PV	pathogenic variant
SPS	serrated polyposis syndrome
SR	segmental resection
TAC/IRA	total abdominal colectomy with ileorectal anastomosis
TPC/IPAA	total proctocolectomy with ileal-pouch anal anastomosis
UTS	universal tumor screening

related to a germline PV in a known cancer-causing gene and is passed down through generations. While only about 5% of CRCs are related to a hereditary cancer syndrome, it is important to note that all CRCs are due to genetic mutations.[2,3]

Understanding CRC genetics is important for many reasons including the opportunity to prevent cancer, optimize cancer treatment, guide surgical decision-making, and inform screening and surveillance of patients and their families. This article will review CRC carcinogenesis, pathology guidelines such as universal tumor screening (UTS), genetic testing guidelines, and hereditary CRC syndrome surveillance and management.

CARCINOGENESIS

Colonocyte genetic and epigenetic mutations accumulate over time and are key drivers of colorectal tumorigenesis. Genetic mutations can either be germline or somatic. Germline mutations can be passed down from parent to child and are incorporated in every cell of the patient's body. Somatic mutations occur in tumor cells only and are the result of a complex combination of environmental and genetic risk factors.[3,4] Epigenetic modifications, such as DNA methylation, are due to alterations in gene function, which do not change the DNA sequence but can cause molecular changes.[5] Colorectal stem cell mutations accumulate over time through a process called the adenoma-carcinoma sequence, which was first described by Fearon and Vogelstein.[6] This was the first major CRC tumorigenesis molecular pathway described and is also known as the chromosomal instability (CIN) pathway. The microsatellite instability (MSI) pathway and CpG island methylator phenotype (CIMP) pathway are 2 other major CRC tumorigenesis pathways.[3]

Chromosomal Instability Pathway

CIN is the most common CRC tumorigenesis pathway (65%–70%) and is a result of the gradual accumulation of small mutations and large chromosomal alterations that typically occur somatically in colonic crypt stem cells. This process occurs over about 10 to 15 years in a stepwise manner. The initial driver of the adenoma-carcinoma sequence is loss of the *APC* tumor suppressor gene, leading to adenoma formation. The first *APC* allele in a crypt stem cell obtains a somatic or inherited mutation, but the *APC* gene is not fully inactivated until the second allele is knocked out, through a process called loss of heterozygosity, rendering the *APC* gene inactive in the crypt stem cell.[3,6,7]

Additional mutations occur in several other driver genes including *KRAS* (Kirsten rat sarcoma viral oncogene homolog), *TP53* (tumor protein p53), and *SMAD4* (Mothers against decapentaplegic homolog 4). An activating mutation in the oncogene, *KRAS*, promotes further proliferation and progression to larger adenomas with tubulovillous or villous histology. The most common late event in this sequence is the loss of tumor suppressor, *TP53*, which removes the DNA damage checkpoint and subsequently leads to high-grade dysplasia and CRC development. Of note, the CIN pathway is the typical CRC carcinogenesis pathway for familial adenomatous polyposis (FAP), which is due to a germline *APC* PV.[3,6–8]

Microsatellite Instability Pathway

The second most common CRC pathway is the MSI pathway. Normally, mismatch repair (MMR) genes encode for MMR proteins, which are involved in a system that recognizes and repairs errors that occur during DNA replication. The most important genes and protein products in this system are *MLH1*, *MSH2*, *MSH6*, and *PMS2*. These MMR proteins function as heterodimeric complexes including MLH1-PMS2, MLH1-PMS1, MSH2-MSH6, and MSH2-MSH3. Microsatellites are repetitive sequences of DNA located in coding and noncoding regions and are frequent sites for MMR errors because of their repetitive nature.[9]

These errors are typically fixed by the MMR system; however, MMR gene mutations can cause MMR system inactivation resulting in mismatches that are left unrepaired, which is called MSI. These mutations can either be germline (15%–25%), in the case of Lynch syndrome (LS), or somatic (75%–85%). A common somatic alteration is *MLH1* promoter hypermethylation, which is an epigenetic change that silences *MLH1* gene expression. This change is frequently associated with a *BRAF V600E* PV and is a sporadic form of CRC due to MSI. MSI in coding regions can inactivate tumor suppressor genes, which leads to cancer development. If 2 or more regions are unstable, then the cancer is considered to have high MSI (MSI-H), which corresponds to MMR deficiency (dMMR) and is a hallmark of LS.[9–12]

LS-associated CRC can progress via the CIN pathway; however, recent literature supports these CRCs commonly forming from dMMR crypts through a “Big Bang” pathway. Møller and colleagues hypothesize that a second hit to the wild-type MMR allele leads to dMMR crypt formation, which increases the development of driver gene mutations in these crypts. These mutations occur in a random process, which may then cause CRC with very short or absent adenoma phases. Alternatively, sporadic dMMR CRCs generally arise in sessile serrated adenomas via the CIMP pathway due to *MLH1* promoter hypermethylation.[3,9–12]

CpG Island Methylator Phenotype Pathway

About 15% to 30% of CRCs arise from the CIMP pathway. Cytosine-phosphate-guanine (CpG) islands are frequently found near gene promoter regions and cytosine

methylation in these islands helps regulate gene expression.[12,13] In tumor cells, significant promoter CpG island hypermethylation can silence tumor suppressor genes and lead to tumorigenesis. When tumors have CpG island hypermethylation at multiple gene loci, they are called CIMP-high (CIMP-H). These tumors commonly have concurrent *BRAF V600E* PVs although *KRAS* variants can occasionally be seen, particularly with traditional serrated adenoma-derived cancers.[12–14] Clinically, sporadic dMMR CRCs can arise from CIMP-H sessile serrated adenomas due to MLH1 promoter hypermethylation; however, CIMP-H, proficient MMR CRCs are thought to arise from pre-existing traditional serrated adenomas. Serrated colorectal polyps include hyperplastic polyps, sessile serrated adenomas, and traditional serrated adenomas, with the latter 2 acting as cancer precursors. Importantly, the CIMP pathway is the typical carcinogenesis pathway for serrated polyposis syndrome (SPS).[13,15]

PATHOLOGY GUIDELINES FOR WORKUP OF COLORECTAL CANCER

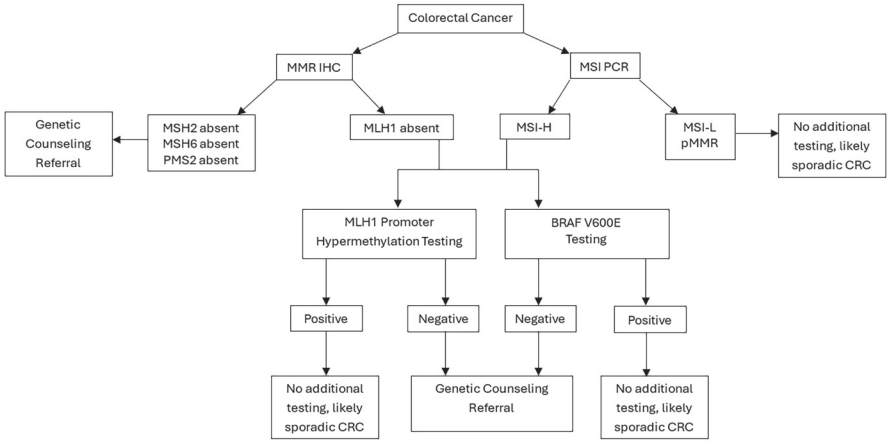
In 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommended all CRCs be screened for LS through microsatellite instability polymerase chain reaction (MSI PCR) or mismatch repair immunohistochemistry (MMR IHC) for evidence of dMMR.[16] This process is known as UTS, and multiple other organizations have made similar recommendations since the EGAPP Working Group's recommendation.[17–19] Prior studies have shown equal accuracy of UTS whether a preoperative, colonoscopy biopsy specimen or a surgical resection specimen are used; however, UTS should ideally be completed on a preoperative biopsy specimen to allow for a diagnosis of LS preoperatively and for consideration of neoadjuvant immunotherapy in the case of locally advanced, dMMR CRC.[20–26]

MMR IHC assesses MLH1, MSH2, MSH6, and PMS2 protein expression. If MSH2, MSH6, or PMS2 expression is absent, germline genetic testing is indicated. If MLH1 expression is absent, testing is required to determine if the dMMR is sporadic in etiology through MLH1 promoter hypermethylation or a *BRAF* V600E variant testing.[27] If the tumor tissue is positive for MLH1 promoter hypermethylation or a *BRAF* V600E variant, then the CRC is considered sporadic because MLH1 promoter hypermethylation is a somatic event and drives tumorigenesis via the CIMP pathway.[27,28] MLH1 promoter hypermethylation testing is considered first-line to distinguish sporadic from LS-associated dMMR CRC, and if this test is negative, then patients should be referred to genetic counseling to discuss germline genetic testing (**Fig. 1**).[29,30]

MSI PCR compares tumor DNA with normal DNA across a panel of microsatellite markers to assess for a change in length due to an insertion or deletion of repeating units at each respective marker. Instability, or change in microsatellite length, at 2 or more markers defines MSI-H, instability at a single marker defines MSI-low, and no instability defines microsatellite stable.[31] If tumor tissue is MSI-H, the tumor is considered MMR deficient and requires further testing to determine if the CRC etiology is sporadic, as earlier. MSI PCR testing is more expensive and less sensitive for detecting dMMR than MMR IHC; thus, MMR IHC is the preferred test for UTS.[29]

GENETIC TESTING GUIDELINES FOR WORKUP OF HEREDITARY COLORECTAL CANCER

Germline genetic testing plays an important role in the management of CRC by diagnosing nonpolyposis and polyposis-associated hereditary CRC syndromes. In general, genetic testing is indicated for all patients with early onset CRC, defined as a CRC diagnosis before the age of 50 years.[32] Patients with dMMR CRC should undergo genetic testing to assess for LS if MSH2, MSH6, or PMS2 protein expression is absent,



MSI-H = microsatellite instability – high; MSI-L = microsatellite instability – low; pMMR = mismatch repair proficient

Fig. 1. Universal tumor screening algorithm. MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; pMMR, mismatch repair proficient.

or when MLH1 protein expression is absent in the setting of negative MLH1 promoter hypermethylation or *BRAF* V600E testing. Other indications to complete genetic testing for LS evaluation include a known LS PV in the family; a first-degree relative with CRC or endometrial cancer diagnosed before the age of 50 years; a first-degree relative with more than 1 LS-associated cancer, 2 or more first-degree or second-degree relatives with LS-associated cancers, with 1 diagnosed before the age of 50 years; or 3 or more relatives with an LS-associated cancers at any age (**Box 1**).[17,33,34]

For polyposis syndromes, the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer recommends genetic testing for patients with 10 or greater lifetime cumulative colorectal adenomas or 3 or greater cumulative gastrointestinal (GI) hamartomatous polyps (hamartomas, ganglioneuromas, Peutz-Jeghers polyps, or Juvenile polyps).[35] Additional gene-specific indications are based on the suspected hereditary polyposis syndrome (**Box 2**).[35–39]

In general, multigene panel testing is the preferred type of genetic test compared to whole genome sequencing or single-site testing and should be obtained prior to the management of CRC when able, unless this would cause a significant delay.[32,35] Current guideline-based testing strategies can miss germline PVs in patients with CRC, which impacts management; therefore, universal germline genetic testing has emerged as a potential strategy to improve detection of hereditary CRC syndromes. This strategy may also be effective for reducing disparities in genetic testing and facilitating cascade testing for family members, although more research is needed prior to universal germline testing becoming standard of care.

MANAGEMENT OF HEREDITARY COLORECTAL CANCER SYNDROMES

Lynch Syndrome

LS is the most common hereditary CRC syndrome and is inherited in an autosomal dominant manner. LS is defined as a genetic predisposition to colorectal, endometrial, ovarian, urinary tract, gastric, duodenal, pancreatic, and other cancers due to a germline PV in the aforementioned MMR genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* (epithelial cell adhesions molecule, which causes epigenetic inactivation of *MSH2*)

Box 1
Indications for genetic testing to evaluate for Lynch syndrome[17,33,34]

- Family history of known LS germline PV or likely PV
- Personal history of an LS-associated cancer with any of the following:
  - Age of diagnosis less than 50 years
  - History of at least one other LS-associated cancer
  - 1 or greater first-degree or second-degree relative with an LS-associated cancer diagnosed age less than 50 years
  - 2 or greater first-degree or second-degree relatives with LS-associated cancers diagnosed at any age
- Family history of cancer meeting the following criteria:
  - 1 or greater first-degree relative with CRC or endometrial cancer diagnosed age less than 50 years
  - 1 or greater first-degree relative with greater than 1 diagnosis of LS-associated cancer
  - 2 or greater first-degree or second-degree relatives with LS-associated cancers and 1 or greater diagnosed age less than 50 years
  - 3 or greater relatives with LS-associated cancers diagnosed at any age
- Genetic risk model score 5% or greater predicted probability of germline MMR PV or likely PV ($PREMM_5$, MMRpro)

Abbreviations: CRC, colorectal cancer; LS, Lynch syndrome; MMR, mismatch repair; PV, pathogenic variant.

resulting in MSI (Fig. 2). Cumulative cancer incidence is dependent upon the affected gene, organ, and patient sex (Table 1).[40]

Patients with LS should undergo lifelong cancer surveillance (Table 2). Most guidelines recommend starting surveillance colonoscopy at the age of 20 to 25 years for patients with *MLH1* or *MSH2* PVs and 30 to 35 years for patients with *MSH6* or *PMS2* PVs or 2 to 5 years prior to the youngest age of CRC diagnosis in the family before the age of 25 years (*MLH1* or *MSH2*) or the age of 35 years (*MSH6* or *PMS2*). Colonoscopy is generally repeated every 1 to 2 years, thereafter.[34,36,41–43] Importantly, studies show that patients with LS are more likely to develop CRC despite regular surveillance with possible etiologies for this including quality of colonoscopy, LS tumor biology, and types of precursor lesions. Regardless, colonoscopy remains an integral pillar of cancer prevention in LS.[44,45]

In addition to endometrial cancer surveillance, the American College of Obstetricians and Gynecology recommends risk-reducing surgery for patients with LS and should consider a patient's LS PV, childbearing potential, comorbidities, menopause status, and family history. Risk reducing total abdominal hysterectomy with bilateral salpingo-oophorectomy is generally recommended starting at the age of 40 years.[19,46]

A diagnosis of CRC in the setting of LS requires careful consideration of all available treatment options, including neoadjuvant immunotherapy and surgery with standard segmental or risk-reducing extended colectomy. Immunotherapy has demonstrated excellent efficacy for dMMR CRCs, including LS-associated CRCs, which also raises the possibility of organ-preservation for some patients with LS. Clinical trials have shown a sustained complete clinical response (cCR) for dMMR, locally advanced rectal cancers (LARCs) treated with neoadjuvant immunotherapy without surgery.[23–25] Specifically, Cercek and colleagues[23] found a 100% cCR in 12 patients after 6 months of follow-up for 12 patients treated with dostarlimab for dMMR LARC. A follow-up study showed a 100% cCR in 41 patients after treatment with dostarlimab and 20

Box 2
Indications for genetic testing to evaluate for polyposis syndromes[35–39]

Adenomatous polyposis syndromes
- FAP, MUTYH-associated polyposis
  - Family history of known *APC* germline PV or likely PV
  - Personal history of 10 or greater cumulative colorectal adenomas
  - History of colorectal adenomas and FAP-type extracolonic manifestations (gastric/duodenal adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of retinal pigment epithelium, osteomas, and so forth)
  - Bilateral or multiple congenital hypertrophy of retinal pigment epithelium lesions
  - Cribriform-morular variant of papillary thyroid cancer

Hamartomatous polyposis syndromes
- PJS
  - 2 or greater histologically confirmed Peutz-Jeghers hamartomatous polyps
  - 1 or greater Peutz-Jeghers polyps with family history of PJS in close relative
  - Perioral or buccal pigmentation with family history of PJS in close relative
  - 1 or greater Peutz-Jeghers polyps with perioral or buccal pigmentation
  - Known family history of PJS
- JPS
  - Greater than 5 juvenile polyps in the colorectum
  - Juvenile polyps in other parts of the gastrointestinal tract
  - Any number of juvenile polyps and a family history of JPS
  - Known family history of JPS
- PTEN hamartoma tumor syndrome/Cowden syndrome
  - 3 or greater gastrointestinal hamartomas or ganglioneuromas
  - Known family history of PTEN hamartoma tumor syndrome
- SPS
  - Greater than 5 serrated polyps proximal to the rectum, all 5 mm or greater in size or with 2 polyps or greater 10 mm or greater in size
  - Greater than 20 serrated polyps of any size within the colorectum and at least 5 proximal to the rectum
  - Genetic testing not routinely recommended since causative pathogenic variants have not been identified

Abbreviations: APC, adenomatous polyposis coli; FAP, familial adenomatous polyposis; JPS, juvenile polyposis syndrome; PJS, Peutz-Jeghers syndrome; PV, pathogenic variant.

patients exhibited a sustained cCR over median follow-up time of 28.9 months.[24] Additionally, the NICHE trial has shown a high number of patients with a pathologic response for locally advanced colon cancer managed with neoadjuvant immunotherapy. Chalabi and colleagues[25] found 98% of 115 patients with locally advanced, dMMR colon cancer exhibited a pathologic response, 95% had a major pathologic response, and 68% had a pathologic complete response. More recent literature has found patients with stage I or II dMMR CRC may also benefit from neoadjuvant immunotherapy.[47] Immunotherapy is quickly becoming an integral component of the management of dMMR CRCs; however, the impact of immunotherapy on metachronous CRC risk and extent of surgical resection in patients with LS requires additional research.

Surgery for LS patients with CRC requires careful consideration of the PV, anatomic location (colon or rectum), and balancing the risk of metachronous CRC with quality-of-life preservation. Patients with colon cancer can undergo an extended resection (ER)—total abdominal colectomy with ileorectal anastomosis (TAC/IRA) or ileosigmoid anastomosis or a segmental resection (SR)—partial colectomy. Eikenboom and colleagues[48] retrospectively assessed 527 patients with LS and found the risk of

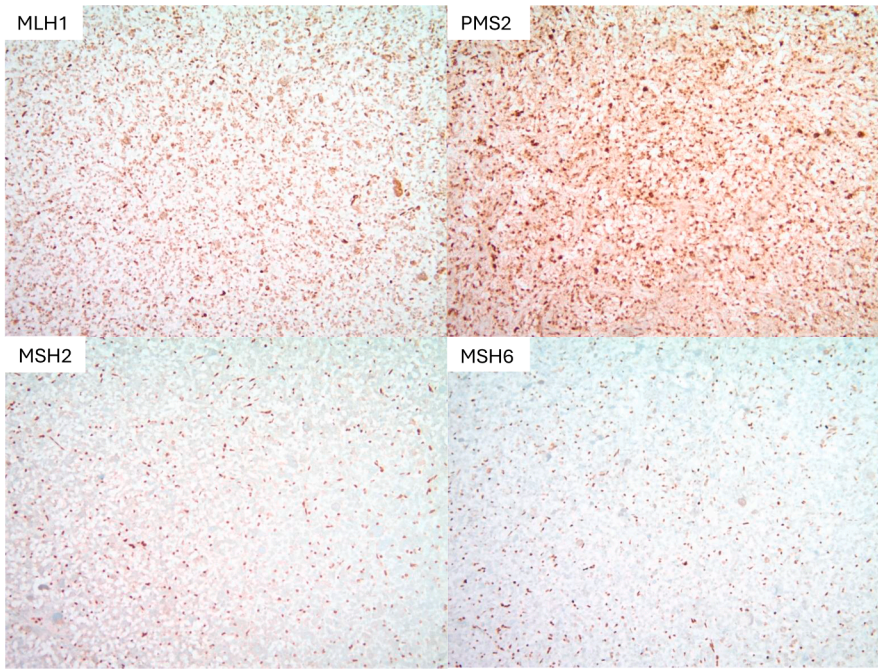


Fig. 2. Example of mismatch repair-deficient colon cancer in a patient with Lynch syndrome. Intact tumor expression for MLH1 and PMS2 and loss of tumor expression for MSH2 and MSH6 on mismatch repair immunohistochemistry for a patient with a newly diagnosed splenic flexure colon cancer. Genetic testing revealed an MSH2 pathogenic variant.

metachronous CRC to be 12% after an ER and 32% after an SR for patients with an *MLH1* or *MSH2* PV. For patients with an *MSH6* or *PMS2* PV, the risk of metachronous CRC was 0% after an ER and 16% after an SR. The study found no significant difference in metachronous CRC risk between patients with an *MLH1* or *MSH2* PV who had an ER compared to patients with an *MSH6* or *PMS2* PV who had an SR.

Other studies have similarly shown *MLH1* and *MSH2* PVs carry a higher risk of metachronous CRC following SR compared to *MSH6* or *PMS2* PVs; therefore, it is generally recommended that, within the context of shared decision-making, LS patients with *MLH1* or *MSH2* PVs have an ER and patients with *MSH6* or *PMS2* PVs have an SR.[44] There are also concerns regarding quality of life and functional outcomes for patients who have an ER compared to an SR. Studies show overall quality of life is worse and restrictions in diet, social, recreational, and travel activities are increased following ER compared to SR.[46,49] An ileosigmoid anastomosis could potentially preserve bowel function compared to an ileorectal anastomosis in patients who need an ER with similar metachronous cancer risk. Regardless, a shared decision-making discussion considering a patient's PV, goals, cancer risk, and quality of life should be completed to determine the most appropriate surgical plan.

For patients with early stage (T1/2N0) rectal cancer, upfront surgical resection remains the standard of care. In contrast, patients with LARC (T3/4 or node-positive disease) are recommended to undergo neoadjuvant immunotherapy rather than traditional TNT with chemoradiation given the high rates of cCR observed with immunotherapy and the relative resistance of dMMR tumors to chemotherapy. In patients with a complete response following neoadjuvant immunotherapy, watch and wait is

Table 1
Cumulative cancer incidence by the age of 75 y in Lynch syndrome based on organ and pathogenic variant[40]

	MLH1 PV		*MSH2* PV		*MSH6* PV		*PMS2* PV	
Organ	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Colorectal	68.5 (60.8–76.0)	80.2 (73.5–86.1)	55.8 (46.8–65.1)	42.6 (35.9–49.9)	16.4 (8.8–29.4)	17.3 (11.2–26.3)	32.8 (12.7–68.6)	8.5 (2.1–31.5)
Endometrium	—	37.2 (30.9–43.3)	—	44.1 (36.3–52.7)	—	45.7 (35.6–57.0)	—	12.7 (5.5–27.9)
Ovary	—	8.0 (5.3–12.0)	—	13.4 (8.9–20.1)	—	6.3 (2.6–15.2)	—	21.2 (8.5–46.9)
Bladder	5.6 (3.1–10.0)	4.8 (2.6–8.9)	13.1 (8.3–20.3)	9.4 (6.0–14.5)	9.0 (4.7–16.9)	2.6 (1.0–6.8)	0 (–)	0 (–)
Ureter/Kidney	4.5 (2.4–8.6)	2.9 (1.4–6.0)	15.8 (11.2–22.0)	19.5 (14.6–25.9)	3.3 (1.2–8.7)	3.9 (1.8–6.8)	5.1 (0.7–30.9)	0 (–)
Gastric	8.9 (5.5–14.4)	4.3 (2.3–7.9)	8.3 (4.8–14.2)	4.0 (2.1–7.4)	0.7 (0.1–4.9)	0.7 (0.1–4.7)	2.7 (0.4–17.5)	0 (–)
Small bowel	8.3 (5.2–13.0)	4.5 (2.6–7.8)	7.0 (4.3–11.3)	3.7 (2.1–6.4)	2.8 (0.9–8.7)	0.6 (0.1–4.0)	3.3 (0.5–21.3)	2.1 (0.3–14.0)
Pancreas	3.1 (1.4–6.9)	3.7 (1.9–7.2)	3.3 (1.5–7.1)	3.5 (1.7–7.3)	1.2 (0.2–8.1)	2.2 (0.7–6.8)	0 (–)	0 (–)
Bile duct/Gall bladder	4.0 (2.2–7.3)	1.5 (0.7–3.3)	4.6 (2.0–10.2)	2.4 (0.9–6.5)	0 (–)	0 (–)	0 (–)	0 (–)
Prostate	15.6 (10.7–22.6)	—	24.0 (17.8–32.0)	—	7.0 (3.5–13.7)	—	3.3 (0.5–21.5)	—
Brain	0.6 (0.1–3.9)	1.4 (0.5–3.4)	6.6 (3.4–12.4)	2.2 (0.8–5.7)	0.8 (0.1–5.3)	1.2 (0.3–4.6)	0 (–)	7.3 (1.1–41.6)

Data from Dominguez-Valentin M, Haupt S, Seppälä TT, et al. Mortality by age, gene and gender in carriers of pathogenic mismatch repair gene variants receiving surveillance for early cancer diagnosis and treatment: a report from the prospective Lynch syndrome database. *EClinicalMedicine* 2023;58:101909. https://doi.org/10.1016/j.eclinm.2023.101909.

Table 2
Lynch syndrome cancer surveillance by pathogenic variant[18,34,36,41–43]

Organ	Method	*MLH1*	*MSH2*	*MSH6*	*PMS2*
Colon/Rectum	Colonoscopy	Onset: 20–25 y Frequency: 1–2 y	Onset: 20–25 y Frequency: 1–2 y	Onset: 30–35 y Frequency: 1–2 y	Onset: 30–35 y Frequency: 1–2 y
Endometrium	Endometrial biopsy	Onset: 30–35 y Frequency: 1–2 y	Onset: 30–35 y Frequency: 1–2 y	Onset: 30–35 y Frequency: 1–2 y	Onset: 30–35 y Frequency: 1–2 y
Gastric/ Duodenal[a]	EGD	Onset: 30–35 y Frequency: 2–4 y	Onset: 30–35 y Frequency: 2–4 y	Onset: 30–35 y Frequency: 2–4 y	Onset: 30–35 y Frequency: 2–4 y
Pancreas[b]	MRCP and/ or EUS[c]	Onset: 50 y Frequency: 1 y	Onset: 50 y Frequency: 1 y	Onset: 50 y Frequency: 1 y	Onset: 50 y Frequency: 1 y
Skin	Skin examination	Onset: uncertain Frequency: 1–2 y	Onset: uncertain Frequency: 1–2 y	Onset: uncertain Frequency: 1–2 y	Onset: uncertain Frequency: 1–2 y

[a] Consider <30 y or frequency <2 y if family history of upper GI cancer or high-risk findings on EGD.
[b] Surveillance generally only recommended in patients with a first-degree or second-degree relative with history of pancreatic cancer.
[c] Consider onset of magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) starting 10 y younger than the earliest diagnosed pancreatic cancer in the family.

an appropriate management option; however, patients with an incomplete response should undergo chemoradiation followed by surgical resection.[41,50,51]

When surgically managing LS patients with rectal cancer, European guidelines recommend standard resection with a low anterior resection or abdominoperineal resection, although if there is synchronous neoplasia or patient preference, an ER with total proctocolectomy and ileal-pouch anal anastomosis (TPC/IPAA) can be considered.[52] Alternatively, the American Society of Colon and Rectal Surgeons recommends an individualized approach when considering the extent of resection for rectal cancer. However, in the era of neoadjuvant immunotherapy with most patients being candidates for organ preservation one would very rarely recommend a TPC/IPAA.[53] Risk of metachronous CRC and quality of life are considered, similar to colon cancer, and use of neoadjuvant immunotherapy and chemoradiotherapy for LARC should also play a role in surgical decision-making.

Finally, aspirin plays an important role in CRC risk-reduction for patients with LS, and the CAPP2 trial showed that patients who took 600 mg aspirin daily for at least 2 years had a 35% risk reduction at 20 years. The CAPP3 trial is nearing completion and is assessing the most ideal aspirin dose for preventing CRC.[44]

Polyposis

Familial adenomatous polyposis

FAP is inherited in an autosomal dominant pattern with 100% penetrance and is caused by germline PVs in the *APC* gene. FAP is typically characterized by the

development of hundreds to thousands of adenomatous polyps throughout the colon and rectum, and nearly all patients will develop CRC if left untreated (Fig. 3). A severe polyposis phenotype is characterized by over 1000 colonic polyps, an intermediate polyposis phenotype is characterized by 100 to 1000 colonic polyps, and an attenuated polyposis phenotype is characterized by 10 to 100 colonic polyps.[54] In addition to colorectal polyposis, patients commonly develop extracolonic manifestations including duodenal and gastric neoplasia, thyroid nodules, desmoid tumors, benign skin and soft tissue lesions, osteomas, and brain tumors among other manifestations.[54,55]

FAP patients with a classic phenotype (intermediate or severe polyposis) should start surveillance colonoscopies between ages 12 and 14 years and patients with an attenuated phenotype should start around the age of 18 to 20 years. Surveillance should continue every 1 to 2 years based on polyp burden until colorectal surgery is indicated, and polyps 5mm or greater should be resected to prolong time to surgery and to prevent progression to advanced neoplasia or CRC.[55,56] Patients should also undergo surveillance esophagogastroduodenoscopy (EGD) for gastroduodenal polyposis starting at the age of 20 to 25 years with surveillance frequency generally dependent upon the Spigelman score, which is a classification system for duodenal

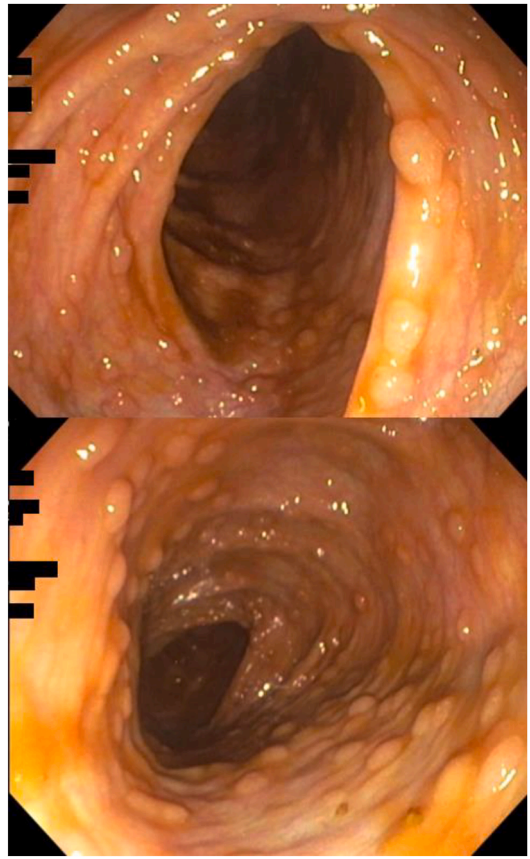


Fig. 3. Colonic polyposis in a familial adenomatous polyposis patient descending colon with approximately 140 polyps, 4 to 6 mm in size.

polyposis. However, one should ultimately consider the site with the most severe disease (stomach vs duodenum), as well as the appearance of the duodenal papilla when considering surveillance interval. Finally, annual thyroid ultrasound is recommended starting in the teenage years to monitor for thyroid cancer.[56–58]

Without colectomy, the lifetime risk of CRC in FAP approaches 100%. Although surgery is therefore inevitable, both its timing and extent should be individualized to best balance cancer risk reduction with quality-of-life implications of surgery. Timing of surgery is individualized based on many factors including the patient's polyposis phenotype, risk of polyp progression and cancer development, psychosocial needs, and risk for development of desmoid disease. Absolute indications for prompt colectomy include a cancer diagnosis and severe symptoms related to polyposis, and relative indications include adenomas with high-grade dysplasia, multiple adenomas greater than 6 mm, significant increase in polyp number between surveillance endoscopies, and inability to adequately survey the colon.[56,59,60]

Generally, the 2 main surgical options for patients with FAP that do not involve a permanent ileostomy include TAC/IRA and TPC/IPAA, and the decision of whether proctectomy is necessary involves balancing cancer prevention and quality-of-life preservation. In rare cases where restoring intestinal continuity is not desired, a TPC with end ileostomy may be considered.

Some centers favor TPC/IPAA for all patients with FAP because it provides the greatest reduction in CRC risk. However, even in high-volume centers, this approach is associated with substantial postoperative morbidity, usually requires a temporary diverting ileostomy, and carries risks including reduced female fecundity, pelvic nerve injury affecting sexual function, and an increased risk of developing intra-abdominal desmoid disease. In terms of function, a meta-analysis of 1002 patients comparing TPC/IPAA with TAC/IRA demonstrated higher rates of stool frequency, nocturnal bowel movements, and incontinence in the IPAA group. Additionally, the risk of unplanned readmission and reoperation within 30 days is higher after TPC/IPAA compared to TAC/IRA.[61] Given these considerations, TAC/IRA is a rational option for appropriately selected patients, as preservation of the rectum avoids pelvic dissection, does not require a temporary stoma, reduces the risk of fertility and sexual dysfunction, and is associated with more predictable bowel function.

Banerjee and colleagues[62] recently assessed the risk of rectal cancer development following TAC/IRA in 197 patients with FAP and reported the risk to be 3.0% overall; however, the rectal cancer risk increased to 10% in patients with 20 or greater rectal polyps at the time of TAC/IRA compared to 2.0% in patients with less than 20 rectal polyps. In comparison, the risk of small bowel or anal transition zone cancer after TPC/IPAA is reportedly less than 1% to 2%.[63,64] Thus, patients with 20 or greater rectal polyps are generally recommended to undergo a TPC/IPAA instead of a TAC/IRA; however, there are many other factors to consider when determining the surgery type.

Desmoid disease is more common in patients with FAP compared to the general population and generally occurs after surgery. Desmoids are locally aggressive fibroblastic, soft-tissue tumors that can develop in any part of the body, although they are usually located intra-abdominally (small bowel mesentery or retroperitoneum) or in the abdominal wall for patients with FAP (**Fig. 4**). Desmoid disease ranges in severity from asymptomatic to severe with complications such as bowel obstructions, bowel perforations, fistulization, bleeding, and ureteral obstruction. Desmoid disease is a leading cause of death in patients with FAP and studies have shown that desmoid disease is more common after TPC/IPAA compared to TAC/IRA. Therefore, the risk of being

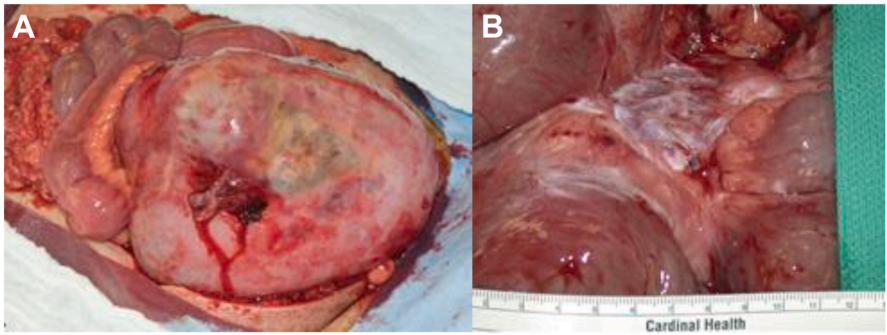


Fig. 4. (*A, B*) Intraoperative images of a desmoid tumor (*A*) and desmoid plaque (*B*).

diagnosed with desmoid disease should also be considered when completing shared decision-making with patients prior to their colorectal surgery.[65,66]

After colorectal surgery, patients need to continue lifelong cancer surveillance. Patients with an IRA or IPAA are typically recommended to have lower GI tract surveillance every 6 to 12 months and patients with an end ileostomy (EI) typically are recommended to have surveillance every 12 to 36 months.[55,56] Additionally, there are multiple chemoprevention medications that have been studied to prevent colorectal polyposis progression with the most common being sulindac and celecoxib, which are effective because COX-2 expression, like β-catenin, is increased by the Wnt/β-catenin signaling pathway, and overexpression of COX-2 leads to colonic adenoma progression.[67]

MUTYH-associated polyposis

MUTYH-associated polyposis (MAP) is an autosomal recessive polyposis syndrome that occurs due to PVs in the *MUTYH* base excision repair gene, which cause G>C and A>T transversions in multiple genes including *APC* and *KRAS*. Patients with MAP commonly have attenuated polyposis (10–100 adenomas); however, they may also have a classic phenotype or less than 10 adenomas. Risk of CRC is up to 48% in patients before the age of 60 years and the lifetime CRC risk is up to 80% to 90% in patients who do not complete surveillance. Therefore, colonoscopy surveillance is recommended annually starting between ages 18 and 20 years. Typically, endoscopic management of polyposis is appropriate for patients with MAP if they have an attenuated phenotype; however, surgical indications and decision-making are similar to FAP. Patients with MAP are also recommended to undergo surveillance EGD for gastroduodenal polyposis starting at the age of 35 years with frequency similar to FAP.[34,36,56]

Juvenile Polyposis syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant hamartomatous polyposis syndrome characterized by PVs in *SMAD4* or *BMPR1A* with a reported lifetime CRC risk between 39% and 68%. The term "juvenile" refers to the histologic polyp subtype that is characterized by abundant lamina propria with elongated, cystically dilated and mucus-filled glands rather than the age of polyposis onset, which typically begins around the age of 20 years. Juvenile polyps have a risk of malignant transformation; therefore, colonoscopy surveillance is recommended starting at the age of 15 years and continuing every 1 to 3 years based on polyp burden. Surgical intervention may be considered for JPS patients with a polyp burden that is not endoscopically manageable. JPS patients with a *SMAD4* PV have a higher risk of developing gastric polyposis and gastric cancer than patients with a *BMPR1A* PV, and it is recommended that patients with a *SMAD4* PV start

upper GI surveillance at the age of 18 years compared to the age of 25 years for patients with a *BMPR1A* PV and continue every 1 to 3 years. JPS is also associated with cranial abnormalities, cleft palate, polydactyly, and hereditary hemorrhagic telangiectasia. Thus, patients can also have epistaxis, mucocutaneous telangiectasias, and arteriovenous malformations.[34,36,68–70]

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant hamartomatous polyposis syndrome due to an *STK11* PV and is characterized by the development of Peutz-Jeghers hamartomatous polyps throughout the GI tract. Polyps most commonly occur in the small bowel followed by the colorectum and the stomach, and these benign polyps can cause intussusception, obstruction, bleeding, pain, or prolapse. Surveillance of the small bowel starts between ages 8 and 10 years, or earlier if symptomatic, with video capsule endoscopy, magnetic resonance enterography, or CT enterography. If no polyps are found, then surveillance resumes at the age of 18 years and continues every 2 to 3 years.[34,36,71] Symptomatic polyps or polyps 10 mm or greater should be removed via double balloon enteroscopy. Intraoperative pan-enteroscopy or a "clean sweep" can be completed for patients with extensive, endoscopically unresectable or unreachable small bowel polyps (**Fig. 5**). This is a hybrid technique combining either laparoscopy or laparotomy with intraoperative enteroscopy to allow

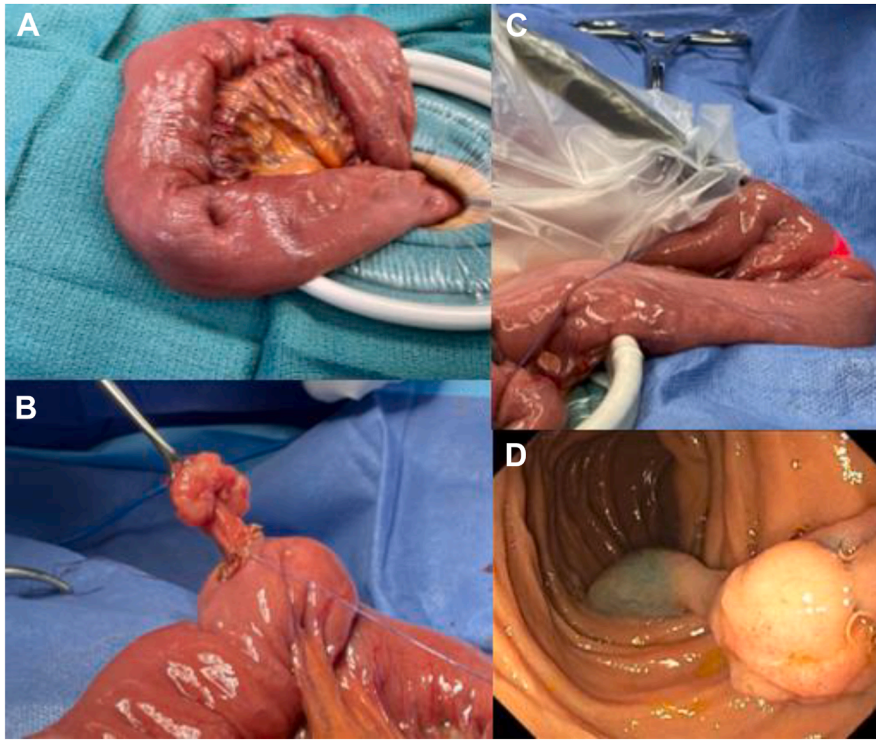


Fig. 5. (*A–D*) Clean sweep procedure for Peutz-Jeghers polyps. (*A*) Extracorporealizing the small bowel with noticeable dimpling related to Peutz-Jeghers polyp. (*B*) Creation of enterotomy and removal of small bowel polyp. (*C*) Insertion of the endoscope into the small bowel for the clean sweep. (*D*) Peutz-Jeghers polyp visualized on endoscopy during the clean sweep.

for complete removal of hamartomas from the entire small bowel.[72] Furthermore, patients should undergo surveillance EGD and colonoscopy in the same manner for gastroduodenal and colorectal polyp surveillance, respectively. Patients with PJS are at an increased risk for breast, pancreas, ovarian, testes, and lung cancer in addition to small bowel, gastric, and CRC and should additionally undergo cancer surveillance via a multidisciplinary approach.[34,36,71]

PTEN hamartomatous tumor syndrome

PTEN hamartomatous tumor syndrome, also called Cowden syndrome, is an autosomal dominant hamartomatous polyposis syndrome characterized by a PV in *PTEN* and multiple GI hamartomas or ganglioneuromas. Colorectal polyps are found in about 95% of patients and polyp types most commonly include juvenile polyps, ganglioneuromas, inflammatory polyps, and adenomas. Lifetime CRC risk for patients with Cowden syndrome is 9% to 16% and the average age of CRC diagnosis is 44 to 48 years. Therefore, surveillance colonoscopy is recommended starting at the age of 15 years and continues every 2 years depending upon findings. Patients are also at an increased risk of thyroid, breast, uterine, renal, and skin cancer (melanoma) and should undergo additional surveillance for each cancer.[34,36]

Serrated polyposis syndrome

Serrated polyps include hyperplastic polyps, traditional serrated adenomas, and sessile serrated polyps. SPS is a clinical diagnosis made for patients meeting 1 of 2 criteria including (1) more than 5 serrated polyps proximal to the rectum, all 5 mm or greater in size or with 2 or more polyps 10 mm or greater in size or (2) more than 20 serrated polyps of any size within the colorectum and at least 5 proximal to the rectum. While some patients with SPS have been shown to have genetic *RNF43* PVs, there is currently no defined monogenic basis in most cases of SPS. Patients with SPS should have an initial colonoscopy to clear all polyps which are 3 or greater to 5 mm followed by repeat colonoscopy surveillance every 1 to 3 years to decrease CRC risk. Colorectal surgery is reserved for patients who developed CRC or have an endoscopically unmanageable polyp burden. Notably, there is an association between Hodgkin's lymphoma and diagnosis of SPS. The specific etiology is unknown, although abdominal radiotherapy and/or chemotherapy with alkylating agents are thought to play a role.[34,36,73]

SUMMARY

CRC genetics carries important clinical implications for the diagnosis and management of patients with CRC and their families. All CRCs should undergo UTS, preoperatively whenever possible, to assess for dMMR due to the ability to diagnose LS preoperatively and for consideration of neoadjuvant immunotherapy in the case of locally advanced, dMMR CRC. Additionally, genetic testing plays an integral role in diagnosing polyposis and nonpolyposis hereditary CRC syndromes; therefore, understanding genetic testing criteria is critical to identify patients with these syndromes. Management of patients with hereditary CRC syndromes is complex and ultimately requires lifelong surveillance and multidisciplinary care to minimize death from cancer and to optimize quality-of-life preservation.

CLINICS CARE POINTS

- All CRCs should undergo UTS (preoperatively when possible) for MMR deficiency and patients with early onset CRC or suggestive family history should undergo germline multigene panel testing.

- Cascade testing (targeted relative testing) is recommended for at-risk family members of patients diagnosed with a hereditary CRC syndrome to identify germline PVs.
- LS patients with CRC may undergo an extended or segmental colonic resection after shared decision-making discussions, although immunotherapy is changing surgical management.
- Patients with familial adenomatous polyposis require colorectal surgery to reduce the risk of CRC, most commonly total colectomy with ileorectal anastomosis or total proctocolectomy with ileal pouch-anal anastomosis with timing and extent of surgery individualized based on polyposis severity, functional and psychosocial considerations, and desmoid risk.
- Management of all hereditary CRC syndromes requires lifelong surveillance and multidisciplinary care to minimize death from cancer and to maximize quality of life preservation.

FUNDING

J.R. Hendren was supported by the James Church, MD, and Sheetz Family Endowed Clinical Fellowship in Hereditary Colorectal Cancer Syndromes.

DISCLOSURE

D. Liska: Freenome, research support to institution.

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