CME

REVIEW

Hereditary Colorectal Polyposis and Cancer Syndromes: A Primer on Diagnosis and Management

Priyanka Kanth, MD, MS[1], Jade Grimmett, MS[2,3], Marjan Champine, MS[2,3], Randall Burt, MD[1,2,4] and N. Jewel Samadder, MD, MSc, FRCPC[1,2,5]

Colorectal cancer (CRC) is the fourth most common cancer amongst men and women. Between 3 and 6% of all CRCs are attributed to well-defined inherited syndromes, including Lynch syndrome, familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), and several hamartomatous polyposis conditions. Identification of these patients through family history and appropriate genetic testing can provide estimates of cancer risk that inform appropriate cancer screening, surveillance and/or preventative interventions. This narrative review examines the hereditary colorectal cancer and polyposis syndromes, their genetic basis, clinical management, and evidence supporting cancer screening.

Am J Gastroenterol 2017; 112:1509–1525; doi:10.1038/ajg.2017.212; published online 8 August 2017

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and second leading cause of death in both men and women in United States (1). Hereditary CRCs occurring due to mutations and defects in certain genes makes up roughly 5% of all CRC. Another 25–30% of CRC patients may have a family member with a diagnosis of CRC in the absence of any known genetic alterations. High-risk hereditary predisposition syndromes have been associated with a 70–100% lifetime risk for development of CRCs and many syndromes carry an increased risk for extra-intestinal malignancies. Given the substantial cancer risk, patients with these mutations are recommended to follow increased surveillance and comprehensive management protocols when compared to the general population with an average CRC risk profile. The role of genetic counseling becomes immensely significant in managing these patients.

The aim of this review is to provide comprehensive literature on most commonly encountered hereditary CRCs and polyposis syndromes including Lynch syndrome (LS), familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), serrated polyposis syndrome (SPS), and other hamartomatous polyposis conditions. We also highlight the evidence supporting the use of endoscopy and potential chemoprevention strategies for the reduction of CRC. An insight into the best utilization of the genetic counseling service is discussed to provide busy clinicians with tools to work tandemly with genetic specialists in optimal management of this high-risk population. Many of the recommendations in this paper are based on the National Comprehensive Cancer Network (NCCN) guidelines (2).

Lynch syndrome

Overview. LS accounts for ~2–4% of all CRCs and is the most common cause of hereditary colon cancer (3). LS also confers an increased risk for extra-colonic cancers such as that of the endometrium, ovaries, stomach, small intestine, hepatobiliary tract, urinary tract, and central nervous system. The lifetime estimated risk of CRC ranges from 50 to 80% followed by the second highest risk of 40 to 60% for endometrial cancer (4). The prevalence of LS is expected to be 1 in 440 (5).**Table 1** describes the lifetime risks to develop the above mentioned cancers in individuals with LS. The prospective LS database now provides the most accurate estimates of cancer risks, according to their age, gender and the underlying gene (http://lscarisk.org/).

Genetics. LS is an autosomal dominant condition that occurs due to dysfunction in DNA mismatch repair (MMR). This is caused by mutations in one of five genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, *and EPCAM*. As DNA replicates, it produces errors that may include single nucleotide mismatch, insertions, and deletion loops (6). The function of the MMR gene system is to assess and maintain the fidelity of DNA by correcting areas of DNA replication errors. Mutations in *MLH1* and *MSH2* account for ~70% of cases of LS. Mutations in *MSH6* cause up to 14% and PMS2 mutations contribute <15% of LS cases (7,8). Most of the data regarding

[1]Department of Medicine (Gastroenterology), University of Utah, Salt Lake City, Utah, USA; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA; [3]Department of Genetic Counseling Resource, University of Utah, Salt Lake City, Utah, USA; [4]Department of Oncological Sciences, University of Utah, Salt Lake City, Utah, USA; [5]Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona, USA. **Correspondence:** N. Jewel Samadder, MD, MSc, FRCPC, Division of Gastroenterology and Hepatology, Mayo Clinic, 13400 E. Shea Blvd, Scottsdale, Arizona, USA. E-mail: nsamadde@gmail.com
Received 3 August 2016; accepted 23 June 2017

Table 1. Cancer risks, genes associated and recommendations for management of hereditary CRC syndromes

Syndrome	Gene(s)	Lifetime cancer risks	% (95% CI)	Screening/surveillance	Preventative surgery
Lynch syndrome	MSH2 (10)	Colorectum	49 (29–85)	Colonoscopy every 1–2 years starting at age 20–25 years	Consider prophylactic hysterectomy once child bearing complete
	EPCAM	Endometrium	57 (22–82)	Consider upper endoscopy every 3–5 years, starting at age 30–35 years	
		Stomach	11–19	Consider endometrial cancer screening	
		Ovary	20 (1–66)		
		Hepatobiliary	2–7		
		Upper urinary tract	4–5		
		Pancreas	3–4		
		Small bowel	1–4		
		CNS (glioblastoma)	1–3		
	MLH1(10)	Colorectum	52 (31–90)	Colonoscopy every 1–2 years starting at age 20–25 years	Consider prophylactic hysterectomy once child bearing complete
		Endometrium	21 (9–82)	Consider upper endoscopy every 3–5 years, starting at age 30–35 years	
		Stomach	11–19	Consider endometrial cancer screening	
		Ovary	38 (3–81)		
		Hepatobiliary	2–7		
		Upper urinary tract	4–5		
		Pancreas	3–4		
		Small bowel	1–4		
		CNS (glioblastoma)	1–3		
Lynch syndrome	MSH6 (10)	Colorectum	18 (13–30)	Colonoscopy every 1–2 years starting at age 20–25 years	Consider prophylactic hysterectomy once child bearing complete
		Endometrium	17 (8–47)	Consider upper endoscopy every 3–5 years, starting at age 30–35 years	
		Stomach	≤3	Consider endometrial cancer screening	
		Ovary	1(0–3)		
		Urinary tract	<1		
Lynch syndrome	PMS2 (11)	Colorectum	15–20	Colonoscopy every 1–2 years starting at age 20–25 years	Consider prophylactic hysterectomy once child bearing complete
		Endometrium	15	Consider upper endoscopy every 3–5 years, starting at age 30–35 years	
				Consider endometrial cancer screening	
FAP: Classic	APC (54,167,168)	Colorectum	100	Colonoscopy every 1–2 years starting at age 10–12 years	Consideration for colectomy when polyp burden too great for endoscopic control
		Duodenum/periampullary	4–12	Upper endoscopy every 1–3 years starting at age 18–25 years	

Table 1 continued on following page

Table 1. Continued

Syndrome	Gene(s)	Lifetime cancer risks	% (95% CI)	Screening/surveillance	Preventative surgery
		Stomach	<1	Consider thyroid ultrasound	
		Pancreas	2		
		Thyroid	1–2		
		Liver (hepatoblastoma)	1–2		
		CNS (medulloblastoma)	<1		
FAP: Attenuated	APC (54,55, 58,169–171)	Colorectum	70	Colonoscopy every 1–2 years, starting at age 20–25 years	Consideration for colectomy when polyp burden too great for endoscopic control
		Duodenum/Periampullary	4–12	Upper endoscopy every 1–3 years	
		Thyroid	1–2	Consider thyroid ultrasound	
MAP	MUTYH (54,58,113, 115,123,172,173)	Colorectum	80	Colonoscopy every 1–2 years, starting at age 20–25 years	Consideration for colectomy when polyp burden too great for endoscopic control
		Duodenum	4		
PJS	STK11(54,140,174)	Breast	54	Upper endoscopy every 2–3 years starting in late teens	
		Colorectum	39	Small bowel screening (CT/MR enterography, small bowel follow-through, capsule endoscopy) every 1–3 years starting at 8–10 years	
		Pancreas	11–36	Colonoscopy every 2–3 year, starting in late teens	
		Stomach	29	Pancreas screening (MRCP or EUS) every 1–2 years, starting at age 25–30 years	
		Ovary	21	Mammogram and breast MRI yearly, starting at age 25 years	
		Lung	15	Testicular examination/ultrasound yearly, starting age 10 years	
		Small bowel	13	Transvaginal ultrasound, yearly, starting at age 18 years	
		Uterine/cervix	9–10		
		Testicle	<1		
JPS	SMAD4 (54,127,175–177)	Colorectum	39	Upper endoscopy every 1–3 years starting at age 15 years	
	BMPR1A	Stomach, pancreas and small bowel	21	Colonoscopy every 1–3 years starting at age 15 years	
SPS	Unknown (143,153,178)	Colorectum	16–42	Colonoscopy every 1–3 years	

APC, Adenomatous Polyposis Coli gene; CI, confidence interval; CNS, central nervous system; CT, computed tomography; EPCAM, epithelial cell adhesion molecule; EUS, endoscopic ultrasound; FAP, familial adenomatous polyposis; JPS, juvenile polyposis syndrome; MAP, MUTYH-associated polyposis; MRCP, magnetic resonance cholangiography and pancreatography; MRI, magnetic resonance imaging; PJS, Peutz–Jeghers syndrome; SPS, serrated polyposis syndrome.

these cancer risks are derived from studies involving the Caucasian population, though similar cumulative risks of cancer have also been noted in the African–American population (9). *MLH1* and *MSH2* mutations confer an elevated risk of cancer development when compared to *MSH6* and *PMS2* (10,11). Epithelial cell adhesion molecule (*EPCAM*), another gene associated with LS, does not belong to the MMR gene family but a germline deletion of this gene leads to inactivation of *MSH2* in about 1–3% of individuals with LS (12,13). Recent literature also suggests that this *EPCAM* deletion may primarily cause CRC with less evidence of development of extra-colonic cancers (14,15).

Diagnosis. Given the high risk of developing CRC and extra-colonic cancers, early detection of patients carrying a gene mutation associated with LS is critical. Routine use of the Amsterdam and revised Bethesda criteria is recommended in

Table 2. Diagnostic guidelines for Lynch syndrome

Criteria Name	Criteria specifics
Amsterdam	
Amsterdam I	Three relatives with colorectal cancer (CRC); all of the following criteria should be present:
	a) one of which is a first-degree relative of the other two
	b) colorectal cancer affecting more than one generation
	c) at least one colorectal cancer diagnosed before age 50 years
	d) familial adenomatous polyposis should be excluded
	e) tumors should be verified by pathologic examination
Amsterdam II	Three relatives with Lynch syndrome-related[a] cancers; all of the following criteria should be present:
	a) One of which is a first-degree relative of the other two;
	b) LS-related cancer affecting more than one generation;
	c) At least one LS-related cancer diagnosed before age 50 years
	d) Familial adenomatous polyposis should be excluded
	e) Tumors should be verified by pathologic examination
Revised Bethesda criteria	Tumors from individuals should be tested for microsatellite instability (MSI) in the following situations:
	a) CRC diagnosed in a patient who is younger than 50 years of age
	b) Presence of synchronous, or metachronous, colorectal or other LS-related tumors; regardless of age
	c) CRC with MSI-high histology diagnosed in a patient who is younger than 60 years of age
	d) CRC diagnosed in a patient with one or more first-degree relatives with a LS-related cancer, with one of the cancers being diagnosed under age 50 years;
	e) CRC diagnosed in a patient with two or more first- or second-degree relatives with LS-related cancer regardless of age

CNS, central nervous system; CRC, colorectal cancer; GI, gastrointestinal; LS, Lynch syndrome; MSI, microsatellite instability.
LS-related[a] cancer sites included the colon, rectum, endometrium, gastric, ovary (including fallopian), sebaceous gland adenomas/carcinoma, small bowel, ureteric/renal pelvis, or CNS gliomas (including glioblastoma and astrocytoma).

clinical practice to diagnose and/or identify at-risk patients and those who warrant additional evaluation (either via tumor tissue testing or germline testing) for LS (**Table 2**) (16). Risk prediction tools are also available to identify patients with possible LS. PREMM($_{1,2,6}$), MMRpro and MMRpredict are frequently used models that use personal and family history of cancer to estimate a patient's risk of carrying a mutation in one of the LS genes (16,17). A study by Kastrinos *et al.* (18) distributed a brief yes/no questionnaire to patients before colonoscopy that appears to be effective in quickly identifying patients with an increased risk of CRC. The final validated questions from this tool include: (a) Do you have a first-degree relative with any of the following conditions diagnosed before age 50? Colon or rectal cancer AND/OR cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, and bladder) bile ducts, pancreas, or brain (b) Have you had any of the following conditions diagnosed under 50? Colon or rectal cancer AND/OR polyps (c) Do you have 3 or more relatives with a history of colon or rectal cancer? This tool could be especially useful in a busy primary care practice or outpatient endoscopy setting to capture patients and families with potential LS or other hereditary CRC syndrome.

Tumor tissue screening for LS includes testing for microsatellite instability (MSI) status and/or immunohistochemistry staining of the adenocarcinoma to evaluate for the expression of the proteins created by the MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Testing of adenomas is generally avoided due to the high risk of false negative results. If immunohistochemistry staining is abnormal, germline testing can be targeted to the gene associated with the absent protein. Depending on the results, reflex to BRAF and/or methylation testing may be indicated. NCCN guidelines provide a table for testing strategy dependent upon tumor testing results. 90% of LS associated CRCs are microsatellite high (MSI-H) tumors whereas around 15% of sporadic CRC could be MSI-H. A recent Dutch study tested tumor tissue of over 1100 CRC patients for MSI status, immunohistochemistry analysis for MMR protein expression and for MLH-1 hypermethylation. The study detected 23 LS patients and was found to be cost effective for identifying LS patients and their families (19). Although no guidelines currently exist regarding universal screening for LS in patients diagnosed with endometrial cancer, studies have found molecular screening of endometrial cancer to be effective in identifying LS (20–23). Current guidelines suggest testing every CRC for MSI or immunohistochemistry to identify LS-related cancers (16). Data also suggest universal screening for LS could be a cost effective strategy (24). With the continually decreasing cost of next generation DNA sequencing, companies have introduced "panels" of multiple genes

involved in colorectal or gastrointestinal cancers that can be completed for a similar price to single-gene testing historically. Evaluation of multiple genes introduces unique complexity including a higher probability of identifying variants of uncertain significance. Without proper background, this result may cause unnecessary concern or anxiety on the part of the clinician and/or patient. Also multi-gene panel testing may identify an otherwise unsuspected pathogenic mutation in a gene not consistent with the patient's medical or family history. Nevertheless, many genetics clinics continue to utilize multi-gene panel testing for at-risk individuals instead of relying solely on tumor or single-gene testing. This is due to several reasons including cost-effectiveness and efficient use of clinical time.

Constitutional mismatch repair deficiency is a rare syndrome caused by biallelic mutations in the MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) (25). These mutations can lead to the development of various malignancies including hematologic, central nervous system, and other LS associated tumors. *PMS2* is the most frequently mutated gene and other MMR genes contribute up to 40% of cases (26). The malignancies usually occur early during childhood (25). Café-au-lait spots and skin-fold freckling are the typical skin lesions and patients with these findings and a suspicious personal or family history of polyposis or CRC should be evaluated for constitutional mismatch repair deficiency. Individuals with a monoallelic MMR mutation should continue to follow LS screening guidelines.

Colorectal surveillance and management. There are substantial data describing reduction in CRC incidence and/or mortality in LS patients undergoing recommended surveillance (27–31). Jarvinen *et al.*'s (27) prospective study from Finland followed 252 first-degree relatives of LS patients for 15 years and showed up to 62% reduction in CRC incidence and 65% reduction in overall mortality.

Colon cancer surveillance by colonoscopy is recommended for all individuals with a confirmed molecular diagnosis of LS and this screening should begin by 20–25 years of age (3). A study by Vasen *et al.* (30) followed 205 LS families and showed lower risk of CRC development when a colonoscopy interval of 1–2 years was followed as compared to screening in 2–3 year intervals. NCCN guidelines recommend surveillance colonoscopy every 1–2 years in confirmed mutation carriers. Given the comparatively lower cancer risk in patients with *MSH6* and *PMS2* mutations, surveillance starting at age 25–30 years may be considered for patients with germline mutations in these two genes (4).

A recent large prospective multicenter study suggested revised cancer risk estimates for LS mutation carriers (32). This study by the European Mallorca group followed 1,942 mutation carriers without prior cancer for an average of 7 years. Even though screening colonoscopy was performed at intervals of 2–3 years, the cumulative CRC incidence at age 70 was found to be 46% for *MLH1* carriers and 35% in *MSH2* carriers with lower incidence in *MSH6* and *PMS*2 carriers. This supports a more aggressive 1–2 year surveillance period to limit interval cancers in this population.

Studies in usage of chromoendoscopy to screen individuals with LS is limited. Huneburg and colleagues showed an increase in adenoma detection using Chromoendoscopy when compared to white light or narrow band imaging (33). Another smaller study by Stoffel *et al.* (34) showed an increase in overall polyp detection with chromoendoscopy but an increase in adenoma detection was not noted. A multicenter study from Europe randomized 78 LS patients to non-high definition white light endoscopy followed by chromoendoscopy during the same visit. 41% of subjects had at least one adenoma detected on chromoendoscopy as compared to 23% of subjects with white light endoscopy, alone (35). A major limitation of chromoendoscopy studies have been the use of standard definition imaging instead of high definition colonoscopes to perform the screening exam. Although there are no current US recommendations, the European Society of Gastrointestinal Endoscopy (ESGE) Guidelines recommends using chromoendoscopy in routine practice for known or suspected LS patients (36). Larger prospective trials using high definition colonoscopy and long-term outcomes are needed to strongly recommend chromoendoscopy in patients with LS.

Extra-colonic cancer surveillance and management. In addition to an increased risk for CRC, individuals with LS, particularly those with an *MLH1*, *MSH2*, and *MSH6* mutation, are also at increased risk of developing extra-colonic cancers, such as endometrial, ovarian, stomach, and small bowel.

There is currently insufficient evidence to support universal screening for endometrial and ovarian cancer in women with LS (37). However, annual endometrial sampling and transvaginal ultrasound is an option. Some clinicians may also order serum CA-125, with the same caveat for insufficient evidence. In a retrospective cohort study of 315 women with LS, those undergoing prophylactic hysterectomy and/or bilateral salpingo-oophorectomy did not have any occurrence of endometrial, ovarian, or primary peritoneal cancer compared to a matched group of women with LS not undergoing preventive surgery (38). Thus, prophylactic hysterectomy with bilateral salpingo-oophorectomy is a consideration in women with LS who have completed child-bearing.

Current evidence regarding the efficacy of screening for gastric cancers in LS patients is lacking. Intestinal type of adenocarcinoma is the primary cancer histology noted in this group (39). Screening and treatment of *Helicobacter Pylori* (*H. Pylori*) infection is recommended in LS patients to decrease the risk of gastric cancer (31). To date, there is only one study from Netherlands reporting *H. Pylori* screening outcomes. This study evaluated 184 LS mutation carriers and found *H. Pylori* prevalence similar to the general population in carriers and patients with a first-degree relative (FDR) with gastric cancer (40). Current ACG recommendations suggest performing a baseline upper endoscopy by age 30–35 with gastric biopsy in patients with or at risk for LS. Surveillance may be considered every 3–5 years for LS patients with a family history of gastric or duodenal cancer although there is very little evidence of support (4). Currently, there are no defined guidelines on gastric mapping biopsies for evaluation of gastric cancer or pre-malignant gastric lesions.

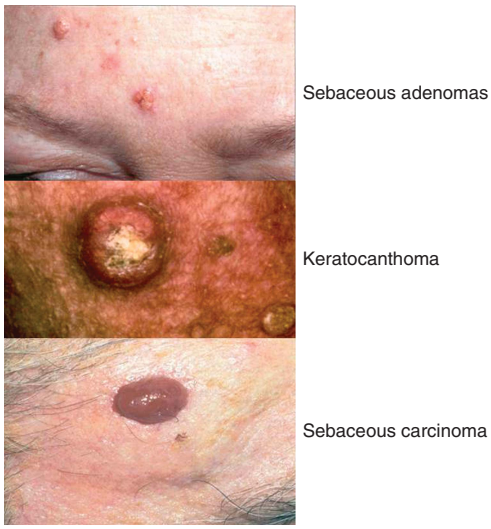

Figure 1. Lynch syndrome associated cutaneous manifestations, including sebaceious adenomas, keratocanthomas, and sebaceous carcinoma.

Risk of small bowel cancer ranges from 0.4 to 12% in LS. Haastra *et al.* (41) found a 1.5% prevalence of small bowel lesions using video capsule endoscopy in 200 patients with LS. As the risk of small bowel cancer in LS patients is relatively low and no effective imaging or endoscopic modality for screening the entire length of the small bowel, there are currently no recommendations to screen for small bowel cancers in individuals with LS.

There is also an elevated risk of pancreatic cancer in LS gene mutation carriers. A large study of 147 families with MMR mutations found a cumulative risk for pancreatic cancer of 3.7% by age 70 years (42). Based on an international expert consensus panel, annual screening is recommended using magnetic resonance imaging (MRI) and/or endoscopic ultrasonography modalities for LS gene mutation carriers who also have at least one FDR with pancreatic cancer (43). NCCN or ACG currently do not recommend screening for pancreatic cancer in LS.

There are currently no standard screening recommendations associated with urinary tract cancers or skin malignancies (**Figure 1**) in individuals with LS.

Individual screening recommendations may be modified based on the ages of onset and type(s) of cancers reported in the patient and/or their family.

Chemoprevention. Chemoprevention offers an attractive option to prevent the occurrence of cancer in high-risk cancer syndromes, such as FAP and LS. However, data, especially from clinical trials, are sparse. In the randomized CAPP2 trial, 861 participants with LS took either daily aspirin (600 mg) or placebo for up to 4 years; the primary endpoint was the development of CRC (44). After a mean follow-up of 55.7 months, participants taking daily aspirin for at least 2 years had a 63% reduction in the incidence of CRC (incidence rate ratio, 0.37; 95% CI, 0.18–0.78; *P*=0.008). These participants also appreciated a reduced risk from all LS cancers (incidence rate ratio, 0.42; 95% CI, 0.25–0.72; *P*=0.001). Risk of colorectal polyps was unaffected, and there was no protection seen for participants who completed <2 years of the intervention. Subgroup analyses from this trial showed that the association between obesity and CRC in patients with LS may be attenuated by taking daily aspirin (45). However, limitations of the CAPP2 trial highlight the need for larger and long-term randomized trials in this area (46,47). Similar findings have been reported in an observational study from the Colon Cancer Family Registry. In 1,858 patients who have LS, aspirin use was associated with reduced risk of CRC, for both patients who took aspirin for 5 or more years (HR, 0.25; 95% CI, 0.10–0.62; *P*=0.003) and between 1 month and 4.9 years (HR, 0.49; 95% CI, 0.27–0.90; *P*=0.02), compared to those who took aspirin for <1 month (48).

In September 2015, the United States Preventive Services Task Force (USPSTF) updated its guidelines and provided low dose aspirin with a grade "B" recommendation for chronic disease prophylaxis, including CRC prevention, among US adults between ages 50 and 59 with a >10% 10-year risk of cardiovascular events. Many patients with LS may fall into this category during their lifetime of surveillance (49).

Since aspirin is an anti-platelet agent, bleeding risk is its most significant side effect. There is a relative increase in risk of hemorrhagic strokes by 32–36% and extracranial (mostly gastrointestinal) bleeds by 30–70% from baseline with low or standard dose aspirin treatment. Hence it is imperative to carry out future studies that will measure the risk-benefit profile of prescribing low dose or high-dose aspirin treatment in individuals at risk of CRC (including those with hereditary predisposition). Cuzick *et al.* (50) have examined the overall risk-benefit ratio for aspirin and found that cardiovascular benefits are offset by adverse events in a whole population approach involving treatment of 55–65 year olds. However, when the protective effect against cancer is factored in, the benefits are clear with an overall 4% reduction in mortality.

Based on the limited evidence above, we suggest that aspirin may be used to prevent cancer in patients with LS, but the optimal dose is currently unknown. This is consistent with the stance of the American Gastroenterological Association (5). In contrast, the American College of Gastroenterology does not recommend standard use of aspirin for chemoprevention (4). Many expert clinicians advise their LS patients to use either 81 mg or 300 mg per day of aspirin, which may provide a chemopreventive benefit while reducing the likelihood of side effects (i.e., peptic ulcer disease, gastrointestinal bleeding, and hemorrhagic stroke)—but again this dosing has yet to be shown to be effective in clinical trials. The CAAPP3 trial is currently enrolling participants in Europe and will involve a double blind dose non-inferiority trial comparing 100, 300, or 600 mg daily in 3,000 LS gene carriers and will provide much needed clarity in the future.

Familial adenomatous polyposis (classic and attenuated)

Overview. FAP is the second most common hereditary CRC syndrome after LS. FAP is an autosomal dominant condition that clinically presents with generally hundreds to thousands of adenomatous polyps distributed throughout the colon and

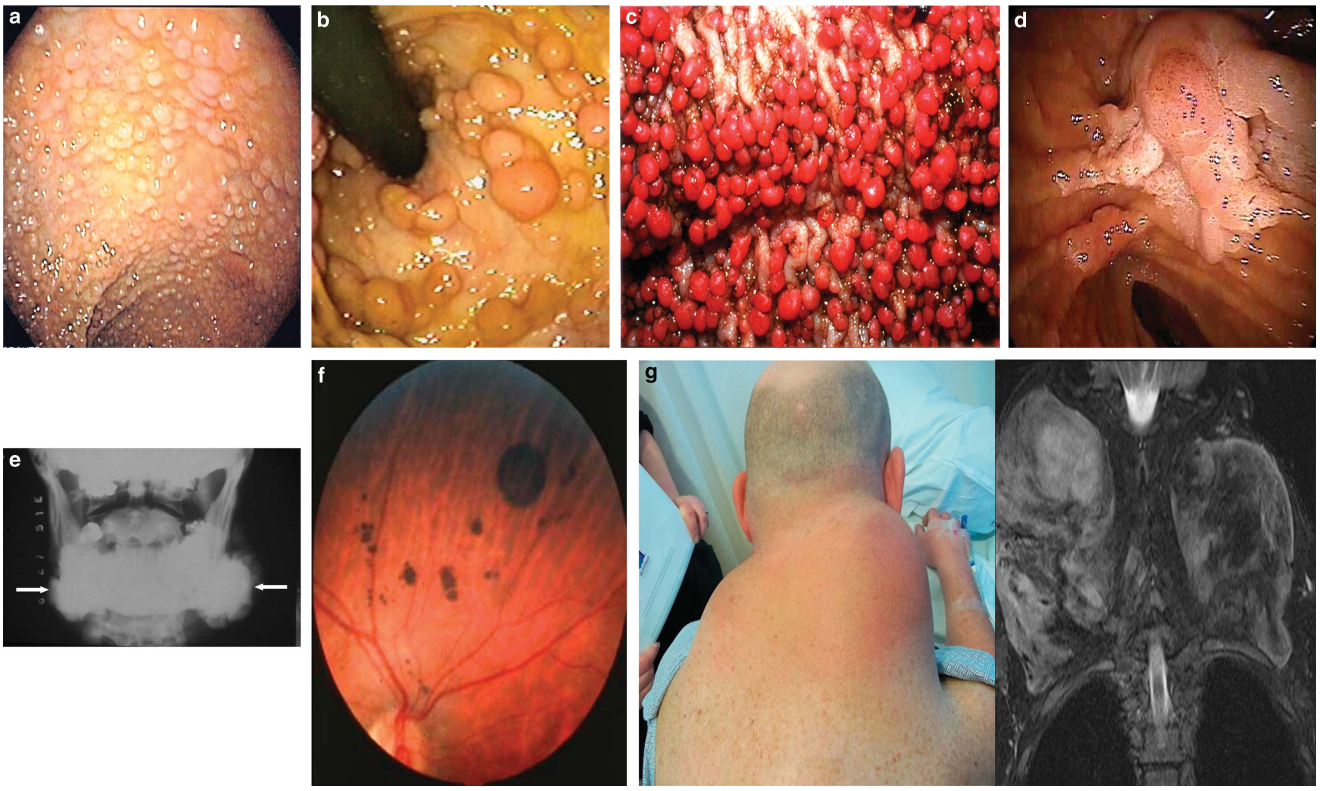

Figure 2. FAP is characterized by the presence of hundreds or thousands of adenomatous polyps in the colons of affected individuals, which often start in adolescence. Panels **a** and **b** are endoscopic views of the colon, while panel **c** is from a gross pathology specimen from a FAP patient undergoing total colectomy and carpeted with thousands of adenomatous polyps. (**d**) Periampullary region in a patient with FAP showing a large adenomatous polyp with beard like extension developing from the ampulla. (**e**) A radiograph of an FAP with osteomas of the mandible. (**f**) Fundus photography of congenital hypertrophy of the retinal pigment epithelium (CHRPE) lesions. One large and multiple peripheral punctiform CHRPE lesions. (**g**) An FAP patient with a 10–13 cm left neck mass and multiple growths on his back. MRI of the neck revealed a diffusely infiltrating soft tissue fibrous tumor involving the upper back and posterior paraspinous soft tissues, consistent with a desmoid tumor.

rectum (**Figure 2a–c**). Large epidemiological polyposis registries have documented FAP prevalence to be around 1 in 10,000 live births (51–53). FAP also accounts for ~1% of all CRCs with equal distribution in men and women. Polyps generally develop in the early teens and lifetime risk of colon cancer reaches up to 100% if colectomy is not performed. In addition, there is a small potential risk for extra-colonic cancers including that of duodenum, thyroid, hepatoblastoma, osteomas, stomach, pancreas, and desmoid tumors (**Table 1**) (54).

Attenuated FAP (AFAP) is a milder form of the disease, but still confers an increased risk of CRC development. Patients with AFAP generally present with lower overall polyp burden usually averaging between 10 and 100 adenomatous polyps in their lifetime. AFAP also tends to present later in life (after age 25 years) compared to FAP, and may predominantly present with polyposis in the proximal colon or throughout the colon (55–57).

Genetics and diagnosis. Both FAP and AFAP are caused by germline mutations in the *APC* gene, which is a tumor suppressor gene associated with the WNT signaling pathway (54,58). Patients with AFAP generally have a mutation in the 5′ or 3′ region of the *APC* gene whereas individuals with FAP carry mutations elsewhere in this gene. A diagnosis of FAP may be suspected when hundreds of polyps are noted on colonoscopy. Patients typically have a family history of FAP, but ~25–30% of FAP and AFAP cases are due to a *de novo APC* mutation (52,59,60). Therefore, family history may not always be suggestive. Genetic testing is recommended when more than 10 cumulative adenomatous polyps are noted on a single colonoscopy, if an individual has 10 or more adenomas and a personal history of CRC, or if an individual is found to have a total >20 adenomatous polyps in their lifetime (61). Genetic testing is useful both for patients diagnosed with FAP and at-risk family members. Around 10–30% of patients with a clinical diagnosis of FAP or AFAP will not have an identifiable mutation in *APC*. Adam *et al.* (62) suggest explanations for this to be possible deep intronic mutations in APC, rare APC missense mutations, rare germline copy-number variants, low penetrant variants, and/or mutations in additional genes that have yet to be identified. To date, there are several other genes whose mutations confer a moderately increased lifetime risk for polyposis, including *POLE*, *POLD1*, and *GREM1*. There have also been cases of mosaic *APC* mutations which cause polyposis in only one segment

Table 3. Duodenal adenomatosis Spigelman staging system[a]

Polyps	1 Point	2 Points	3 Points
Number	<5	5–20	>20
Size	0–4 mm	5–10 mm	>10 mm
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe
Spigelman stage	Total points	Management/surveillance frequency[b]	
0	0	Every 4 years	
I	<5	Every 2–3 years	
II	5–6	Every 1–3 years	
III	7–8	Every 6–12 months	
IV	9–12	Expert surveillance every 3–6 months and surgical evaluation	

[a]Adapted from Spigelman AD. *Lancet* 1989 (77).
[b]Adapted from 2014 NCCN Guidelines.

of the colon. Somatic mutations found only in the tissue do not confer a reproductive risk.

Colorectal surveillance and management. FAP patients have a CRC risk that increases over time starting as early as the second decade of life (7% by age 21 and 95% by age 50). Early diagnosis and management is warranted due to complete penetrance and an almost 100% lifetime risk of CRC without intervention in classic FAP. Screening colonoscopy has generally been shown to decrease the risk of CRC in individuals with FAP until polyp burden can no longer be effectively managed by colonoscopy alone (51,63–66). CRC screening with colonoscopy is recommended annually and should be initiated by age 10–12 years in patients with an *APC* mutation or with family history of clinically diagnosed FAP (4). Earlier screening may be considered based on family history of colon cancer. Individuals with a confirmed diagnosis of AFAP often develop CRC at a later age; therefore, screening is recommended to begin by late teens to early 20's and performed every 1–2 years in these patients (4,67). A third of AFAP patients may have lesser polyp burden and therefore, surveillance may be sufficient and negate the need for colectomy. However, the Achilles heel of such an intensive surveillance program is patient adherence and understanding of cancer risk (68). The diagnosis of cancer on colonoscopy is an obvious indication for colectomy in patients with FAP or AFAP. Colectomy is also considered appropriate in patients with FAP undergoing surveillance for large adenomas (>1 cm), advanced polyp histology, or increasing polyp burden that is no longer manageable by colonoscopy (usually defined as >20). The main surgical options available are total colectomy with ileorectal anasatomosis (IRA) or proctocolectomy with ileal-pouch-anal anastomosis (IPAA). The primary determination of which procedure to use is based on the rectal polyp burden. There is a risk of rectal cancer development in the remaining rectum in patients with IRA and annual rectal surveillance is still recommended for patients who undergo this procedure. A study from the Finland polyposis registry compared the long and short-term outcomes of both prophylactic surgical techniques (140 IRA and 88 IPAA) and found improved long-term survival in patients who pursued IPAA with no difference in post-operative complications when compared with those who elected colectomy with IRA (69). The increased risk of death noted in this study in patients with colectomy and IRA was likely related to the residual risk of rectal cancer. Patients with ileostomy or IPAA are also recommended to undergo surveillance due to the risk of developing adenomas in the ileum and in the anal transition zone. There are multiple studies demonstrating high prevalence of pouch adenomas after proctocolectomy and IPAA, although the cancer risk in the IPAA with adenomas is less well understood (70–72). Endoscopic surveillance is recommended every 6 months to a year in these patients (4,73).

Extra-colonic cancer surveillance and management. Duodenal carcinoma is the most common extra-colonic cancer observed in patients with FAP and is a major cause of mortality in FAP patients with prior prophylactic colectomy. There is up to a 12% lifetime risk of duodenal cancer in individuals with FAP and ~65% of patients will present with duodenal adenomas (74,75). A large multi-national study followed 368 FAP patients for a median of 7 years and found that the severity of duodenal adenomas increased with age (76). The high prevalence and risk of cancer development warrants regular surveillance, and screening is recommended to begin by age 25–30 years based on the Spigelman staging system (**Table 3**) (73,77). Spigelman classification is a scoring system ranging from stage 0 to IV and points are calculated based on the number, size, histology, and dysplasia noted on endoscopic and histological exam. Endoscopic surveillance intervals are determined using the points obtained, and ranges between 6 months to 4 years (4). Roughly 50% of duodenal cancers are located in the ampullary or periampullary region and side-viewing duodenoscope should be used along with regular upper endoscopy

in patients undergoing surveillance (**Figure 2d**). Most duodenal adenomas can be safely removed endoscopically but there is a significant risk of adenoma recurrence, which emphasizes the importance of continued surveillance (78–82). Polyp removal in the periampullary region (ampullectomy) carries additional risks of procedure related pancreatitis and chronic biliary, and pancreatic duct strictures and should be performed in expert centers. Duodenal cancer risk is increased in patients with Spigelman II and higher stage (83). Guidelines suggest pancreas preserving duodenectomy can be considered in patients with Spigelman stage IV. FAP patients diagnosed with periampullary neoplasm are surgically treated by performing a pancreatico-duodenectomy and post-surgical neoplastic recurrences have been reported (84).

Lifetime risk of gastric cancer for patients with FAP is <1% (4). FAP patients usually present with multiple gastric polyps, both fundic gland and adenomatous types on histology. Fundic gland polyps occur in almost 90% of patients with FAP and around half of them may be dysplastic (85). However, progression to high grade dysplasia or adenocarcinoma is reported to be low in these polyps (86). Generally, the gastric polyps can be observed and biopsied to ensure they are not developing adenomatous changes or high grade dysplasia. FAP patients are at risk for neoplasm of the thyroid gland. Lifetime risk of thyroid carcinoma is ~2% with papillary carcinoma as the most predominant histology. A recent study from Puerto Rico suggests that the thyroid cancer risk may be significantly higher in the Hispanic population. 90% of thyroid cases that are diagnosed in patients with FAP are diagnosed in women (87). Both benign and malignant thyroid lesions have been reported in multiple FAP cohorts (88–91). Due to the risk of neoplasm of the thyroid gland in individuals with FAP, annual thyroid clinical examination starting in late teens with consideration for annual ultrasound is an option recommended by NCCN.

Multiple benign lesions are known to occur in FAP. Most commonly found are osteomas which are bone growths predominantly noted in the skull and mandibular regions (**Figure 2e**) (92). Cutaneous lesions like sebaceous and epidermoid cysts, fibromas (not fibromatosis/desmoid tumors), and lipomas are also known to occur. Gardner syndrome, now a historical term was used for FAP families with prominent extra-intestinal manifestations including osteomas, sebaceous cysts, and fibromas. FAP and Gardner syndrome were later determined to occur from the same mutations in the *APC* gene (93). Congenital hypertrophy of the retinal pigment epithelium (CHRPE), another common manifestation described in FAP are pigmented retinal areas and develop in ~58% of patients with FAP. Of individuals with CHRPE, ~44% are found to harbor a pathogenic mutation in the *APC* gene (94). Therefore, genetic testing for FAP should be considered particularly in individuals who present with bilateral CHRPE (**Figure 2f**).

Desmoid tumors are solid tumors of connective tissue and are seen in up to 20% of patients with FAP (95,96) (**Figure 2g**). These are usually benign lesions but can be locally invasive. They carry higher morbidity due to progressive tumor enlargement and pressure to adjacent organs leading to complications and even death (97). Treatment includes a multidisciplinary approach using non-steroidal anti-inflammatory medications, tamoxifen, chemotherapy, or surgical management if conservative therapies fail (73,98). Desmoid tumors are observed more often in patients who have had colectomy; therefore, this should be considered when discussing colectomy (99).

Hepatoblastoma is very rare and noted in children usually up to 5 years of age with a male predominance. Screening can be considered for at-risk children using serum alpha-fetoprotein and ultrasound of liver every 3–6 months (4,100). Often this aggressive screening can become tedious for children and burdensome on their parents, thus a discussion between the parents, and their pediatrician regarding the symptoms of hepatoblastoma necessitating further work up are important if biannual screening is not elected. In utero screening is not currently recommended.

Malignancies of pancreas, bile ducts, and gallbladder have been reported in FAP; however, due to the lower risk of development of these tumors there are currently no related standard screening guidelines.

Chemoprevention. FAP has always been first and foremost a surgical disease, whose treatment with colectomy has long been known to reduce risk of premature cancer death. As prophylactic colectomy carries appreciable short and long-term complications, there has always been a desire to reduce polyp burden and potentially delaying surgical intervention through the use of medications. However, most of the clinical trials efforts to date have dealt with patients who have already undergone prophylactic colectomy and in whom recurrent adenomas in the retained rectum are being managed. Non-steroidal anti-inflammatory agents have been the most commonly employed chemopreventive agents, with sulindac being the most extensively studied and used clinically. Review of all the historical clinical trials is beyond the scope of this paper but several trials will be selectively highlighted here. The most influential and often cited study supporting the use of sulindac is a relatively small but controlled trial by Giardiello *et al.* (101) 22 FAP patients (18 of who had not yet undergone colectomy) were treated for 9 months with sulindac at a dose of 150 mg twice a day and assessed at intervals of 3 months. A 56% reduction in adenoma count and 65% reduction in average adenoma diameter were observed. However, no complete adenoma regression was observed and regrowth occurred by 3 months following discontinuation of sulindac, implying the need for continuous therapy. Similar findings have been shown in a number of other studies, varying the dose of the sulindac or route of delivery and length of follow-up (102–104). There is concern that sulindac therapy changes the morphology of adenomas from protruding to flat lesions and that such lesions continue to serve as precursors for CRC development but are more difficult to visualize and remove with optic colonoscopy (105,106). Celecoxib, a selective Cox-2 inhibitor which potentially has the advantage of reduced gastrointestinal side effects, was found to have an adenoma regression effect only at higher doses of 400 mg twice a day. However, the Food and Drug Administration indication of FAP for Celebrex was withdrawn recently due to a failure to perform a postmarketing study intended to verity clinical benefit.

Sulindac, though not available in all countries, is used in the US at a dose of 150 mg twice daily primarily for the control of polyposis in the retained rectum of FAP patient who have already undergone a colectomy with an ileorectal anastamosis or an ileal-pouch-anal anastamosis with a rectal cuff. It is imperative these patients continue to undergo annual surveillance due to the risk of subsequent cancers.

Patients with FAP are also at greatly increased risk for duodenal neoplasia, with duodenal adenomas eventually forming in >50% of patients and duodenal adenocarcinoma occurring in up to 12% (54,107) Following colectomy, duodenal adenocarcinoma is the leading cause of cancer death in these patients, and prevention of duodenal adenocarcinomas by endoscopic surveillance with polyp resection, duodenectomy, Whipple surgical procedure, and ampullectomy are often challenging and suboptimal (108). NSAIDs have much less efficacy in duodenal adenomas (109,110). A recent trial involving 92 FAP patients randomized to therapy with dual COX and epidermal growth factor receptor inhibition, with sulindac 150 mg twice daily and erlotinib 75 mg daily respectively, reported a 71% decrease in duodenal polyp burden after 6 months of therapy (111). However, the frequency of side effects, primarily an acne-like rash, may limit the use of these medications at the doses used in this study. Follow-up clinical trials with epidermal growth factor receptor inhibition are now underway to explore reduced dosing options to mitigate the side effects while retaining chemopreventive efficacy.

MUTYH associated polyposis

Overview. MUTYH associated polsyposis (MAP) is an autosomal recessive condition that is associated with an increased risk of CRC development. Biallelic *MUTYH* mutations lead to the development of multiple colorectal adenomas, usually 15–100 in a patient's lifetime (112). The colonic phenotype may resemble that of patients with FAP and AFAP given the multiplicity of adenomatous polyps noted on colonoscopy (113). A higher prevalence of serrated polyps has also been observed in patients with MAP (114).

Genetics and diagnosis. The *MUTYH* gene is a DNA base excision repair gene that repairs DNA injury from oxidative stress. This gene identifies and corrects the areas on DNA where adenosine inappropriately binds to the residue from oxidative damage. The two most common mutations in the *MUTYH* gene are specifically denoted as Y179C and G396D (115,116). Due to the recessive inheritance of this disease, it is important to elicit a complete family history and ask about consanguinity in the family as this may contribute to a higher risk of being homozygous for the mutations in *MUTYH*. Individuals with MAP have a lifetime CRC risk of 80% (117). The CRC risk in monoallelic *MUTYH* mutation carriers is shown to be none or minimally increased as compared to biallelic subjects. However, a study by Win *et al.* (118) observed an increased CRC risk in monoallelic carriers who also had a history of a first-degree relative with CRC. Current NCCN guidelines recommend testing for *MUTYH* gene mutations to be considered if patients clinically present with one or more of the following: (a) >20 colorectal adenomas, (b) known family history of MAP, (c) 10–20 adenomas, or (d) meets criteria for SPS with at least some adenomas noted on exam (37).

Colorectal/gastrointestinal cancer surveillance and management. Screening with colonoscopy should be initiated in homozygous *MUTYH* mutation carriers between 25–30 years and repeated every 2–3 years if negative and every 1–2 years if polyps are found (37). Given the slight increased risk of CRC in monoallelic carriers they may be screened with colonoscopy starting at age 40 years and repeat every 5 years, especially depending on their family history. More frequent screening should be considered based on the number and types of polyps identified on exam. A European study reported better survival outcomes in CRC originating in MAP patients when compared to other sporadic CRC, but the underlying mechanism for this is still unclear (119). Surgical management is reserved for patients with unmanageable adenomas on colonoscopy or if cancer develops.

Increased risk of duodenal polyposis and carcinoma have been observed in patients with MAP between 17 and 34% (120–123). NCCN recommends a baseline upper endoscopy beginning at age 30–35 years and future screening dependent upon findings. A number of extra-colonic cancers have been reported in a large study of 276 MAP patients, including ovarian, bladder, skin, and breast cancers. However, the relative advanced age of onset of tumors in this study did not support additional screening for these cancer sites (122).

Hamartomatous polyposis syndrome

Overview. Peutz–Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS) are two forms of hamartomatous polyposis syndrome. They are rare, autosomal dominant conditions and carry an increased risk of developing colorectal and extra-colonic neoplasia. *PTEN*-hamartoma tumor syndrome/Cowden syndrome (CS) is another rare hamartomatous polyposis condition with risk for colorectal and extra-intestinal malignancies.

PJS presents with hamartomatous polyps of the gastrointestinal tract and classic appearance of muco-cutaneaous melanin pigmentation (**Figure 3**). The incidence of PJS is ~0.9 per 100,000 individuals (124). Individuals with PJS are expected to have an increased lifetime risk for both gastrointestinal cancers (colon, pancreas, gastroesophageal, small bowel, and stomach) and extra-intestinal malignancies (breast, gynecological, lung, and testicular) as outlined in **Table 1**.

JPS presents with characteristic multiple (≥3–5) juvenile polyps of the gastrointestinal tract. These colon polyps are mostly large and pedunculated in appearance and histologically demonstrate inflammation of lamina propria, thick mucin filled cystic glands, but minimal smooth muscle proliferation compared to polyps typically seen in individuals with PJS (125). Similar to PJS, individuals with JPS are expected to have an increased risk of CRC and other gastrointestinal cancers, including that of the small bowel, stomach, and pancreas (**Table 1**) (126,127). Features of hereditary hemorrhagic telangiectasia have also been described in individuals with specific genetic mutations in the SMAD4 gene associated

with JPS. Affected patients and/or families may present with an increased risk for CRC as well as chronic nosebleeds and other severe bleeding problems caused by solid organ arteriovenous malformations. Upper GI manifestations of JPS can also overlap with presentations of Crohnkhite-Canada, Menetriers or hyperplastic fundic gland polyposis syndromes. Importantly, patients with JPS also have an increased risk of gastric cancer.

PTEN-hamartoma tumor syndrome (PHTS) refers to a spectrum of syndromes that include CS and Bannayan–Riley–Ruvalcaba syndrome. The prevalence of CS is 1 in 200,000. A recent systematic review reported 92% of CS patients had colonic polyps and prevalence of CRC was found between 9 and 18% (128,129). Hamartomatous polyps may also be found in the stomach, duodenum, and small bowel. An increased risk of several extra-intestinal cancers have also been noted including breast, endometrium, thyroid, and renal cancers (**Table 1**). A recent report indicated that finding two or more hamartomatous polyps (inflammatory/juvenile, expansive lymphoid follicle, ganglioneuromatous, and intramucosal lipomas) or any intramucosal lipomas or gangioneuromas in a patient is a highly prevalent feature of CS (125). Cerebral manifestations may also be observed and may include cerebellar tumors, autistic spectrum disorder, and macrocephaly. CS should be suspected in individuals presenting with multiple characteristic benign cutaneous findings including: facial trichilemmomas, papillomas of the face, lips, tongue, oral mucosa, or lipomas (**Figure 4**) (130).

Diagnosis. The clinical diagnosis for PJS is given when a patient meets two or more of the following criteria (a) ≥2 Peutz–Jeghers type hamartomatous polyps of the small intestine, (b) muco-cutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers (**Figure 3**), and (c) family history of PJS. *SKT11* (previously called *LKB1*) is a tumor suppressor gene and mutations in *SKT11* are found in 50–70% of patients with a clinical diagnosis of PJS. Around 30% of patients may have a de-novo mutation. Solitary Peutz–Jeghers type hamartomatous polyps have been described in the gastrointestinal tract, without associated mucocutanous pigmentation or a family history of PJS and have been considered a variant or a separate disease with a lower risk of cancer. If concern exists for PJS, referral to an expert clinic is recommended (131–133).

A patient should be given a clinical diagnosis of JPS if they meet one of the following criteria (a) At least 3–5 juvenile colon polyps; (b) multiple juvenile polyps throughout the gastrointestinal tract; or (c) any number of juvenile polyps in an individual with a family history of JPS (37). *SMAD4* and *BMPR1A* mutations are identified in only 50% of patients with JPS (134,135). JPS patients with a *SMAD4* mutation can have overlapping features with hereditary hemorrhagic telangiectasia (37,136).

Individuals with a mutation in the *PTEN* gene have a molecular diagnosis of PHTS. If a mutation is not identified, a patient may still be given a clinical diagnosis of this syndrome and followed appropriately if they meet the criteria listed in **Table 4**.

Due to the rarity of these polyps, it is prudent for patients who present with >5 hamartomatous polyps on colonoscopy, particularly those under the age of 40, to be evaluated for a possible hereditary cancer syndrome (125).

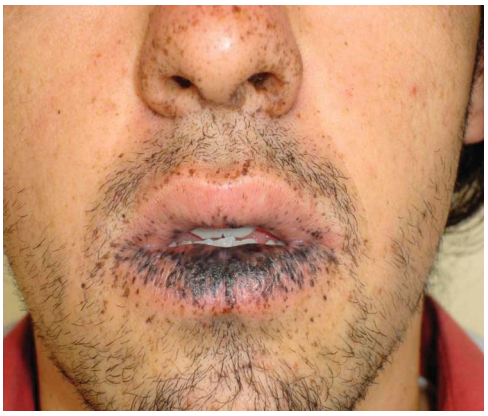

Figure 3. Perioral and cutaneous findings associated with Peutz–Jeghers syndrome.

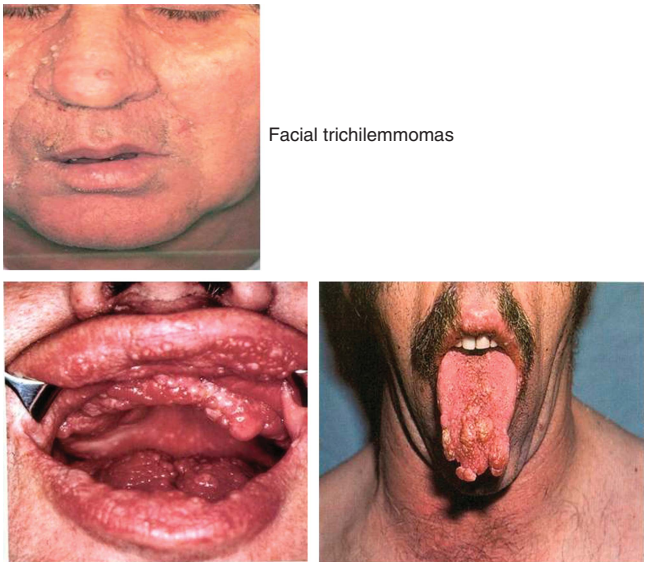

Figure 4. Perioral and cutaneous findings associated with Cowdens syndrome.

Cancer surveillance and management. PJS: current NCCN guidelines recommend initiating upper endoscopy and colonoscopy by late teens and repeating every 2–3 years for surveillance if normal. The small bowel should be assessed using baseline CT or MRI enterography by late teens and repeated thereafter every 2–3 years (37). Surveillance helps in identification and removal of small bowel lesions which may clinically present with complications such as intussusception. In a study of 8 PJS patients, MR enterography showed 95% concordance with deep enteroscopy (137).Video capsule endoscopy may be used as another modality to detect small bowel lesions (138). European guidelines

Table 4. Diagnostic criteria for PTEN Hamartoma tumor syndrome

Clinical diagnosis for an individual (either of the following):	
1. Three of more major criteria, one must be macrocephaly, Lhermitte-Duclos disease, or GI hamartomas; OR	
2. Two major and three minor criteria	
Clinical diagnosis in a family when one individual meets the revised PTEN hamartoma tumor syndrome criteria or has a PTEN mutation:	
1. Any two major criteria with or without minor criteria; OR	
2. One major and two minor criteria; OR Three minor criteria.	
Major criteria	*Minor criteria*
Breast cancer	Autism spectrum disorder
Endometrial cancer (epithelial type)	Colon cancer
Follicular thyroid cancer	Esophageal glycogenic acanthosis (≥3)
GI hamartomas (includes ganglioneuromas, but excludes hyperplastic polyps; ≥3)	Lipomas (≥3)
Lhermitte-Duclos disease (adult)	Intellectual disability (ie, IQ ≤75)
Macrocephaly (≥97th percentile: 58 cm for women, 60 cm for men)	Renal cell carcinoma
Macular pigmentation of the glans penis	Testicular lipomatosis
Multiple muco-cutaneous lesions (any of the following):	Papillary or follicular variant of papillary thyroid cancer
Multiple trichilemmomas (≥3, at least one of which is biopsy proven)	Structural lesions of the thyroid (eg, adenoma and multinodular goiter)
Acral keratosis (≥3 palmoplantar keratotic pits an/or acral hyperkeratotic papules)	Vascular anomalies (includes multiple intracranial developmental venous anomalies)
Muco-cutaneous neuromas (≥3)	
Oral papillomas (tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed.	

Adapted from Pilarski *et al.* (130).

recommend removing all large (>10–15 mm) small bowel polyps by deep enteroscopy (139).

Screening for pancreatic cancer is recommended using MRI/MRCP or endoscopic ultrasonography every 1–2 years beginning by 30–35 years of age (37). According to NCCN, women with PJS are also recommended to undergo additional screening associated with the risk for breast, ovarian, and cervical cancer. Breast cancer screening is recommended with mammography or MRI beginning at age 25 (140). Ovarian and cervical cancer surveillance is performed annually using pelvic exam and PAP smear with consideration of transvaginal ultrasound starting at age 18–20. Men with PJS are recommended to undergo testicular examination and observation for feminization changes starting at age 10. Smoking cessation is also recommended for both men and women with PJS to reduce the risk of lung cancer.

JPS: colonoscopy and upper endoscopy are recommended starting at age 15 and should be repeated annually if polyps are found on exam. If no polyps are noted, screening can be performed every 2–3 years (37). No recommendations currently exist for screening for small bowel or pancreatic cancer in patients with JPS.

PHTS/CS: NCCN guidelines recommend screening colonoscopy starting by age 35. If a family history of CRC exists before age 35, then screening should begin 5–10 years before the earliest known cancer in the family or before age 40 (37). Though a recent clinical practice guideline suggested screening with upper endoscopy and colonoscopy beginning at a much younger age (15 years) than that suggested by NCCN, this may be too aggressive and we continue to support initiation of screening by age 35–40 years (4,141).

Women with a mutation in the *PTEN* gene should also consider screening for breast cancer with annual mammogram or MRI starting by age 30–35 or earlier based on family history. Annual thyroid ultrasound beginning at the time of PHTS diagnosis and annual renal ultrasound can be considered starting by age 40 years.

Serrated polyposis syndrome

Overview. SPS previously known as hyperplastic polyposis syndrome presents with multiple serrated colon polyps and an increased lifetime risk for CRC up to 42% (142,143). A patient must meet at least one of the following criteria designated by WHO to be given a clinical diagnosis of SPS: (1)≥5 serrated polyps proximal to sigmoid colon with 2 or more>10 mm or (2) any number of serrated polyps proximal to sigmoid colon and a first-degree relative (FDR) with SPS or 3) >20 serrated polyps of any size distributed throughout colon (144). Broadly, serrated polyps are classified into sessile serrated adenoma/polyps and hyperplastic polyps by WHO (World Health Organization) criteria (144). sessile serrated adenoma/polyps are considered pre-neoplastic and overlap morphologically with hyperplastic polyps. A recent multicenter cross-sectional study from Europe

evaluated prevalence rates of SPS in four countries (UK, Poland, Spain, The Netherlands) (145). They found a prevalence of 0–0.5% in initial colonoscopy and up to 0.8% in follow-up colonoscopy from the Spanish cohort. SPS is currently an under-diagnosed condition and the world-wide prevalence is unclear likely due to the histological difficulty in differentiating sessile serrated adenoma/polyps from hyperplastic polyps and the actual prevalence may be much higher (146). Similarly, hereditary mixed polyposis is a rare condition with occurrence of multiple polyps with different morphologies and histological features such as that of juvenile polyps, and adenomas and serrated lesions. Due to its rarity and unclear genetic inheritance it is not discussed in detail here, but readers are referred to the article by Plesec *et al.* (147).

Diagnosis. The genetic make-up of SPS is poorly understood. MSI, CpG island methylation and silencing of *MLH-1* have been suggested in serrated pathway to colon cancer. Genetic mutations commonly noted in hamartomatous polyposis syndrome and FAP have not been identified in SPS (148). Recent studies have described various unique differentially expressed genes in SSP (149,150). There are reports of overlap between patients with SPS and MAP (4,151,152). The evidence to support routine screening for *MUTYH* mutations in SPS patients is weak but may be considered when multiple adenomatous polyps are noted on colonoscopy. It is important to note that a normal test result does not preclude a diagnosis of SPS. Currently, the diagnosis of SPS remains clinical and no definitive genetic testing is available.

Colorectal cancer surveillance and management. There is a known increased risk of CRC in patients with SPS. Studies have described CRC risk ranging between 16 and 42% in individuals with a clinical diagnosis of SPS (142,143,153–155). Hazewinkel *et al.* followed 50 patients with SPS undergoing annual colonoscopy for a median period of 3 years and found no cases of CRC; however 9 and 34% of patients developed advanced adenomas and large serrated polyps respectively (156). Current NCCN practice guidelines recommend surveillance with colonoscopy at least every 1–3 years, while other groups have favored a more aggressive program of annual colonoscopy (157). Surgery should be considered for patients with multiple polyps not manageable by colonoscopy or if cancer is found on exam. Higher CRC risk in family members of patients with a clinical diagnosis of SPS has also been reported. The incidence of cancer in relatives is noted to vary widely between 4 and 55% (151,155,158–160). FDR's can be at a higher risk of presenting with SPS. In one study, over 30% of FDR's of SPS undergoing colonoscopy met criteria for the syndrome themselves (159). Given the risk of CRC and adenomas, it is reasonable to consider earlier and more frequent colonoscopy in FDR's of patients with SPS compared to the general population. NCCN currently recommends surveillance in FDR's of patients with SPS at the earliest age of the following: starting at age 40 years; or at the same age as the youngest SPS diagnosis; or 10 years before the age of CRC diagnosis in the family. Screening should be repeated every 5 years if no polyps are found and every 1–3 years if proximal serrated polyps or multiple adenomas are found (37).

Table 5. National comprehensive Cancer Network Criteria for further genetic risk evaluation

Individuals meeting the revised Bethesda Guidelines
Individuals with a family history that meets Amsterdam Criteria
Individuals with papillary thyroid cancer that is the cribriform-morular variant, or hepatoblastoma
Individuals with a diagnosis of CRC and >10 colorectal adenomas
Individuals with a personal history of ≥20 adenomas
Individuals with multiple gastrointestinal hamartomatous polyps or serrated polyposis syndrome
Individuals from a family with a known hereditary syndrome associated with CRC with or without a known mutation
Individuals with a desmoid tumor, multifocal OR bilateral CHRPE

CRC, colorectal cancer; CHRPE, congenital hypertrophy of the retinal pigment epithelium.

Extra-colonic cancer surveillance and management. A number of extra-colonic cancers have been reported in patients with SPS, but the literature is limited. Studies have documented 8–28% of SPS patients with extra-colonic cancers (142,155,161,162). Most extra-colonic cancers seen in these individuals are also commonly found in the general population (e.g., breast and prostate). No special screening guidelines currently exist for extra-colonic cancer surveillance for patients with a clinical diagnosis of SPS and patients should follow appropriate general population cancer screening guidelines based on their medical and family histories.

Working with a genetics clinic or genetic counselor. As genetic testing continues to evolve, the complexity of the interpretation of this information in the context of the patient's medical and family history is significantly increased. Pre-and post-test counseling is recommended by ASCO as part of the germline genetic testing process to ensure that appropriate and comprehensive information is communicated (163). Genetic counselors are specially trained providers whose primary role is to perform cancer risk assessment based on a combination of personal factors and family history. These providers can also discuss current legal protections in place for patients who undergo genetic testing, which may otherwise be a patient perceived barrier to genetic evaluation (164,165). Indications for referral to a genetics clinic or genetic counselor are outlined in **Table 5** (2). Increased patient understanding leads to increased communication between family members who are at risk, and may also increase adherence to screening/ risk-reduction recommendations (166).

CONCLUSION

High-risk colorectal polyposis and cancer patients require early detection and intense surveillance to prevent and manage several life-threatening malignancies. We provide a comprehensive overview of the genetics, surveillance, and management of common hereditary colorectal polyposis and cancer syndromes for

clinicians to successfully navigate in a busy clinical practice. Using available tools like incorporating simple questionnaires of personal and family history of cancer in outpatient settings may improve the identification of high-risk patients and/or families. In the era of gene sequencing and other molecular technologies, a number of new genes/mutations are being identified and will require a multidisciplinary approach including primary care physicians, gastroenterologists, surgeons, gynecologist, oncologists, genetic counselors, nurses, and ancillary staff for successful prevention and management of hereditary colorectal cancers.

CONFLICT OF INTEREST

Guarantor of Article: N. Jewel Samadder, MD, MS, MSc, FRCPC.

Specific author contributions: Drs Samadder, Kanth, Burt, and Ms. Grimmett and Champine had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: N. Jewel Samadder, Priyanka Kanth, Randall Burt, Jade Grimmett, and Marjan Champine; acquisition, analysis, and interpretation of data: N. Jewel Samadder, Priyanka Kanth, Randall Burt, Jade Grimmett, and Marjan Champine; drafting of the manuscript: N. Jewel Samadder, Priyanka Kanth, Randall Burt, Jade Grimmett, and Marjan Champine; critical revision of the manuscript for important intellectual content: N. Jewel Samadder, Priyanka Kanth, Randall Burt, Jade Grimmett, and Marjan Champine.

Financial support: The study was funded by the National Cancer Institute, American Society for Gastrointestinal Endoscopy, American College of Gastroenterology, and the Huntsman Cancer Foundation. The funding sources did not play a role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication. Support for this project was provided by NCI grants P01-CA073992 (R.W.B.), R01-CA040641 (R.W.B.), an Endoscopic Research Award from the American Society for Gastrointestinal Endoscopy (N.J.S.), and a junior faculty career development award from the American College of Gastroenterology (N.J.S.). Partial support for the shared Genetic counseling resource and this project was provided by the Huntsman Cancer Institute Cancer Center Support Grant P30CA042014 from the National Cancer institute and the Huntsman Cancer Foundation.

Potential competing interests: Randall Burt is a consultant for Myriad Genetics and N. Jewel Samadder is a consultant for Cook Medical. The remaining authors declare no conflict of interest.

REFERENCES

1. Deans GT, Krukowski ZH, Irwin ST. Malignant obstruction of the left colon. Br J Surg 1994;81:1270–6.
2. Zhang S, Folsom AR, Sellers TA *et al.* Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa Women's Health Study. Cancer 1995;76:275–83.
3. Burt RW, DiSario JA, Cannon-Albright L. Genetics of colon cancer: impact of inheritance on colon cancer risk. Annu Rev Med 1995;46:371–9.
4. Syngal S, Brand RE, Church JM *et al.* ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110:223–62.quiz 263.
5. Rubenstein JH, Enns R, Heidelbaugh J *et al.* American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. Gastroenterology 2015;149:777–82.quiz e16-7.
6. Rustgi AK. The genetics of hereditary colon cancer. Genes Dev 2007;21:2525–38.
7. Palomaki GE, McClain MR, Melillo S *et al.* EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 2009;11:42–65.
8. Dowty JG, Win AK, Buchanan DD *et al.* Cancer risks for MLH1 and MSH2 mutation carriers. Hum Mutat 2013;34:490–7.
9. Guindalini RS, Win AK, Gulden C *et al.* Mutation spectrum and risk of colorectal cancer in African American families with Lynch syndrome. Gastroenterology 2015;149:1446–53.
10. Bonadona V, Bonaiti B, Olschwang S *et al.* Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304–10.
11. Senter L, Clendenning M, Sotamaa K *et al.* The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008;135:419–28.
12. Kempers MJ, Kuiper RP, Ockeloen CW *et al.* Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol 2011;12:49–55.
13. Weissman SM, Burt R, Church J *et al.* Identification of individuals at risk for Lynch syndrome using targeted evaluations and genetic testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer joint practice guideline. J. Genet Couns 2012;21:484–93.
14. Lynch HT, Riegert-Johnson DL, Snyder C *et al.* Lynch syndrome-associated extracolonic tumors are rare in two extended families with the same EPCAM deletion. Am J Gastroenterol 2011;106:1829–36.
15. Grandval P, Baert-Desurmont S, Bonnet F *et al.* Colon-specific phenotype in Lynch syndrome associated with EPCAM deletion. Clin Genet 2012;82:97–9.
16. Giardiello FM, Allen JI, Axilbund JE *et al.* Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. Am J Gastroenterol 2014;109:1159–79.
17. Kastrinos F, Ojha RP, Leenen C *et al.*; Lynch Syndrome prediction model validation study group. Comparison of prediction models for Lynch Syndrome among individuals with colorectal cancer. J Natl Cancer Inst 2016;108:1–9.
18. Kastrinos F, Allen JI, Stockwell DH *et al.* Development and validation of a colon cancer risk assessment tool for patients undergoing colonoscopy. Am J Gastroenterol 2009;104:1508–18.
19. Leenen CH, Goverde A, de Bekker-Grob EW *et al.* Cost-effectiveness of routine screening for Lynch syndrome in colorectal cancer patients up to 70 years of age. Genet Med 2016;18:966–73.
20. Resnick K, Straughn JMJr, Backes F *et al.* Lynch syndrome screening strategies among newly diagnosed endometrial cancer patients. Obstet Gynecol 2009;114:530–6.
21. Hampel H, Frankel W, Panescu J *et al.* Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res 2006;66:7810–7.
22. Mills AM, Liou S, Ford JM *et al.* Lynch syndrome screening should be considered for all patients with newly diagnosed endometrial cancer. Am J Surg Pathol 2014;38:1501–9.
23. Goodfellow PJ, Billingsley CC, Lankes HA *et al.* Combined microsatellite instability, MLH1 methylation analysis, and immunohistochemistry for lynch syndrome screening in endometrial cancers from GOG210: an NRG Oncology and Gynecologic Oncology Group Study. J Clin Oncol 2015;33:4301–8.
24. Ladabaum U, Wang G, Terdiman J *et al.* Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med 2011;155:69–79.
25. Wimmer K, Etzler J. Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? Hum Genet 2008;124:105–22.
26. van der Klift HM, Mensenkamp AR, Drost M *et al.* Comprehensive mutation analysis of PMS2 in a large cohort of probands suspected of lynch syndrome or constitutional mismatch repair deficiency syndrome. Hum Mutat 2016;37:1162–79.
27. Jarvinen HJ, Aarnio M, Mustonen H *et al.* Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000;118:829–34.
28. Vasen HF, Taal BG, Nagengast FM *et al.* Hereditary nonpolyposis colorectal cancer: results of long-term surveillance in 50 families. Eur J Cancer 1995;31A:1145–8.

29. Dove-Edwin I, Sasieni P, Adams J *et al.* Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005;331:1047.
30. Vasen HF, Abdirahman M, Brohet R *et al.* One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. Gastroenterology 2010;138:2300–6.
31. Vasen HF, Blanco I, Aktan-Collan K *et al.* Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut 2013;62:812–23.
32. Moller P, Seppala T, Bernstein I *et al.* Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 2015;66:464–72.
33. Huneburg R, Lammert F, Rabe C *et al.* Chromocolonoscopy detects more adenomas than white light colonoscopy or narrow band imaging colonoscopy in hereditary nonpolyposis colorectal cancer screening. Endoscopy 2009;41:316–22.
34. Stoffel EM, Turgeon DK, Stockwell DH *et al.* Missed adenomas during colonoscopic surveillance in individuals with Lynch Syndrome (hereditary nonpolyposis colorectal cancer). Cancer Prev Res (Phila) 2008;1:470–5.
35. Rahmi G, Lecomte T, Malka D *et al.* Impact of chromoscopy on adenoma detection in patients with Lynch syndrome: a prospective, multicenter, blinded, tandem colonoscopy study. Am J Gastroenterol 2015;110:288–98.
36. Kaminski MF, Hassan C, Bisschops R *et al.* Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2014;46:435–49.
37. 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;14:1010–30.
38. Schmeler KM, Lynch HT, Chen LM *et al.* Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354:261–9.
39. Capelle LG, Van Grieken NC, Lingsma HF *et al.* Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology 2010;138:487–92.
40. Soer EC, Leicher LW, Langers AM *et al.* Equivalent Helicobacter pylori infection rates in Lynch syndrome mutation carriers with and without a first-degree relative with gastric cancer. Int J Colorectal Dis 2016;31:693–7.
41. Haanstra JF, Al-Toma A, Dekker E *et al.* Prevalence of small-bowel neoplasia in Lynch syndrome assessed by video capsule endoscopy. Gut 2015;64:1578–83.
42. Kastrinos F, Mukherjee B, Tayob N *et al.* Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009;302:1790–5.
43. Canto MI, Harinck F, Hruban RH *et al.* International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013;62:339–47.
44. Burn J, Mathers JC, Bishop DT. Chemoprevention in Lynch syndrome. Fam Cancer 2013;12:707–18.
45. Movahedi M, Bishop DT, Macrae F *et al.* Obesity, aspirin, and risk of colorectal cancer in carriers of hereditary colorectal cancer: a prospective investigation in the CAPP2 study. J Clin Oncol 33:3591–7.2015.
46. Cleland JG. Does aspirin really reduce the risk of colon cancer? Lancet 2012;379:1586–author reply 1587.
47. Jankowski J, Barr H, Moayyedi P. Does aspirin really reduce the risk of colon cancer? Lancet 2012;379:1586–7.author reply 1587.
48. Ait Ouakrim D, Dashti SG, Chau R *et al.* Aspirin, ibuprofen, and the risk of colorectal cancer in Lynch syndrome. J Natl Cancer Inst 2015;107:1–11.
49. Chan AT, Ladabaum U. Where do we stand with aspirin for the prevention of colorectal cancer? The USPSTF recommendations. Gastroenterology 2016;150:14–18.
50. Cuzick J, Thorat MA, Bosetti C *et al.* Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann Oncol 2015;26:47–57.
51. Jarvinen HJ. Epidemiology of familial adenomatous polyposis in Finland: impact of family screening on the colorectal cancer rate and survival. Gut 1992;33:357–60.
52. Bisgaard ML, Fenger K, Bulow S *et al.* Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. Hum Mutat 1994;3:121–5.
53. Bulow S, Faurschou Nielsen T, Bulow C *et al.* The incidence rate of familial adenomatous polyposis. Results from the Danish Polyposis Register. Int J Colorectal Dis 1996;11:88–91.
54. Jasperson KW, Tuohy TM, Neklason DW *et al.* Hereditary and familial colon cancer. Gastroenterology 2010;138:2044–58.
55. Burt RW, Leppert MF, Slattery ML *et al.* Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology 2004;127:444–51.
56. Knudsen AL, Bulow S, Tomlinson I *et al.* Attenuated familial adenomatous polyposis: results from an international collaborative study. Colorectal Dis 2010;12:e243–e249.
57. Ibrahim A, Barnes DR, Dunlop J *et al.* Attenuated familial adenomatous polyposis manifests as autosomal dominant late-onset colorectal cancer. Eur J Hum Genet 2014;22:1330–3.
58. Nielsen M, Hes FJ, Nagengast FM *et al.* Germline mutations in APC and MUTYH are responsible for the majority of families with attenuated familial adenomatous polyposis. Clin Genet 2007;71:427–33.
59. 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;34:1230–5.
60. 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;12:52–8.
61. Grover S, Kastrinos F, Steyerberg EW *et al.* Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. JAMA 2012;308:485–92.
62. Adam R, Spier I, Zhao B *et al.* Exome sequencing identifies biallelic MSH3 germline mutations as a recessive subtype of colorectal adenomatous polyposis. Am J Hum Genet 2016;99:337–51.
63. Vasen HF, Griffioen G, Offerhaus GJ *et al.* The value of screening and central registration of families with familial adenomatous polyposis. A study of 82 families in The Netherlands. Dis Colon Rectum 1990;33:227–30.
64. Mallinson EK, 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;59:1378–82.
65. Bulow S. Results of national registration of familial adenomatous polyposis. Gut 2003;52:742–6.
66. Gibbons DC, Sinha A, Phillips RK *et al.* Colorectal cancer: no longer the issue in familial adenomatous polyposis? Fam Cancer 2011;10:11–20.
67. Knudsen AL, Bisgaard ML, Bulow S. Attenuated familial adenomatous polyposis (AFAP). A review of the literature. Fam Cancer 2003;2:43–55
68. Kinney AY, Hicken B, Simonsen SE *et al.* Colorectal cancer surveillance behaviors among members of typical and attenuated FAP families. Am J Gastroenterol 2007;102:153–62.
69. Koskenvuo L, Mustonen H, Renkonen-Sinisalo L *et al.* Comparison of proctocolectomy and ileal pouch-anal anastomosis to colectomy and ileorectal anastomosis in familial adenomatous polyposis. Fam Cancer 2015;14:221–7.
70. Pommaret E, Vienne A, Lefevre JH *et al.* Prevalence and risk factors for adenomas in the ileal pouch and the afferent loop after restorative proctocolectomy for patients with familial adenomatous polyposis. Surg Endosc 2013;27:3816–22.
71. Parc YR, Olschwang S, Desaint B *et al.* Familial adenomatous polyposis: prevalence of adenomas in the ileal pouch after restorative proctocolectomy. Ann Surg 2001;233:360–4.
72. M'Koma AE, Herline AJ, Adunyah SE. Subsequent adenomas of ileal pouch and anorectal segment after prophylactic surgery for familial adenomatous polyposis. World J Colorectal Surg 2013;3:1–29.
73. Vasen HF, Moslein G, Alonso A *et al.* Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008;57:704–13.
74. Bulow S, Alm T, Fausa O *et al.* Duodenal adenomatosis in familial adenomatous polyposis. DAF Project Group. Int J Colorectal Dis 1995;10:43–6.
75. Church JM, McGannon E, Hull-Boiner S *et al.* Gastroduodenal polyps in patients with familial adenomatous polyposis. Dis Colon Rectum 1992;35:1170–3.
76. Bulow S, Bjork J, Christensen IJ *et al.* Duodenal adenomatosis in familial adenomatous polyposis. Gut 2004;53:381–6.
77. Spigelman AD, Williams CB, Talbot IC *et al.* Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989;2:783–5.
78. Laleman W, Verreth A, Topal B *et al.* Endoscopic resection of ampullary lesions: a single-center 8-year retrospective cohort study of 91 patients with long-term follow-up. Surg Endosc 2013;27:3865–76.
79. Jaganmohan S, Lynch PM, Raju RP *et al.* Endoscopic management of duodenal adenomas in familial adenomatous polyposis--a single-center experience. Dig Dis Sci 2012;57:732–7.
80. Alderlieste YA, Bastiaansen BA, Mathus-Vliegen EM *et al.* "High rate of recurrent adenomatosis during endoscopic surveillance after duodenectomy in patients with familial adenomatous polyposis". Fam Cancer 2013;12:699–706.

REVIEW

81. Ma T, Jang EJ, Zukerberg LR *et al.* Recurrences are common after endoscopic ampullectomy for adenoma in the familial adenomatous polyposis (FAP) syndrome. Surg Endosc 2014;28:2349–56.
82. van Heumen BW, Nieuwenhuis MH, van Goor H *et al.* Surgical management for advanced duodenal adenomatosis and duodenal cancer in Dutch patients with familial adenomatous polyposis: a nationwide retrospective cohort study. Surgery 2012;151:681–90.
83. Serrano PE, Grant RC, Berk TC *et al.* Progression and management of duodenal neoplasia in familial adenomatous polyposis: a cohort study. Ann Surg 2015;261:1138–44.
84. Ruo L, Coit DG, Brennan MF *et al.* Long-term follow-up of patients with familial adenomatous polyposis undergoing pancreaticoduodenal surgery. J Gastrointest Surg 2002;6:671–5.
85. Bianchi LK, Burke CA, Bennett AE *et al.* Fundic gland polyp dysplasia is common in familial adenomatous polyposis. Clin Gastroenterol Hepatol 2008;6:180–5.
86. Arnason T, Liang WY, Alfaro E *et al.* Morphology and natural history of familial adenomatous polyposis-associated dysplastic fundic gland polyps. Histopathology 2014;65:353–62.
87. Casellas-Cabrera N, Diaz-Algorri Y, Carlo-Chevere VJ *et al.* Risk of thyroid cancer among Caribbean Hispanic patients with familial adenomatous polyposis. Fam Cancer 2016;15:267–74.
88. Feng X, Milas M, O'Malley M *et al.* Characteristics of benign and malignant thyroid disease in familial adenomatous polyposis patients and recommendations for disease surveillance. Thyroid 2015;25:325–32.
89. Steinhagen E, Guillem JG, Chang G *et al.* The prevalence of thyroid cancer and benign thyroid disease in patients with familial adenomatous polyposis may be higher than previously recognized. Clin Colorectal Cancer 2012;11:304–8.
90. Jarrar AM, Milas M, Mitchell J *et al.* Screening for thyroid cancer in patients with familial adenomatous polyposis. Ann Surg 2011;253:515–21.
91. Herraiz M, Barbesino G, Faquin W *et al.* Prevalence of thyroid cancer in familial adenomatous polyposis syndrome and the role of screening ultrasound examinations. Clin Gastroenterol Hepatol 2007;5:367–73.
92. Wijn MA, Keller JJ, Giardiello FM *et al.* Oral and maxillofacial manifestations of familial adenomatous polyposis. Oral Dis 2007;13:360–5.
93. Bisgaard ML, Bulow S. Familial adenomatous polyposis (FAP): genotype correlation to FAP phenotype with osteomas and sebaceous cysts. Am J Med Genet A 2006;140:200–4.
94. Rossato M, Rigotti M, Grazia M *et al.* Congenital hypertrophy of the retinal pigment epithelium (CHRPE) and familial adenomatous polyposis (FAP). Acta Ophthalmol Scand 1996;74:338–42.
95. Slowik V, Attard T, Dai H *et al.* Desmoid tumors complicating Familial Adenomatous Polyposis: a meta-analysis mutation spectrum of affected individuals. BMC Gastroenterol 2015;15:84.
96. Bertario L, Russo A, Sala P *et al.* Genotype and phenotype factors as determinants of desmoid tumors in patients with familial adenomatous polyposis. Int J Cancer 2001;95:102–7.
97. Campos FG, Martinez CA, Novaes M *et al.* Desmoid tumors: clinical features and outcome of an unpredictable and challenging manifestation of familial adenomatous polyposis. Fam Cancer 2015;14:211–9.
98. Desurmont T, Lefevre JH, Shields C *et al.* Desmoid tumour in familial adenomatous polyposis patients: responses to treatments. Fam Cancer 2015;14:31–9.
99. Nugent KP, Spigelman AD, Phillips RK. Life expectancy after colectomy and ileorectal anastomosis for familial adenomatous polyposis. Dis Colon Rectum 1993;36:1059–62.
100. Kennedy RD, Potter DD, Moir CR *et al.* The natural history of familial adenomatous polyposis syndrome: a 24 year review of a single center experience in screening, diagnosis, and outcomes. J Pediatr Surg 2014;49:82–6.
101. Giardiello FM, Hamilton SR, Krush AJ *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 1993;328:1313–6.
102. Winde G, Gumbinger HG, Osswald H *et al.* The NSAID sulindac reverses rectal adenomas in colectomized patients with familial adenomatous polyposis: clinical results of a dose-finding study on rectal sulindac administration. Int J Colorectal Dis 1993;8:13–17.
103. Winde G, Schmid KW, Schlegel W *et al.* Complete reversion and prevention of rectal adenomas in colectomized patients with familial adenomatous polyposis by rectal low-dose sulindac maintenance treatment. Advantages of a low-dose nonsteroidal anti-inflammatory drug regimen in reversing adenomas exceeding 33 months. Dis Colon Rectum 1995;38:813–30.
104. Cruz-Correa M, Hylind LM, Romans KE *et al.* Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. Gastroenterology 2002;122:641–5.
105. Lynch HT, Thorson AG, Smyrk T. Rectal cancer after prolonged sulindac chemoprevention. A case report. Cancer 1995;75:936–8.
106. Matsumoto T, Nakamura S, Esaki M *et al.* Effect of the non-steroidal anti-inflammatory drug sulindac on colorectal adenomas of uncolectomized familial adenomatous polyposis. J Gastroenterol Hepatol 2006;21:251–7.
107. Biasco G, Pantaleo MA, Di Febo G *et al.* Risk of duodenal cancer in patients with familial adenomatous polyposis. Gut 2004;53:1547–author reply 1547.
108. Conio M, Gostout CJ. Management of duodenal adenomas in 98 patients with familial adenomatous polyposis. Gastrointest Endosc 2001;53:265–6.
109. Debinski HS, Trojan J, Nugent KP *et al.* Effect of sulindac on small polyps in familial adenomatous polyposis. Lancet 1995;345:855–6.
110. 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;80:1618–9.
111. Samadder NJ, Neklason DW, Boucher KM *et al.* Effect of sulindac and erlotinib vs placebo on duodenal neoplasia in familial adenomatous polyposis: a randomized clinical trial. JAMA 2016;315:1266–75.
112. Sieber OM, Lipton L, Crabtree M *et al.* Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med 2003;348:791–9.
113. Sampson JR, Dolwani S, Jones S *et al.* Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. Lancet 2003;362:39–41.
114. Guarinos C, Juarez M, Egoavil C *et al.* Prevalence and characteristics of MUTYH-associated polyposis in patients with multiple adenomatous and serrated polyps. Clin Cancer Res 2014;20:1158–68.
115. Nielsen M, Joerink-van de Beld MC, Jones N *et al.* Analysis of MUTYH genotypes and colorectal phenotypes in patients With MUTYH-associated polyposis. Gastroenterology 2009;136:471–6.
116. Cheadle JP, Sampson JR. MUTYH-associated polyposis--from defect in base excision repair to clinical genetic testing. DNA Repair (Amst) 2007;6:274–9.
117. Jenkins MA, Croitoru ME, Monga N *et al.* Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomarkers Prev 2006;15:312–4.
118. Win AK, Dowty JG, Cleary SP *et al.* Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer. Gastroenterology 2014;146:1208–11.e1-5.
119. Nielsen M, van Steenbergen LN, Jones N *et al.* Survival of MUTYH-associated polyposis patients with colorectal cancer and matched control colorectal cancer patients. J Natl Cancer Inst 2010;102:1724–30.
120. Nielsen M, Franken PF, Reinards TH *et al.* Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with MYH associated polyposis coli (MAP). J Med Genet 2005;42:e54.
121. 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;119:807–14.
122. Vogt S, Jones N, Christian D *et al.* Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology 2009;137:1976–1985.e10.
123. Walton SJ, Kallenberg FG, Clark SK *et al.* Frequency and features of duodenal adenomas in patients with MUTYH-associated polyposis. Clin Gastroenterol Hepatol 2016;14:986–92.
124. Riegert-Johnson D, Gleeson FC, Westra W *et al.* Peutz-Jeghers syndrome. In: Riegert-Johnson DL, Boardman LA, Hefferon T, Roberts M eds. Cancer Syndromes National Center for Biotechnology Information (US): Bethesda (MD), Douglas L Riegert-Johnson 2009.
125. Shaco-Levy R, Jasperson KW, Martin K *et al.* Morphologic characterization of hamartomatous gastrointestinal polyps in Cowden syndrome, Peutz-Jeghers syndrome, and juvenile polyposis syndrome. Hum Pathol 2016;49:39–48.
126. Jarvinen H, Franssila KO. Familial juvenile polyposis coli; increased risk of colorectal cancer. Gut 1984;25:792–800.
127. Brosens LA, van Hattem A, Hylind LM *et al.* Risk of colorectal cancer in juvenile polyposis. Gut 2007;56:965–7.
128. Stanich PP, Pilarski R, Rock J *et al.* Colonic manifestations of PTEN hamartoma tumor syndrome: case series and systematic review. World J Gastroenterol 2014;20:1833–8.

129. Nieuwenhuis MH, Kets CM, Murphy-Ryan M *et al.* Is colorectal surveillance indicated in patients with PTEN mutations? Colorectal Dis 2012;14:e562–6.
130. Pilarski R, Burt R, Kohlman W *et al.* Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607–16.
131. Rathi CD, Solanke DB, Kabra NL *et al.* A rare case of solitary peutz jeghers type hamartomatous duodenal polyp with dysplasia!. J Clin Diagn Res 2016;10:OD03–4.
132. Suzuki K, Higuchi H, Shimizu S *et al.* Endoscopic snare papillectomy for a solitary Peutz-Jeghers-type polyp in the duodenum with ingrowth into the common bile duct: case report. World J Gastroenterol 2015;21:8215–20.
133. Kitaoka F, Shiogama T, Mizutani A *et al.* A solitary Peutz-Jeghers-type hamartomatous polyp in the duodenum. A case report including results of mutation analysis. Digestion 2004;69:79–82.
134. Howe JR, Roth S, Ringold JC *et al.* Mutations in the SMAD4/DPC4 gene in juvenile polyposis. Science 1998;280:1086–8.
135. Howe JR, Bair JL, Sayed MG *et al.* Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. Nat Genet 2001;28:184–7.
136. Gallione C, Aylsworth AS, Beis J *et al.* Overlapping spectra of SMAD4 mutations in juvenile polyposis (JP) and JP-HHT syndrome. Am J Med Genet A 2010;152a:333–9.
137. Maccioni F, Al Ansari N, Mazzamurro F *et al.* Surveillance of patients affected by Peutz-Jeghers syndrome: diagnostic value of MR enterography in prone and supine position. Abdom Imaging 2012;37:279–87.
138. Urquhart P, Grimpen F, Lim GJ *et al.* Capsule endoscopy versus magnetic resonance enterography for the detection of small bowel polyps in Peutz-Jeghers syndrome. Fam Cancer 2014;13:249–55.
139. Pennazio M, Spada C, Eliakim R *et al.* Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2015;47:352–76.
140. van Lier MG, Wagner A, Mathus-Vliegen EM *et al.* High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol 2010;105:1258–64.author reply 1265.
141. Heald B, Burke CA, Kalady M *et al.* ACG guidelines on management of PTEN-Hamartoma Tumor syndrome: does the evidence support so much so young? Am J Gastroenterol 2015;110:1733–4.
142. Kalady MF, Jarrar A, Leach B *et al.* Defining phenotypes and cancer risk in hyperplastic polyposis syndrome. Dis Colon Rectum 2011;54:164–70.
143. Rosty C, Buchanan DD, Walsh MD *et al.* Phenotype and polyp landscape in serrated polyposis syndrome: a series of 100 patients from genetics clinics. Am J Surg Pathol 2012;36:876–82.
144. Snover DC, BR , Odze RD. In: Bosman FT, Carneiro F, Hruban RH *et al.* ed. WHO Classification of Tumors of the Digestive System International Agency for Research on Cancer: Lyon, France, 2010, 160–5.
145. IJspeert JEG, Bevan R, Senore C *et al.* Detection rate of serrated polyps and serrated polyposis syndrome in colorectal cancer screening cohorts: a European overview. Gut 2016;66:1225–32.
146. Vemulapalli KC, Rex DK. Failure to recognize serrated polyposis syndrome in a cohort with large sessile colorectal polyps. Gastrointest Endosc 2012;75:1206–10.
147. Plesec T, Brown K, Allen C *et al.* Clinicopathologic features of a kindred with SCG5-GREM1-associated hereditary mixed polyposis syndrome. Hum Pathol 2016;60:75–81.
148. Clendenning M, Young JP, Walsh MD *et al.* Germline mutations in the polyposis-associated genes, and are not common in individuals with serrated polyposis syndrome. PLoS One 2013;8:e66705.
149. Delker DA, McGettigan BM, Kanth P *et al.* RNA sequencing of sessile serrated colon polyps identifies differentially expressed genes and immunohistochemical markers. PLoS ONE 2014;9:e88367.
150. Kanth P, Bronner MP, Boucher KM *et al.* Gene signature in sessile serrated polyps identifies colon cancer subtype. Cancer Prev Res (Phila) 2016;9:456–65.
151. Chow E, Lipton L, Lynch E *et al.* Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology 2006;131:30–9.
152. 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;135:2014–8.
153. Win AK, Walters RJ, Buchanan DD *et al.* Cancer risks for relatives of patients with serrated polyposis. Am J Gastroenterol 2012;107:770–8.
154. Boparai KS, Mathus-Vliegen EM, Koornstra JJ *et al.* Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. Gut 2010;59:1094–100.
155. Jasperson KW, Kanth P, Kirchhoff AC *et al.* Serrated polyposis: colonic phenotype, extracolonic features, and familial risk in a large cohort. Dis Colon Rectum 2013;56:1211–6.
156. Hazewinkel Y, Tytgat KM, van Eeden S *et al.* Incidence of colonic neoplasia in patients with serrated polyposis syndrome who undergo annual endoscopic surveillance. Gastroenterology 2014;147:88–95.
157. Rex DK, Ahnen DJ, Baron JA *et al.* Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315–29.quiz 1314, 1330.
158. Buchanan DD, Sweet K, Drini M *et al.* Phenotypic diversity in patients with multiple serrated polyps: a genetics clinic study. Int J Colorectal Dis 2010;25:703–12.
159. Oquinena S, Guerra A, Pueyo A *et al.* Serrated polyposis: prospective study of first-degree relatives. Eur J Gastroenterol Hepatol 2013;25:28–32.
160. Boparai KS, Reitsma JB, Lemmens V *et al.* Increased colorectal cancer risk in first-degree relatives of patients with hyperplastic polyposis syndrome. Gut 2010;59:1222–5.
161. Edelstein DL, Axilbund JE, Hylind LM *et al.* Serrated polyposis: rapid and relentless development of colorectal neoplasia. Gut 2013;62:404–8.
162. Hazewinkel Y, Reitsma JB, Nagengast FM *et al.* Extracolonic cancer risk in patients with serrated polyposis syndrome and their first-degree relatives. Fam Cancer 2013;12:669–73.
163. Lu KH, Wood ME, Daniels M *et al.* American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. J Clin Oncol 2014;32:833–40.
164. Kushi LH, Potter JD, Bostick RM *et al.* Dietary fat and risk of breast cancer according to hormone receptor status. Cancer Epidemiol Biomarkers Prev 1995;4:11–19.
165. Wood ME, Kadlubek P, Pham TH *et al.* Quality of cancer family history and referral for genetic counseling and testing among oncology practices: a pilot test of quality measures as part of the American Society of Clinical Oncology Quality Oncology Practice Initiative. J Clin Oncol 2014;32:824–9.
166. Stoffel EM, Mercado RC, Kohlmann W *et al.* Prevalence and predictors of appropriate colorectal cancer surveillance in Lynch syndrome. Am J Gastroenterol 2010;105:1851–60.
167. Iwama T, Mishima Y, Utsunomiya J. The impact of familial adenomatous polyposis on the tumorigenesis and mortality at the several organs. Its rational treatment. Ann Surg 1993;217:101–8.
168. Giardiello FM, Brensinger JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. Gastroenterology 2001;121:198–213.
169. Neklason DW, Stevens J, Boucher KM *et al.* American founder mutation for attenuated familial adenomatous polyposis. Clin Gastroenterol Hepatol 2008;6:46–52
170. Lynch HT, Smyrk T, McGinn T *et al.* Attenuated familial adenomatous polyposis (AFAP). A phenotypically and genotypically distinctive variant of FAP. Cancer 1995;76:2427–33.
171. Hernegger GS, Moore HG, Guillem JG. Attenuated familial adenomatous polyposis: an evolving and poorly understood entity. Dis Colon Rectum 2002;45:127–34.discussion 134-6.
172. Lubbe SJ, Di Bernardo MC, Chandler IP *et al.* Clinical implications of the colorectal cancer risk associated with MUTYH mutation. J Clin Oncol 2009;27:3975–80.
173. Vogt S, Jones N, Christian D *et al.* Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology 2009;137:1976–85.e1-10.
174. Giardiello FM, Brensinger JD, Tersmette AC *et al.* Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000;119:1447–53.
175. Giardiello FM, Hamilton SR, Kern SE *et al.* Colorectal neoplasia in juvenile polyposis or juvenile polyps. Arch Dis Child 1991;66:971–5.
176. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol 1998;5:751–6.
177. Jass JR, Williams CB, Bussey HJ *et al.* Juvenile polyposis--a precancerous condition. Histopathology 1988;13:619–30.
178. Orlowska J. Hyperplastic polyposis syndrome and the risk of colorectal cancer. Gut 2012;61:470–1.author reply 471-2.