Hereditary Colorectal Cancer Syndromes

Katerina Wells, MD, MPH[a], Paul E. Wise, MD[b,*]

KEYWORDS

• Inherited colon cancer • Hereditary nonpolyposis colorectal cancer
• Lynch syndrome • Familial adenomatous polyposis • MUTYH-associated polyposis
• Serrated polyposis syndrome

KEY POINTS

- Hereditary colorectal cancer syndromes are rare and affected patients are at increased risk for early onset, synchronous and metachronous colorectal malignancies, and extracolonic malignancies.
- Understanding the genetic basis of cancer syndromes and unique genotype-phenotype profiles allows clinicians to tailor surveillance and treatment strategies based on individual risk.
- Lynch syndrome follows an autosomal-dominant inheritance pattern characterized by early onset, aggressive colorectal cancer, and extracolonic malignancies. The genetic basis is a defect in mismatch repair genes.
- Familial adenomatous polyposis (FAP) follows an autosomal-dominant inheritance pattern characterized by intestinal polyposis and extracolonic malignancies. Patients exhibit a spectrum of disease severity from attenuated to extensive disease with clinical overlap with *MUTYH*-associated polyposis.
- Serrated polyposis syndrome is characterized by multiple, sometimes large, serrated polyps and associated with increased colorectal cancer risk. The morphology of the precursor polyps makes endoscopic management challenging, underscoring the need for short interval surveillance.

INTRODUCTION

It is estimated that 20% to 30% of colorectal cancers (CRCs) are familial with 5% to 10% related to a known genetic syndrome.[1,2] The hereditary CRCs are broadly divided into nonpolyposis and polyposis syndromes. Individuals with hereditary CRC syndromes are at risk for earlier development of cancer, increased risk of

Disclosure Statement: The authors have nothing to disclose.

[a] Department of Surgery, Division of Colon and Rectal Surgery, Baylor University Medical Center, 3409 Worth Street, Suite 640, Dallas, TX 75246, USA; [b] Division of General Surgery, Section of Colon and Rectal Surgery, Washington University Inherited Colorectal Cancer and Polyposis Registry, Washington University General Surgery Residency, Washington University in St Louis School of Medicine, 660 South Euclid Avenue, Campus Box 8109, St Louis, MO 63110, USA
* Corresponding author.
E-mail address: wisep@wustl.edu

Surg Clin N Am 97 (2017) 605–625
http://dx.doi.org/10.1016/j.suc.2017.01.009 **surgical.theclinics.com**

metachronous cancers, and extracolonic manifestations. As such, identification of these individuals is critical for prevention and early detection and treatment of associated malignancies to reduce associated morbidity and mortality. Although there are a multitude of hereditary syndromes associated with increased risk of CRC, this article focuses on the most common nonpolyposis and polyposis syndromes.

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER/LYNCH SYNDROME

Hereditary nonpolyposis CRC (HNPCC), also often used synonymously with the term Lynch syndrome, is the most common hereditary CRC syndrome, accounting for at least 2% to 3% of all CRCs. Lynch syndrome and HNPCC are associated with a predisposition to CRC and other cancers following an autosomal-dominant inheritance pattern, although rare sporadic mutations are described.[3] HNPCC defines a patient who meets particular clinical criteria (**Box 1**), regardless of the results of genetic assessment. Lynch syndrome is reserved for patients with a known mismatch repair (MMR) gene mutation regardless of whether they fulfill the clinical criteria for HNPCC (**Fig. 1**).

Both syndromes are associated with onset of CRC earlier than the general population with a mean age at CRC diagnosis of 45 years. Cancers are typically proximal to the splenic flexure; have a high degree of microsatellite instability (MSI-high); and have histologic features including poor differentiation, Crohn's-like host-lymphocytic infiltration, lymphoid aggregation at the tumor margins, and mucinous features.[4,5] They are associated with synchronous cancers,[6,7] and metachronous cancers are common with an annual incidence rate of 2.1%.[8,9] Despite the apparent high-risk histologic features, HNPCC-related CRC demonstrates less nodal and distant metastatic spread compared with sporadic CRC.[5,10] The "nonpolyposis" label of HNPCC can be misleading to less experienced physicians, because colorectal adenomatous polyps are the precursor lesions in these syndromes, with adenomas typically demonstrating a villous growth pattern and having a high degree of dysplasia.[4,11] Degeneration through the adenoma-carcinoma sequence is accelerated with CRC developing within a 5-year interval compared with 10 or more years in the case of sporadic CRC.[12,13]

Risk of Cancer

Regardless of the patient populations studied, the risk of CRC extracolonic malignancy is clearly elevated in HNPCC. Most studies present these risks reported in

Box 1
Revised HNPCC criteria (Amsterdam criteria II)

Criterion

1. There should be at least three relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis)
2. One should be a first-degree relative of the other two
3. At least two successive generations should be affected
4. At least one should be diagnosed before age 50
5. Familial adenomatous polyposis should be excluded in the CRC cases if any
6. Tumors should be verified by pathologic examination

From Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999;116(6):1455; with permission.

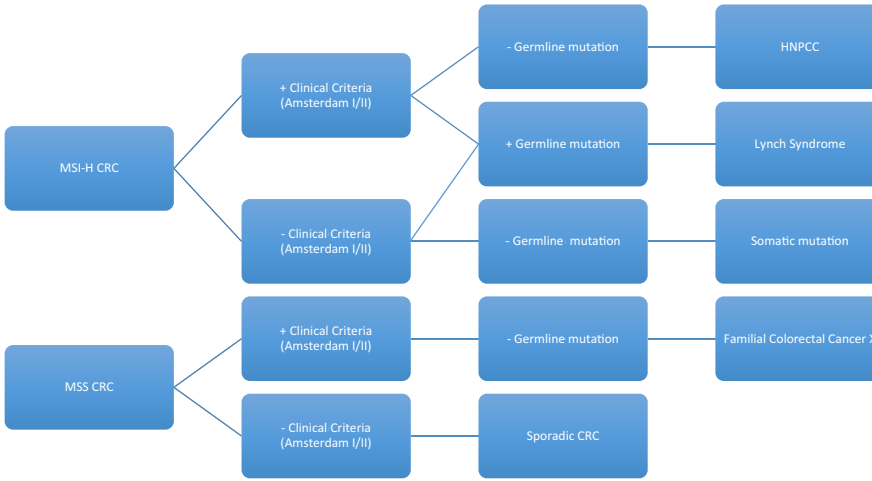

Fig. 1. Relationship between HNPCC and Lynch syndrome. MSI-H, microsatellite instability, high; MSS, microsatellite stable.

aggregate of all potentially associated gene mutations; however, each MMR mutation confers a unique genotype-phenotype cancer-risk profile.[14,15] Prior literature reports higher lifetime risk of CRC, up to 69% in men and 52% in women by the age of 70 years,[16,17] emphasizing the variable penetrance among individuals. Dowty and colleagues reports an average CRC cumulative risk by age 70 years for patients with *MLH1* and *MSH2* mutations of 34% and 47% for male carriers and 36% and 37% for female carriers, respectively; however, there is significant heterogeneity within these groups with some proportion of carriers having CRC risk similar to that of the general population and some having near absolute likelihood of developing CRC.[18,19]

Patients are also at increased risk of extracolonic malignancies, in particular endometrial, ovarian, gastric and small bowel, pancreatic, hepatobiliary, brain, and upper urothelial tract.[7,18] The average endometrial cancer risk is 18% to 60% with a mean age of diagnosis at 50 years.[19–21] *MSH6* is associated with a higher risk of endometrial cancer and a one-third lower risk of CRC compared with *MLH1* and *MSH2* carriers.[22,23] The estimated risk for gastric cancer is 6% to 13%[3]; however, this varies by the endemicity of gastric cancer in the population. For example, in Korea the lifetime risk of Lynch-related gastric cancer approaches 30% and surpasses endometrial cancer risk.[24] There are also subtypes of HNPCC/Lynch syndrome including Muir-Torre syndrome, associated with sebaceous carcinomas and keratocanthomas, and Turcot syndrome, which is associated with brain malignancies and colonic adenomas.[25]

Diagnosis of Hereditary Nonpolyposis Colorectal Cancer

The Amsterdam I clinical criteria for HNPCC were created in 1990 to standardize inclusion criteria for clinical research studies.[4] For kindred of families meeting Amsterdam criteria, the chance of identifying a germline mutation is 45% to 50%.[26] However, 40% of patients with an identified genetic mutation fail to meet Amsterdam criteria.[17] Concern of the Amsterdam I criteria missing clear familial clustering of extracolonic malignancies led to establishment of the Amsterdam II criteria (see **Box 1**), which broadens the HNPCC definition to include associated cancers (eg, endometrial, small

bowel).[4] The revised Bethesda guidelines were then published in 2004 to identify CRC patients who should undergo pathologic examination for HNPCC/Lynch syndrome (**Box 2**).[27] For patients meeting these criteria, further pathologic analysis of the CRC specimen includes MSI testing or immunohistochemistry (IHC) assessment for the presence of the MMR proteins. Jerusalem guidelines further broaden the indications for MSI or IHC testing to CRC in individuals younger than 70 years.[28] Regardless, Amsterdam criteria fail to identify approximately 50% of cases, and Bethesda guidelines fail to identify at least 30% of cases,[29] which has led to increased support for the universal application of polymerase chain reaction (for detection of MSI-high tumors) and/or IHC testing (for MMR protein deficiency) to all CRC specimens.[30] This justification also supports universal testing of endometrial cancer.[31] Universal testing followed by germline testing offers the highest sensitivity (and somewhat lower specificity) than alternative screening strategies, although the increase in the diagnostic yield is modest compared with criteria-based screening techniques (**Table 1**).[32] Cost-effectiveness analyses demonstrate varying results.[33,34]

Etiology of Lynch Syndrome

Lynch syndrome is caused by a germline mutation in DNA MMR genes (most common being *MLH1*, *MSH2*, *MSH6*, and *PMS2*). As cellular division occurs, errors in replicated DNA are identified and corrected by the MMR protein complexes. Loss-of-function mutations in the MMR genes may result in DNA replication errors, which can occur in tumor suppressor genes or proto-oncogenes leading to carcinogenesis. DNA replication errors are propagated through daughter cells, leading to repetitive DNA sequences called microsatellites, making them unstable (MSI-high). MSI testing via polymerase chain reaction is an effective and highly reproducible method for identifying tumors with an underlying germline MMR defect (93% sensitivity).[35] Using a panel of microsatellite markers, tissue is classified as being MSI-high if two or more of five core markers show instability.[36] If more expansive panels are used, a greater than 30% rate of instability is considered MSI-high.[37] Sporadic CRC MSI

Box 2
Revised Bethesda guidelines

Criterion

1. CRC in a patient <50 years of age
2. Synchronous or metachronous CRC or the presence of other HNPCC-associated tumors,[a] regardless of age
3. Pathologic features of a microsatellite instability–high cancer (tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) in a patient <60 years
4. CRC in one or more first-degree relatives with an HNPCC-related tumor[a] with one of the cancers diagnosed by the age of 50 years (including adenoma by the age of 40 years)
5. CRC in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

[a] Endometrial, stomach, ovarian, pancreas, small bowel, biliary tract, ureter or renal pelvis, brain, sebaceous gland adenoma, or keratoacanthoma.

From Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96(4):266; with permission.

Table 1
Sensitivity, specificity, and diagnostic yield of screening techniques for HNPCC

Screening Approach	Sensitivity (%)	Specificity (%)	Diagnostic Yield (%)
Universal screening	100 (95% CI, 99.3–100)	93 (95% CI, 92–93.7)	2.2 (95% CI, 1.7–2.7)
Bethesda guidelines	87.8 (95% CI, 78.9–93.2)	97.5 (95% CI, 96.9–98.0)	2.0 (95% CI, 1.5–2.4)
Jerusalem recommendations	85.4 (95% CI, 77.1–93.6)	96.7 (95% CI, 96–97.2)	1.9 (95% CI, 1.4–2.3)
Selective MMR testing CRC in patients <70 y meeting Bethesda guidelines	95.1 (95% CI, 89.8–99)	95.5 (95% CI, 94.7–96.1)	2.1 (95% CI, 1.6–2.6)

Abbreviation: CI, confidence interval.
From Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308(15):1555; with permission.

testing typically reveals no instability and are considered microsatellite stable (MSS)[36]; however, 15% of sporadic CRCs are identified as being MSI-high and likely occur through the epigenetic pathway of hypermethylation of the *MLH1* promoter region and also harbor *BRAF* mutations, distinguishing them from germline-related pathways, which are typically BRAF wild-type.[15] Of note, a small percentage of CRCs that fulfill HNPCC clinical criteria are found to be MSS. Patients meeting these criteria have been designated "familial colorectal cancer type X" and have a moderately increased risk of CRC but no increased risk for extracolonic cancers (see **Fig. 1**).[38,39]

Genetic Testing for Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome

Genetic testing should always be done in a thoughtful, stepwise fashion in the setting of effective counseling to ensure that the patient and kindred understand the implications of any test results, whether they confirm the presence of a mutation or not. When an MSI-high CRC is identified through tumor testing, IHC for the MMR proteins is performed to identify the likely mutated gene. Alternatively, IHC can replace MSI as the initial tumor test because IHC is technically easy to perform and has demonstrated 92% sensitivity in identifying mutations.[3] Although identification of a particular MMR protein loss on IHC guides germline testing, the finding of the loss of *MLH1* or *MLH1/PMS2* in the tumor is not sufficient for the diagnosis of Lynch because of the potential for sporadic loss from hypermethylation as described previously and requires additional testing for hypermethylation[40,41] or *BRAF* testing to identify somatic mutations. The presence of a *BRAF* mutation is thought to be rare in Lynch syndrome and usually excludes the diagnosis.[42]

When genetic testing is initiated after MMR IHC tumor testing, the implicated genes are tested for first with further gene testing performed only if the result is unrevealing. There are times when the clinical criteria for HNPCC are so impressive in a family (eg, significant phenotypes with multiple associated cancers in multiple individuals) that it is logical to proceed directly to germline testing of an affected individual without prior tumor testing. This is performed using a multigene panel to test for the MMR genes and any other CRC-related genes. Cost for these tests has decreased significantly in recent years because of more affordable testing methods; however, panels may vary greatly between laboratories. Regardless of method used, if a pathogenic mutation is found, the patient's at-risk kindred can be tested for that particular mutation.

Surveillance of Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome

The recommendation for CRC surveillance of at-risk and affected individuals is colonoscopy every 1 to 2 years initiated at 20 to 25 years of age or 2 to 5 years before the age of the earliest diagnosed CRC, whichever comes first (**Table 2**).[6,43] Compliance with surveillance is paramount to reduce the incidence of CRC in affected individuals. In a prospective cohort study, 95% compliance rates of colonoscopic and gynecologic screening over a 10-year period found no difference in mortality in affected individuals compared with their nonaffected relatives.[44] Additional screening guidelines for extracolonic malignancies are outlined in **Table 2**.[6]

Surgical Approach to Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome

Surgical options include segmental or extended resection, both requiring informed consent regarding implications on future cancer development balanced with the changes in bowel function and quality of life associated with each procedure. Extended colectomy is the recommended treatment of young to middle-aged patients with colon cancer, both for treatment of the primary lesion and risk reduction for metachronous CRC.[45] Subtotal colectomy or total abdominal colectomy with ileorectal anastomosis (TAC/IRA) decreases the risk of metachronous cancer by 31% for every 10 cm of bowel removed.[46] In the elderly, incontinent, and/or comorbid patient, the morbidity of and quality-of-life implications of an extended resection must be weighed heavily against the benefit of cancer risk reduction, and in some cases, a segmental colectomy may be more appropriate. In the case of rectal cancer, a total proctocolectomy with end ileostomy or restorative ileal pouch-anal anastomosis (IPAA) should be considered; however, when patients have a locally advanced rectal cancer with high risk for metastatic disease, prophylactic surgery becomes less of a concern, and low anterior resection or abdominoperineal resection may be more appropriate.[47] The decision to perform an extended versus segmental resection for CRC is also influenced by the patient's anticipated compliance with surveillance, which is paramount for early detection of recurrence and metachronous lesions.

There is not an established role for prophylactic colectomy in the asymptomatic Lynch syndrome patient. However, the role of prophylactic hysterectomy with bilateral salpingoophorectomy is well supported and recommended for women who have completed child bearing. In the setting of a planned CRC resection, concomitant prophylactic hysterectomy with bilateral salpingoophorectomy should be considered.[15]

FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis (FAP) has an incidence of 0.6 to 2.3 per million and accounts for approximately 0.5% to 1% of all CRCs.[48] FAP is characterized by the development of numerous (>100) colorectal adenomatous polyps (**Fig. 2**), often exceeding effective endoscopic management, and follows an autosomal-dominant inheritance pattern, although 20% to 30% of cases present as a result of a *de novo* mutation.[49] Onset of polyposis occurs in adolescence with progression to CRC by middle-age. The penetrance of FAP is 100%, with an incidence of CRC approaching 100% by the age of 50 years.[50] Enhanced awareness of this disease and more aggressive strategies for screening and surveillance have substantially decreased the incidence of CRC and associated mortality.[51,52]

Patients with FAP may present with extracolonic findings depending on the specific gene mutation involved. Duodenal adenomas are a significant contributor to FAP-related mortality with the risk of malignant progression guided by the Spigelman classification.[53] Desmoid tumors occur in approximately 15% to 20% of patients over the

Table 2
National Comprehensive Cancer Network surveillance recommendations for hereditary CRC syndromes

Syndrome	Site	Age to Begin Surveillance (y)	Surveillance Interval (y)	Procedures
HNPCC	Colon	20–25 or 2–5 y before earliest CRC diagnosis	1–2	Colonoscopy
	Endometrial and ovarian	No evidence to support	1	Consider annual endometrial sampling Consider prophylactic hysterectomy/BSO in women who have completed childbearing No evidence to support routine ovarian screening (transvaginal ultrasound or CA-125)
	Urinary tract	30–35	1	Consider annual urinalysis
	Small bowel and gastric	30–35 No evidence to support	3–5	Consider EGD with extended duodenoscopy in at-risk individuals
Familial adenomatous polyposis	Colon	10–15	1	Flexible sigmoidoscopy or colonoscopy
	Upper GI	20–25 Earlier if colectomy at <20 y	1–5	EGD with complete visualization of the papilla Surveillance by Spigelman staging Consider CT or MRI for small bowel if duodenal polyposis is advanced
	Thyroid	Late teenage years	1	Annual thyroid examination Consider annual thyroid ultrasound
	Intra-abdominal desmoids	No evidence to support	1	Annual abdominal examination Consider CT or MRI 1–3 y after colectomy, then every 5–10 y or symptom-based

(*continued on next page*)

Table 2
(*continued*)

Syndrome	Site	Age to Begin Surveillance (y)	Surveillance Interval (y)	Procedures
Attenuated familial adenomatous polyposis	Colon	Late teenage years	2–3	Colonoscopy
	Upper GI	20–25 Earlier if colectomy at <20 y	1–5	EGD with complete visualization of the papilla
	Thyroid		1	Annual thyroid examination and thyroid ultrasound
MUTYH-associated polyposis	Colon	25–30	2–3	Colonoscopy
	Upper GI	30–35	1–5	EGD with complete visualization of the papilla
Serrated polyposis syndrome	Colon	40 10 y before earliest CRC diagnosis	1–3	Colonoscopy

Abbreviations: BSO, bilateral salpingoophorectomy; CT, computed tomography; EGD, esophagogastroduodenoscopy; GI, gastrointestinal.

Adapted from Provenzale D, Gupta S, Ahnen DJ, et al. Genetic/familial high-risk assessment: colorectal version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016;14(8):1010–30; with permission.

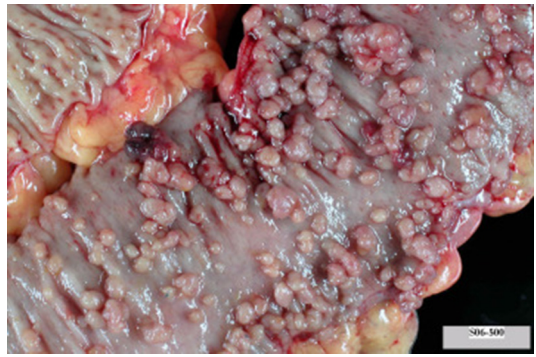

Fig. 2. Gross pathology of a colectomy specimen from a patient with FAP. (*From* Hawkins AT, Wise PE. Colon cancer in hereditary syndromes. Semin Colon Rectal Surg 2016. http://dx.doi.org/10.1053/j.scrs.2016.04.021; with permission.)

second and third decades of life (**Fig. 3**) with risk factors being prior abdominal surgery,[54,55] positive family history, and *APC* mutation 3′ to codon 1399.[56] Thyroid cancer risk is five times higher than that of the general population with a strong female preponderance.[57] Other benign findings include osteomas (~20%); lipomas; epidermoid cysts; fibromas; dental abnormalities; and congenital hypertrophy of the retinal pigment epithelium, which is pathognomonic for the diagnosis, albeit without known clinical import.[57] These unusual extracolonic manifestations often precede colonic symptoms and may aid in early diagnosis.[58]

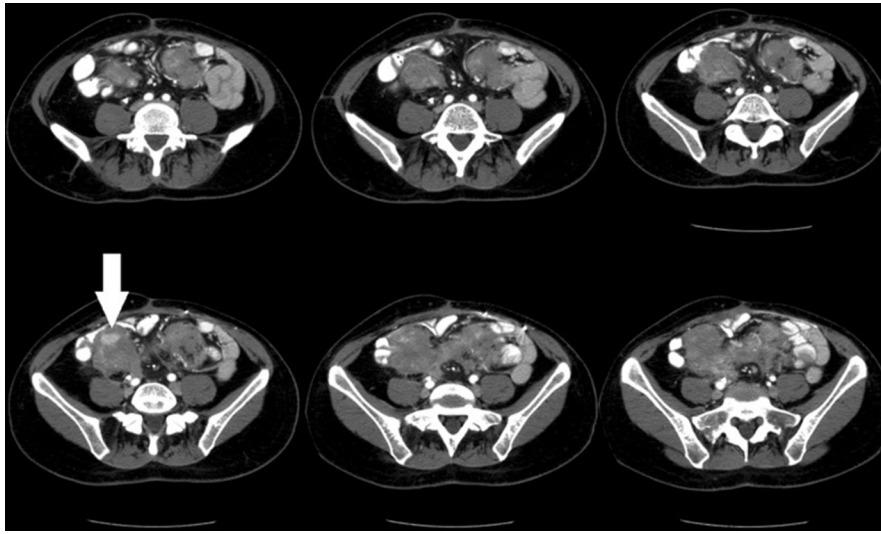

Fig. 3. Sections from a contrasted abdominal computed tomography scan of a patient with FAP with intra-abdominal desmoid originating from the mesentery and retroperitoneum, including areas with fistulization with oral contrast within the desmoid (*arrow*). (*From* Hawkins AT, Wise PE. Colon cancer in hereditary syndromes. Semin Colon Rectal Surg 2016. http://dx.doi.org/10.1053/j.scrs.2016.04.021; with permission.)

Etiology of Familial Adenomatous Polyposis

FAP is caused by a mutation in the adenomatous polyposis coli (*APC*) gene. The *APC* gene encodes a large multifunctional scaffolding protein that acts as a tumor suppressor within the *wnt*-signaling pathway to downregulate the activity of β-catenin. With loss of APC function, accumulation of β-catenin upregulates several genes that mediate cell proliferation, differentiation, and apoptosis. APC also mediates microtubule stabilization, with defects resulting in aberrant mitosis. More than 1100 mutations of the *APC* gene are identified, mostly resulting in a loss of function.[59]

Variations in the loci of *APC* mutations and other genetic modifiers result in genotype-phenotype variation in FAP. Three major phenotypes are described. The first is profuse polyposis exhibiting an aggressive phenotype with early onset of polyposis, symptoms, and CRC-related death at an average of 10 years earlier than typically described. Deletions at codon 1309 and truncating mutations at codons 1250 and 1464 are associated with this phenotype.[60] Second, intermediate polyposis, with most mutations located between codon 157 and codon 1595.[61] Third, attenuated polyposis (AFAP) characterized by a reduced polyp burden (10–100 polyps) with later age of onset and lower risk of CRC.[61] Diagnosis of AFAP is challenging because some features of AFAP are similar to those of *MUTYH*-associated polyposis (MAP), discussed later.[11]

Work-up of Familial Adenomatous Polyposis

It is important to emphasize that approximately 20% to 30% of patients with FAP present without a family history of CRC often via *de novo APC* mutations.[49,62] Historically, up to 40% to 50% of patients with FAP included in hereditary cancer registries are diagnosed based on symptomatic presentation (eg, rectal bleeding, changes in bowel habits) in the third or fourth decade and are significantly more likely to have an initial diagnosis of CRC compared with those diagnosed based on family history or other risk factors for FAP.[51,63,64] At the time of clinical diagnosis, the patient should be referred to a genetic counselor and testing performed to confirm the diagnosis. If a genetic mutation is identified, gene testing is extended to all at-risk kindred. If a genetic mutation is not identified for testing, surveillance must be extended to all at-risk kindred. In kindred born into an FAP family, genetic screening is recommended in mid-adolescence, before the initiation of cancer screening.

The gold standard and current method for genetic testing is direct sequencing of the *APC* gene. This method identifies greater than 85% of mutations with remaining mutations resulting from large gene rearrangements that are diagnosed on multiplex ligation-dependent probe amplification testing.[37] Approximately 20% of clinically diagnosed patients with FAP do not have an identified *APC* mutation. If the patient expresses a polyposis phenotype despite negative *APC* testing, genetic testing for MAP should be considered.[65] Occasionally, panel testing identifies other genotypes beyond those typically associated with FAP and MAP.

Surveillance for Familial Adenomatous Polyposis

In a study of 170 patients by Bussey,[66] rectal involvement with polyposis was identified in all cases. Based on this finding, it is reasonable for affected individuals, at-risk kindred, and those who have not had genetic testing or in whom genetic testing is uninformative to undergo annual flexible sigmoidoscopy beginning in the early teenage years. If polyps are detected, full colonoscopy is indicated. Annual surveillance should be life-long regardless of findings because of 100% penetrance of the disease.[67] In the case of AFAP, onset of CRC is later and there is a propensity for right-sided

adenomas, so screening can be initiated in late teenage years, but colonoscopy should be used instead of flexible sigmoidoscopy. Further screening recommendations are outlined in **Table 2**.

Chemoprevention for Familial Adenomatous Polyposis

Various chemoprevention strategies have been considered to delay proctocolectomy in young patients and to manage upper and lower gastrointestinal polyps when surgical intervention is unfavorable. Sulindac and celecoxib are the most widely studied agents. The mechanism of nonsteroidal anti-inflammatory drug–mediated chemoprevention is not completely understood; however, cyclooxygenase-2 inhibition is known to inhibit angiogenesis and neovascularization, and restore normal apoptosis signaling in CRC cells.[68] These agents demonstrate significantly reduced colon polyp burden in placebo-controlled trials[69,70] and offer a moderate effect in the reduction in duodenal epithelial proliferation[71]; however, effects are incomplete and temporary with recurrence following cessation of therapy. It is also not clear that a reduced polyp burden translates into reduced CRC risk. Currently, chemoprophylaxis is not a suitable alternative to surgical therapy. Chemoprevention is considered if contraindications or unavoidable delay to surgery exist and also serves as an effective adjunct to endoscopic polypectomy in the management of ileal pouch polyposis.[72] Studies are underway examining other therapeutic agents and combination therapies for chemoprevention.[73]

Surgery for Familial Adenomatous Polyposis

Surgery is the mainstay of CRC risk reduction for FAP. Timing is not clearly defined by guidelines because multiple factors must play into the decision-making process shared by the surgeon and the patient. Ideally, surgical intervention is an elective procedure with the indication of prophylaxis in the asymptomatic patient. This can be delayed until adolescence, usually 15 to 20 years of age, considering the psychological impact to the young patient, because the incidence of CRC before that age is low.[67] Patients with large or dysplastic lesions, severe disease either clinically or by genotype, or with symptoms should proceed to colectomy as soon as possible because of the risk of underlying CRC. Patients with a family history or genotype predisposing to desmoid disease may opt to delay surgery provided CRC risk allows for this. It is reasonable for patients with AFAP or mild disease to delaying surgery into young adulthood (21–25 years of age) or later, especially if the disease can be endoscopically controlled.[74] Three main surgical options for FAP are described next (**Table 3**).

Total proctocolectomy with end ileostomy

Total proctocolectomy with end ileostomy is the gold standard treatment and offers complete extirpation of at-risk colorectal mucosa at the expense of permanent ileostomy. Although less commonly performed, this procedure should be included in the discussion of surgical options for patients with low rectal cancers that preclude IPAA, those with poor sphincter function, and desmoid disease or other anatomic constraints that prevent IPAA construction.

Total proctocolectomy with ileal pouch–anal anastomosis

Total proctocolectomy with IPAA is the most widely used procedure and is considered standard of care for the treatment of FAP other than for the previously noted contraindications. This is a near-complete extirpative procedure with the benefit of preserved continence. Historically, mucosectomy with handsewn IPAA was the recommended approach to remove remaining at-risk mucosa from the retained

Table 3
Surgical management options for FAP

Surgery	Indications	Contraindications
Total proctocolectomy with end ileostomy	• Low rectal cancer precluding sphincter preservation • Mesenteric foreshortening (desmoids) • Poor sphincter function • Refusal of IPAA • Noncompliance to surveillance	• Refusal of permanent ileostomy
Total abdominal colectomy with ileorectal anastomosis	• AFAP/mild polyposis • <1000 colonic adenomas • <20 rectal adenomas • Desire for preserved fertility/potency	• Noncompliance to surveillance • Rectal polyposis (>20 rectal adenomas) • Rectal dysplasia/carcinoma • Rectal polyp >3 cm • Predisposition to desmoid disease • APC mutation predisposing to rectal cancer
Total proctocolectomy with ileal pouch–anal anastomosis	• Acceptable anticipated functional outcome	• Poor baseline sphincter function • Low rectal cancer precluding sphincter preservation • Noncompliance to surveillance

rectal cuff; however, the incidence of dysplasia is not statistically different in comparisons of either method.[75] The relative procedural ease and functional benefit afforded by stapled IPAA makes this the preferred method in most clinical scenarios.[76] The risk of cancer in the residual rectal cuff or anal transition zone or pouch approaches 1.2%.[77] Risk factors related to pouch cancer include preoperative diagnosis of dysplasia or carpeting polyposis of the rectum.[76] Endoscopic surveillance of the anal transition zone and pouch should be performed every 1 to 3 years depending on polyp burden. Surveillance should be increased to every 6 months in the case of large polyps, villous architecture, and/or dysplasia in the pouch or cuff.[6]

Total abdominal colectomy with ileorectal anastomosis

TAC/IRA is technically easier to perform with the benefit of improved fecal and urinary continence and sexual function compared with IPAA.[78–80] This option is considered in patients who have a limited rectal polyp burden (<20 polyps), a low-risk genotype, and are able to comply with surveillance. This is a good option for patients with AFAP and rectal sparing. Endoscopic surveillance of the residual rectum should be performed every 6 to 12 months depending on the extent of polyp burden.[6] Patients considering IRA must be counseled regarding the risk of metachronous lesions within the retained rectum and progression to polyposis that exceeds endoscopic management because both are indications for completion proctectomy. In a registry-based review of 427 patients undergoing IRA for FAP, 11% of patients developed rectal cancer with 50% of patients undergoing proctectomy by age 60. Risk factors for progression of rectal disease include rectal polyp burden greater than 20, colonic polyp burden greater than

500, and an *APC* mutation at codon 1250 to 1450 suggesting that IRA may not be appropriate for these patients.[8]

MUTYH-ASSOCIATED POLYPOSIS

MAP was first described in 2002 with a report of a biallelic germline mutation in the *MUTYH* gene in a family expressing a recessive inheritance pattern of colon adenomas and CRC.[10] As the body of knowledge regarding genotypic contributors to polyposis has grown, MAP shares clinical features with FAP/AFAP such that 10% to 20% of patients with suspected FAP/AFAP without an identified *APC* mutation exhibit a mutation in *MUTYH*.[11] Affected patients have a 50-fold increased lifetime risk of CRC with a mean age of diagnosis at 50 years. Heterozygote carriers exhibit a three-fold increased risk of CRC.[12] MAP polyposis includes conventional adenomas, serrated adenomas, and hyperplastic polyps.[14] A family history of polyposis is rarely evident because of an autosomal-recessive inheritance pattern. Affected individuals are also at risk for extracolonic neoplasm with duodenal adenomas found in 17% to 25%[18] of patients with a 4% lifetime risk of duodenal cancer.[16] MAP is also associated with late-onset gynecologic, urothelial, and skin cancers.[18]

Etiology of MUTYH-Associated Polyposis

The *MUTYH* gene encodes a glycosylase involved in base excision repair. *MUTYH* deficiency results in genetic instability of the *APC* gene and perhaps others, including *KRAS* and *p53*. The pathogenesis of MAP-related tumors is unique but has overlap with FAP, perhaps accounting for phenotypic similarities.[20]

Diagnosis of MUTYH-Associated Polyposis

Genetic testing for MAP should be considered in the case of clinically diagnosed polyposis without an identified *APC* mutation. Genetic testing is initially mutation-specific, because 80% of patients exhibit one of two major mutations. If a mutation is identified, then sequencing of the remaining allele is performed to confirm the presence of biallelic mutations. If a known mutation is not identified, primary sequencing is performed.[81]

Surveillance and Surgical Approach to MUTYH-Associated Polyposis

Colonoscopic surveillance is recommended to start at 25 years of age with surveillance every 1 to 2 years and extracolonic screening as outlined in **Table 2**. Screening for heterozygote carriers is similar to population screening guidelines for high-risk individuals. Indications for surgical intervention and considerations for type of resection are similar to those outlined for FAP/AFAP.[6]

SERRATED POLYPOSIS SYNDROME

Serrated polyposis syndrome (SPS) has an incidence of 1:100,00,0[82] and is characterized by the presence of multiple or large serrated polyps and a predisposition to CRC. SPS is associated with a lifetime risk of CRC approaching 70%. There is no known genetic basis for SPS, and identifying at-risk patients is limited because a positive family history is reported in 0% to 59% of patients without a consistent mode of inheritance.[83] Therefore, diagnosis is based on specific clinical criteria outlined by the World Health Organization (**Box 3**),[84] which underscore the considerable phenotypic variation of the condition (eg, patients may have multiple lesions throughout their colons or few, large, right-sided lesions on cumulative surveillance).

Box 3
World Health Organization criteria for diagnosis of SPS

Criterion

1. At least five serrated class polyps proximal to the sigmoid of which at least two are greater than 1 cm in size
2. Any serrated class polyp proximal to the sigmoid in a first-degree relative with SPS
3. ≥20 serrated class polyps distributed throughout the colon.

Satisfaction of any one of the three criteria establishes the diagnosis of SPS.

Data from Snover DC, Ahnen DJ, Burt RW, et al. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman FT, Carneiro F, Hruban RH, et al, editors. WHO Classification of Tumours of the Digestive System. 4th edition. Lyon: IARC; 2010. p. 160–65.

Sessile serrated polyps (SSPs) account for 25% of serrated lesions and seem to be the precursor lesions for SPS-associated CRC. SSPs are flat with an overlying mucus cap making identification and complete endoscopic clearing challenging. SSPs are generally located in the proximal colon but up to 30% are found distally.[85] SPS-associated CRCs can present with synchronous and/or metachronous lesions. Interval cancers most often occur in the proximal colon and are often MSI-high via an epigenetically mediated pathway involving CpG island hypermethylation. This pathway is described in greater detail next.

Etiology of Serrated Polyposis Syndrome

Although no gene mutation has clearly been linked to SPS, the serrated adenoma–carcinoma pathway is well described. This is an epigenetically mediated mechanism whereby hypermethylation of CpG islands occurs in the promoter region of tumor suppressor genes. Hypermethylation results in silencing of the tumor promoter region resulting in MSI. Tumors arising via this pathway are characterized by the CpG island mutation phenotype (CIMP-high). CIMP-high phenotypes are found in 15% to 20% of sporadic colon carcinomas.[86] The serrated adenoma–carcinoma pathway is also associated with methylation of *MLH1*, wherein gene dysfunction predisposes to dysplasia and rapid progression to carcinoma, much like MSI-high lesions seen in HNPCC/Lynch syndrome.[87] There is significant heterogeneity in the molecular profiles of SSPs suggesting that other pathways for carcinogenesis exist (**Fig. 4**).[88] *KRAS* mutations are associated with CIMP-low, SPS-associated CRC.[89] Germline mutations in genes that regulate cellular senescence pathways have also been identified in SSPs of patients with SPS.[90]

Screening and Surveillance for Serrated Polyposis Syndrome

Surveillance recommendations for patients with SPS include colonoscopy every 1 to 3 years depending on polyp burden (see **Table 2**).[43] In at-risk kindred, colonoscopy should begin at age 40 or 10 years earlier than the youngest relative diagnosed with SPS if complicated by CRC, whichever is earlier. Colonoscopy is repeated every 5 years in the absence of findings or every 1 to 3 years if polyps are identified.[6]

Although based on best available data, screening guidelines may underdiagnose patients resulting in prolonged screening intervals before a diagnosis is realized, placing patients at increased risk for interval carcinomas. Some argue that the finding of two or more serrated lesions on colonoscopy qualifies as screening criteria for close interval surveillance despite not meeting World Health Organization criteria. In a retrospective review of 500 patients with at least two or more serrated lesions, a median of

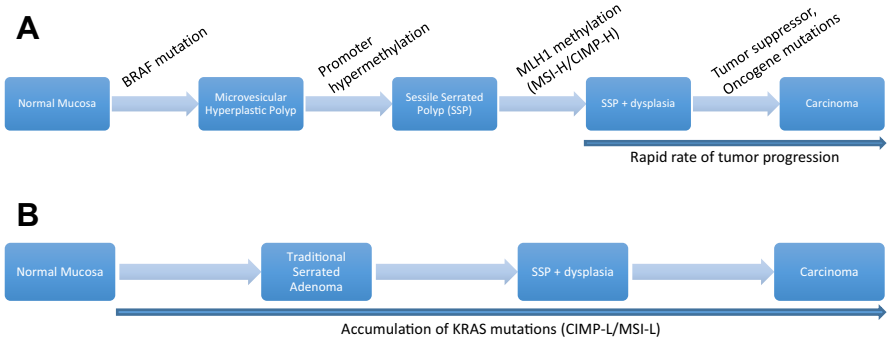

Fig. 4. Pathways for SPS-associated carcinogenesis. (*A*) Serrated adenoma-carcinoma pathway: hypermethylation of CpG islands results in MSI-H, CIMP-H carcinoma similar to Lynch-associated CRC. (*B*) KRAS serrated polyp pathway: resulting in MSI-L, CIMP-L carcinoma. (*Data from* Snover DC, Ahnen DJ, Burt RW, et al. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman FT, Carneiro F, Hruban RH, et al, editors. WHO Classification of Tumours of the Digestive System. 4th edition. Lyon: IARC; 2010. p. 160–65.)

four colonoscopies was performed before the diagnosis of SPS was made. Of the 40 patients (8%) with SPS, only one was diagnosed at initial colonoscopy and all 16 patients with CRC were diagnosed with SPS at the time of cancer diagnosis.[91]

Because of the subtle appearance of serrated polyps, chromoendoscopy or virtual chromoendoscopy with narrow band imaging is recommended to aid in detection of these lesions.[82] Increased withdrawal times of at least 9 minutes are associated with improved adenoma detection rates.[92] SSPs have indistinct borders and complete removal of these flat lesions is challenging. The rate of incomplete resection for SSPs is higher than conventional adenomas at 31% versus 7.2%.[93] This may contribute to the higher rate of interval carcinomas previously discussed and emphasizes the need for shorter screening intervals for lesions greater than 1 cm. In the case of numerous (>5), large (>2 cm), or dysplastic lesions, some authors support the use of serial endoscopic mucosal resection every 3 to 6 months until endoscopically cleared.[94]

Surgical Approach to Serrated Polyposis Syndrome

Surgical intervention is warranted when the polyp burden exceeds endoscopic management or when dysplasia/CRC is diagnosed. There is limited experience regarding the benefit of segmental versus TAC/IRA; however, the rate of synchronous and metachronous CRC approaches 26%, favoring extended colectomy.[88] In the case of segmental resection, annual colonoscopy of the remaining colon is recommended. If at least two successive colonoscopies reveal no lesions greater than 1 cm, no dysplastic lesions, or the mean number and size of the lesions is declining, this interval can be expanded to every 2 years.[94]

SUMMARY

Inherited CRC syndromes are a rare cause of CRC within the general population. Nevertheless, awareness of these unique syndromes leads to early diagnosis and prevention of cancer-related morbidity and mortality in affected individuals and families. Moreover, screening, counseling, and testing of at-risk kindred can translate into significant benefit across multiple generations, emphasizing the tremendous importance of understanding the heritable risks of each syndrome. Currently, surgery is the mainstay of CRC prevention and treatment of all of these syndromes. Operative

decision-making must take into account the life-long cancer risk of each patient and balance this against long-term function. The pathogenesis of most heritable CRC syndromes remains poorly understood. The use of cancer registries, genetic counseling and testing, and ongoing academic pursuits are instrumental in defining the genetic basis of this heterogeneous group, broadening the understanding of unique genotype-phenotype profiles, and customizing treatment strategies based on individual risk.

REFERENCES

1. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer: analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343(2):78–85.
2. Jasperson KW, Tuohy TM, Neklason DW, et al. Hereditary and familial colon cancer. Gastroenterology 2010;138(6):2044–58.
3. Kohlmann W, Gruber SB. Lynch syndrome [updated 2014 May 22]. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews [Internet]. Seattle (WA): University of Washington; 2004. p. 1993–2016.
4. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999;116(6):1453–6.
5. Guillem JG, Calle JP-L, Cellini C, et al. Varying features of early age-of-onset "sporadic" and hereditary nonpolyposis colorectal cancer patients. Dis Colon Rectum 1999;42(1):36–42.
6. Provenzale D, Gupta S, Ahnen DJ, et al. Genetic/familial high-risk assessment: colorectal version 1.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2016;14(8):1010–30.
7. Lynch HT, la Chapelle de A. Hereditary colorectal cancer. N Engl J Med 2003; 348(10):919–32.
8. Sinha A, Tekkis PP, Rashid S, et al. Risk factors for secondary proctectomy in patients with familial adenomatous polyposis. Br J Surg 2010;97(11):1710–5.
9. Lin KM, Shashidharan M, Ternent CA, et al. Colorectal and extracolonic cancer variations in MLH1/MSH2 hereditary nonpolyposis colorectal cancer kindreds and the general population. Dis Colon Rectum 2016;41(4):428–33.
10. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MYH associated with somatic G: C→T: A mutations in colorectal tumors. Nat Genet 2002;30(2):227–32.
11. Burt RW, Leppert MF, Slattery ML, et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology 2004; 127(2):444–51.
12. Jenkins MA. Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomarkers Prev 2006;15(2):312–4.
13. Edelstein DL, Axilbund J, Baxter M, et al. Rapid development of colorectal neoplasia in patients with Lynch syndrome. Clin Gastroenterol Hepatol 2011; 9(4):340–3.
14. Boparai KS, Dekker E, van Eeden S, et al. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. Gastroenterology 2008;135(6):2014–8.
15. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 2006;296(12):1507–17.

16. Nielsen M, Poley JW, Verhoef S, et al. Duodenal carcinoma in MUTYH-associated polyposis. J Clin Pathol 2006;59(11):1212–5.
17. Hampel H, Stephens JA, Pukkala E, et al. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. Gastroenterology 2005;129(2): 415–21.
18. Vogt S, Jones N, Christian D, et al. Expanded extracolonic tumor spectrum. Gastroenterology 2009;137(6):1976–85.e1-e10.
19. Dowty JG, Win AK, Buchanan DD, et al. Cancer risks for MLH1and MSH2 mutation carriers. Hum Mutat 2013;34(3):490–7.
20. Lipton L, Halford SE, Johnson V, et al. Carcinogenesis in MYH-associated polyposis follows a distinct genetic pathway. Cancer Res 2003;63(22):7595–9.
21. Win AK, Lindor NM, Young JP, et al. Risks of primary extracolonic cancers following colorectal cancer in Lynch syndrome. J Natl Cancer Inst 2012; 104(18):1363–72.
22. Plaschke J. Lower incidence of colorectal cancer and later age of disease onset in 27 families with pathogenic MSH6 germline mutations compared with families with MLH1 or MSH2 Mutations: the German Hereditary Nonpolyposis Colorectal Cancer Consortium. J Clin Oncol 2004;22(22):4486–94.
23. Hendriks YMC, Wagner A, Morreau H, et al. Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. Gastroenterology 2004;127(1):17–25.
24. Park YJ, Shin KH, Park JG. Risk of gastric cancer in hereditary nonpolyposis colorectal cancer in Korea. Clin Cancer Res 2000;6(8):2994–8.
25. Felton K, Gilchrist DM, Andrew SE. Constitutive deficiency in DNA mismatch repair: is it time for Lynch III? Clin Genet 2007;71(6):499–500.
26. Wijnen J, Khan PM, Vasen H, et al. Hereditary nonpolyposis colorectal cancer families not complying with the Amsterdam criteria show extremely low frequency of mismatch-repair-gene mutations. Am J Hum Genet 1997;61:329–35.
27. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch Syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96(4):261–8.
28. Boland CR, Shike M. Report from the Jerusalem workshop on Lynch syndrome-hereditary nonpolyposis colorectal cancer. Gastroenterology 2010;138(7): 2197.e1–7.
29. Sjursen W, Haukanes BI, Grindedal EM, et al. Current clinical criteria for Lynch syndrome are not sensitive enough to identify MSH6 mutation carriers. J Med Genet 2010;47(9):579–85.
30. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009; 11(1):35–41.
31. Moline J, Mahdi H, Yang B, et al. Implementation of tumor testing for Lynch syndrome in endometrial cancers at a large academic medical center. Gynecol Oncol 2013;130(1):121–6.
32. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308(15):1555.
33. Chen Y-E, Kao S-S, Chung R-H. Cost-effectiveness analysis of different genetic testing strategies for Lynch syndrome in Taiwan. PLoS One 2016;11(8):e0160599.
34. Severin F, Stollenwerk B, Holinski-Feder E, et al. Economic evaluation of genetic screening for Lynch syndrome in Germany. Genet Med 2015;17(10):765–73.

35. Shia J. Immunohistochemistry versus microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. Part I. The utility of immunohistochemistry. J Mol Diagn 2008; 10(4):293–300.
36. Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute workshop on microsatellite instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 1998;58(22):5248–57.
37. Hegde M, Ferber M, Mao R, et al. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). Genet Med 2014;16(1):101–16.
38. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA 2005;293(16):1979–85.
39. Stoffel EM, Chittenden A. Genetic testing for hereditary colorectal cancer: challenges in identifying, counseling, and managing high-risk patients. Gastroenterology 2010;139(5):1436–41.e1.
40. Niessen RC, Hofstra RMW, Westers H, et al. Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome. Genes Chromosomes Cancer 2009;48(8):737–44.
41. Nagasaka T, Rhees J, Kloor M, et al. Somatic hypermethylation of MSH2 is a frequent event in Lynch syndrome colorectal cancers. Cancer Res 2010;70(8): 3098–108.
42. Bouzourene H, Hutter P, Losi L, et al. Selection of patients with germline MLH1 mutated Lynch syndrome by determination of MLH1 methylation and BRAF mutation. Fam Cancer 2009;9(2):167–72.
43. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110(2):223–62.
44. Järvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, et al. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. J Clin Oncol 2009;27(28):4793–7.
45. Natarajan N, Watson P, Silva-Lopez E, et al. Comparison of extended colectomy and limited resection in patients with Lynch syndrome. Dis Colon Rectum 2010; 53(1):77–82.
46. Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut 2011;60(7):950–7.
47. Maeda T, Cannom RR, Beart RW, et al. Decision model of segmental compared with total abdominal colectomy for colon cancer in hereditary nonpolyposis colorectal cancer. J Clin Oncol 2010;28(7):1175–80.
48. Järvinen HJ. Epidemiology of familial adenomatous polyposis in Finland: impact of family screening on the colorectal cancer rate and survival. Gut 1992;33(3): 357–60.
49. Aretz S, Uhlhaas S, Caspari R, et al. Frequency and parental origin of de novo APC mutations in familial adenomatous polyposis. Eur J Hum Genet 2004; 12(1):52–8.
50. Bisgaard ML, Fenger K, Bülow S, et al. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. Hum Mutat 1994;3:121–3.
51. Bülow S. Results of national registration of familial adenomatous polyposis. Gut 2003;52(5):742–6.

52. Mallinson EKL, Newton KF, Bowen J, et al. The impact of screening and genetic registration on mortality and colorectal cancer incidence in familial adenomatous polyposis. Gut 2010;59(10):1378–82.
53. Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989;2(8666):783–5.
54. Sinha A, Tekkis PP, Gibbons DC, et al. Risk factors predicting desmoid occurrence in patients with familial adenomatous polyposis: a meta-analysis. Colorectal Dis 2010;13(11):1222–9.
55. Nieuwenhuis MH, Lefevre JH, Bülow S, et al. Family history, surgery, and APC mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. Dis Colon Rectum 2011;54(10):1229–34.
56. Church J, Xhaja X, LaGuardia L, et al. Desmoids and genotype in familial adenomatous polyposis. Dis Colon Rectum 2015;58(4):444–8.
57. Groen EJ, Roos A, Muntinghe FL, et al. Extra-intestinal manifestations of familial adenomatous polyposis. Ann Surg Oncol 2008;15(9):2439–50.
58. Kubo K, Miyatani H, Takenoshita Y, et al. Widespread radiopacity of jaw bones in familial adenomatosis coli. J Craniomaxillofac Surg 1989;17(8):350–3.
59. Balaguer F, Leoz M, Carballal S, et al. The genetic basis of familial adenomatous polyposis and its implications for clinical practice and risk management. Appl Clin Genet 2015;8:95–107.
60. Caspari R, Friedl W, Mandl M, et al. Familial adenomatous polyposis: mutation at codon 1309 and early onset of colon cancer. Lancet 1994;343(8898):629–32.
61. Nieuwenhuis MH, Vasen HFA. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. Crit Rev Oncol Hematol 2007;61(2):153–61.
62. Ripa R, Bisgaard ML, Bülow S, et al. De novo mutations in familial adenomatous polyposis (FAP). Eur J Hum Genet 2002;10(10):631–7.
63. Ho JW, Chu KM, Tse CW. Phenotype and management of patients with familial adenomatous polyposis in Hong Kong: perspective of the hereditary gastrointestinal cancer registry. Hong Kong Med J 2002;8(5):342–7.
64. Bjork J, Akerbrant H, Iselius L, et al. Epidemiology of familial adenomatous polyposis in Sweden: changes over time and differences in phenotype between males and females. Scand J Gastroenterol 1999;34(12):1230–5.
65. Aretz S, Uhlhaas S, Goergens H, et al. MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. Int J Cancer 2006;119(4):807–14.
66. Bussey H. Familial polyposis coli: family studies, histopathology, differential diagnosis, and results of treatment. Baltimore (MD): Johns Hopkins University Press; 1975.
67. Vasen HFA, Moslein G, Alonso A, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008;57(5):704–13.
68. Herendeen JM, Lindley C. Use of NSAIDs for the chemoprevention of colorectal cancer. Ann Pharmacother 2003;37(11):1664.
69. Giardiello FM, Hamilton SR, Krush AJ. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 1993;328(18):1313–6.
70. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000;342(26):1946–52.
71. Nugent KP, Farmer KC, Spigelman AD, et al. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. Br J Surg 1993;80(12):1618–9.

72. O'Brien D. Polyps in the ileal pouch. Clin Colon Rectal Surg 2008;21(04):300–3.
73. Samadder NJ, Neklason DW, Boucher KM, et al. Effect of sulindac and erlotinib vs placebo on duodenal neoplasia in familial adenomatous polyposis. JAMA 2016;315(12):1266.
74. Campos FG. Surgical treatment of familial adenomatous polyposis: dilemmas and current recommendations. World J Gastroenterol 2014;20(44):16620.
75. Lovegrove RE, Constantinides VA, Heriot AG, et al. A comparison of hand-sewn versus stapled ileal pouch anal anastomosis (IPAA) following proctocolectomy. Ann Surg 2006;244(1):18–26.
76. Chambers WM, McC Mortensen NJ. Should ileal pouch-anal anastomosis include mucosectomy? Colorectal Dis 2007;9(5):384–92.
77. Fazio VW, Kiran RP, Remzi FH, et al. Ileal pouch anal anastomosis. Ann Surg 2013;257(4):679–85.
78. Aziz O, Athanasiou T, Fazio VW, et al. Meta-analysis of observational studies of ileorectalversus ileal pouch–anal anastomosis for familial adenomatous polyposis. Br J Surg 2006;93(4):407–17.
79. Soravia C, Klein L, Berk T, et al. Comparison of ileal pouch-anal anastomosis and ileorectal anastomosis in patients with familial adenomatous polyposis. Dis Colon Rectum 1999;42(8):1028–33 [discussion1033–4].
80. Olsen KO, Juul S, Bülow S, et al. Female fecundity before and after operation for familial adenomatous polyposis. Br J Surg 2003;90(2):227–31.
81. Burt R, Neklason DW. Genetic testing for inherited colon cancer. Gastroenterology 2005;128(6):1696–716.
82. Rodriguez-Moranta F, Rodriguez-Alonso L, Guardiola Capon J. Serrated polyposis syndrome. Cir Esp 2014;92(10):643–4.
83. Rosty C, Parry S, Young JP. Serrated polyposis: an enigmatic model of colorectal cancer predisposition. Patholog Res Int 2011;2011(4):1–13.
84. Snover DC, Ahnen DJ, Burt RW, et al. Serrated polyps of the colon and rectum and serrated ("hyperplastic") pol-yposis. In: Bosman ST, Carneiro F, Hruban RH, et al, editors. WHO Classification of tumours of the digestive system. Berlin: Springer-Verlag; 2010.
85. Langner C. Serrated and non-serrated precursor lesions of colorectal cancer. Dig Dis 2015;33(1):28–37.
86. Kanth P, Bronner MP, Boucher KM, et al. Gene signature in sessile serrated polyps identifies colon cancer subtype. Cancer Prev Res (Phila) 2016;9(6):456–65.
87. Anderson JC. Pathogenesis and management of serrated polyps: current status and future directions. Gut Liver 2014;8(6):582–9.
88. Rosty C, Walsh MD, Walters RJ, et al. Multiplicity and molecular heterogeneity of colorectal carcinomas in individuals with serrated polyposis. Am J Surg Pathol 2013;37(3):434–42.
89. Elorza G, Enríquez-Navascués JM, Bujanda L, et al. Phenotype characteristics of patients with colonic serrated polyposis syndrome: a study of 23 cases. Cir Esp 2014;92(10):659–64.
90. Gala MK, Mizukami Y, Le LP, et al. Germline mutations in oncogene-induced senescence pathways are associated with multiple sessile serrated adenomas. Gastroenterology 2014;146(2):520–9.
91. Hui VW, Steinhagen E, Levy RA, et al. Utilization of colonoscopy and pathology reports for identifying patients meeting the world health organization criteria for serrated polyposis syndrome. Dis Colon Rectum 2014;57(7):846–50.

92. Butterly L, Robinson CM, Anderson JC, et al. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire colonoscopy registry. Am J Gastroenterol 2014;109(3):417–26.
93. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy: results of the complete adenoma resection (CARE) study. Gastroenterology 2013;144(1):74–80.e1.
94. Hassan C, Repici A, Rex DK. Serrated polyposis syndrome: risk stratification or reduction? Gut 2016;65(7):1070–2.