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Genetics in Gastroenterology Practice (B Katona, Section Editor)

Hereditary Polyposis Syndromes

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Abstract

Purpose of Review Colorectal cancer (CRC) is the third most common cancer in the USA and inherited cancer syndromes are responsible for approximately 3–5% of all CRCs. Genetic testing costs have plummeted in recent years; however, awareness and referral of high-risk patients for testing is still very low. We review the salient clinical features, genetics, and management of well-defined gastrointestinal (GI) hereditary polyposis syndromes including familial adenomatous polyposis, MUTYH-associated polyposis, and the hamartomatous polyposis syndromes.
Recent Findings Comprehensive endoscopic surveillance has the potential to prevent the development of GI cancer and to identify early-stage cancer; newer developments like high-definition endoscopes, chromoendoscopy, and the use of cap-assisted endoscopy have shown promise for enhanced lesion detection rates. Several chemoprevention trials have yielded promising results but safety and efficacy data for long-term use is still awaited. Several new polyposis genes have

also been identified in the recent years.
Summary Multiple societies have recently published updated surveillance guidelines to aid clinicians in the detection and management of patients with hereditary GI polyposis syndromes. Although these syndromes are rare, it is crucial for the clinicians to recognize these in a timely manner, for the appropriate management plans for both the patient and their at risk family members.

Introduction

Colorectal cancer (CRC) is the third most common cancer in both men and women in the USA (after excluding skin cancer). About 3–5% of all CRC is attributed to hereditary cancer syndromes, including Lynch syndrome, familial adenomatous polyposis (FAP), attenuated FAP, MUTYH-associated polyposis (MAP), and the hamartomatous polyposis syndromes. *POLD1*, *POLE* (polymerase proofreading–associated polyposis), and *GREM1* (hereditary mixed polyposis syndrome) and biallelic *NTHL1* are some of the newer genes associated with polyposis and CRC. Next-generation sequencing (NGS) has increased the availability of low-cost genetic testing in recent years; however, in a large study, only 11–26% of high-risk CRC patients were referred for genetic risk assessment [1]. Our aim is to summarize key clinical features, genetics, screening, and surveillance of these syndromes, with a focus on the gastrointestinal tract. Lynch syndrome and serrated polyposis syndrome are covered in other reviews in this issue. Most of the recommendations set forth in this article are based on National Comprehensive Cancer Network (NCCN) [2], American College of Gastroenterology (ACG) [3•], and European Society of Gastrointestinal Endoscopy (ESGE) [4•] guidelines.

Gastrointestinal polyposis syndromes—when to consider them?

The gastrointestinal polyposis syndromes are a unique set of inherited cancer predisposition syndromes with complex presentation [5–7]. The phenotype may vary among individuals having a specific germline mutation, and even within family members carrying the same mutation. Notably, in some of these patients with clinical polyposis, no germline mutation can be identified. These patients should be treated according to their clinical diagnosis [4•].

Hereditary polyposis syndromes and referral for genetics evaluation should be considered in patients with ten or more colonic adenomatous polyps or two or more hamartomatous polyps. Polyps in other parts of the gastrointestinal tract, polyps in young individuals, family history of polyposis, and multiple gastrointestinal cancers should also raise concern for hereditary polyposis syndromes. The specific condition is often determined by a combination of clinical assessment, inquiry of the family history, review of polyp pathology, and germline testing for causative genes [8]. The polyposis conditions with pathologic categories, related genes, and disease management are summarized in Tables 1 and 2.

Table 1. Overview of polyposis syndromes

Syndrome	Gene (germline mutation found)	CRC risk	Other GI cancer risk	Extra-intestinal manifestations/tumors
Adenomatous polyposis syndrome				
Familial adenomatous polyposis/(AA)	*APC* (70–90%)	FAP 100% AFAP 70%	Duodenum/ampulla: 4–12% Gastric < 1% Pancreas 1.7%	Osteomas, sebaceous/epidermoid cysts, fibromas, lipomas (Gardner syndrome variant); CHRPE; hepatoblastomas, desmoids, CNS (< 1%), thyroid (1–12%)
MUTYH-associated polyposis (aa)	*MUTYH* (16–40%)	19–43%	Gastric 1% Duodenum 4%	Ovary, bladder, breast, endometrium-rare undefined risk
Hamartomatous polyposis syndrome				
Peutz-Jeghers syndrome (AA)	*STK11* (80–94%)	15–57%	Stomach 29% Small bowel 13% Pancreas 11–36%	Perioral pigmentation, breast (32–54%), testes (15%), uterus (9%), cervix (10%), and ovaries (21%), lung (7–17%)
Juvenile polyposis syndrome (AA)	*SMAD4*; *BMPR1A* (40–60%)	39–68%	Stomach/small bowel/pancreas (21%)	Mitral valve prolapse, ventricular septal defect, epilepsy, ocular defects, telangiectasia, arterial aneurysms
Cowden syndrome (AA)	*PTEN* (70–80%)	9–16%	No clear association with upper GI or pancreatic cancer	Macrocephaly, macular pigmentation of the glans penis, trichilemmomas, palmoplantar keratoses, verrucous facial papules, autism spectrum disorder; breast (25–85%), thyroid (3–38%), endometrium (5–28%), kidney (15–34%), melanoma (6%)

Abbreviations: *APC*, adenomatous polyposis coli; *AFAP*, attenuated FAP; *BMPR1A*, bone morphogenetic protein receptor type 1A; *CRC*, colorectal cancer; *CHRPE*, congenital hypertrophy of the retinal pigmented epithelium; *FAP*, familial adenomatous polyposis; *GI*, gastrointestinal; *MUTYH*, MutY-homolog; *PTEN*, phosphatase and tensin homolog on chromosome ten; *SMAD4*, mothers against decapentaplegic homolog 4; *STK11*, serine/threonine kinase 11; *AA*, autosomal dominant; *aa*, autosomal recessive

Familial adenomatous polyposis/attenuated familial adenomatous polyposis

Overview

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome characterized by the presence of 100 or more synchronous adenomas of the

Table 2. Gastrointestinal tract and pancreatic surveillance recommendations

Syndrome	Age to begin surveillance (years)	Surveillance interval (years)
Adenomatous polyposis syndromes		
Familial adenomatous polyposis		
EGD	25–30	1–3*
Colonoscopy	ACG 10–15 ESGE 12–14	1–2
Attenuated Familial adenomatous polyposis		
EGD	25–30	1–3*
Colonoscopy	ACG 18–20 ESGE 12–14	1–2
MUTYH-associated polyposis		
EGD	30–35	1–3*
Colonoscopy	ACG 25–30 ESGE 18	1–2
Hamartomatous polyposis		
Peutz-Jeghers Syndrome		
EGD	8 (if no polyps, repeat at 18)	ACG 3 ESGE 1–3
Colonoscopy	8 (if no polyps, repeat at 18)	ACG 3 ESGE 1–3
Video capsule small bowel endoscopy or MRI	8 (if no polyps, repeat at 18)	ACG 3 ESGE 1–3
EUS of pancreas or MRCP	30	ACG 3 ESGE 1–3
Juvenile polyposis syndrome		
EGD	ACG12–15 ESGE *SMAD4* 18 *BMPR1A* 25	1–3
Colonoscopy	12–15	1–3
Video capsule endoscopy	Undefined rare risk, periodic assessment	--
Pancreatic assessment	No recommendations, rare undefined risk	--
Cowden syndrome		
EGD	15	2–3
Colonoscopy	15	2

Abbreviations: *AFAP*, attenuated FAP; *EUS*, endoscopic ultrasound; *EGD*, esophagogastroduodenoscopy; *FAP*, familial adenomatous polyposis; *JPS*, juvenile polyposis syndrome; *MRCP*, magnetic resonance cholangiopancreatography; *PJS*, Peutz-Jeghers syndrome; *based on Spigelman score/ampullary/gastric findings; European Society of Gastrointestinal Endoscopy (ESGE)

colon which arises from germline mutations in the *APC* gene [3•]. FAP carries a nearly 100% lifetime risk of colorectal cancer (CRC) if left untreated; it accounts for less than 1% of CRC with a worldwide incidence of 1 in 10,000 [9]. Up to

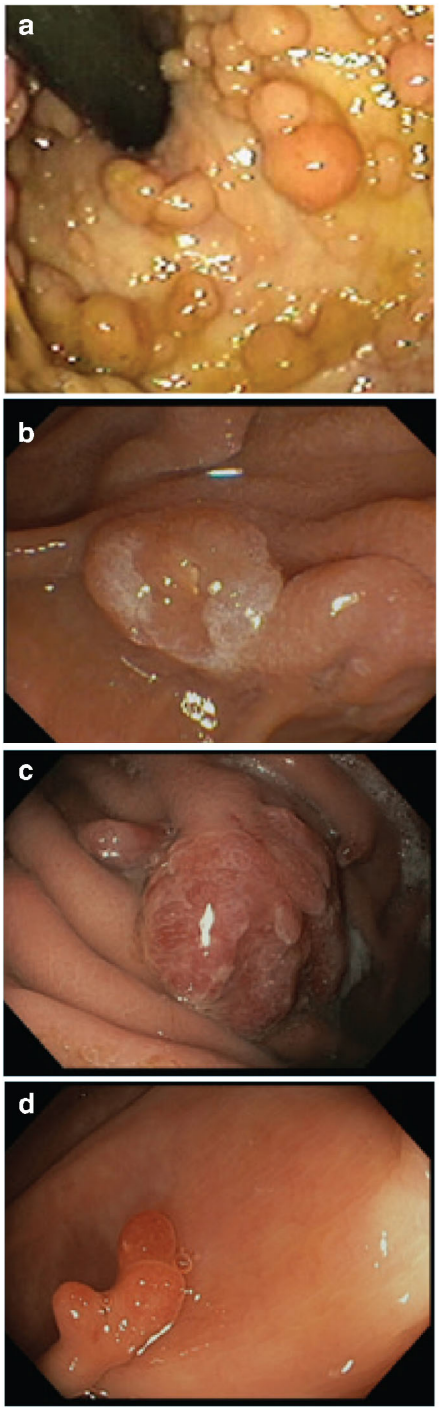

Fig. 1. Endoscopic view of polyps from patients with polyposis syndromes. **a** ampullary adenoma in MuTYH-associated polyposis. **b** Gastric polyps in familial adenomatous polyposis. **c** Hamartomatous gastric polyp in juvenile polyposis syndrome. **d** Hamartomatous colon polyp in Cowden's syndrome

one-third of newly diagnosed FAP cases occur in patients without a family history and likely represent de novo mutations or mosaicism [3•]. These

patients do not have a positive family history; therefore, they are often missed and diagnosed at a later stage.

Attenuated FAP (AFAP), as the name implies, is a milder form of the disease caused by germline mutations in the same *APC* gene; clinically it presents with fewer colonic polyps (arbitrarily defined as < 100 adenomas), is typically diagnosed later in life (average age of diagnosis, 40 years) due to delayed onset of polyps, and carries a lower lifetime CRC risk (70% by the age of 80) [9, 10]. Mutations in AFAP patients have been reported in three distinct regions of the *APC* gene, including the 5′ end spanning exons 3 to 5, exon 9, and the 3′ distal end [11].

Clinical presentation and diagnosis

The hallmark of FAP and AFAP is the presence of colonic polyposis, but extracolonic manifestations (benign and malignant) are present in both syndromes. Other commonly affected organs include the thyroid (papillary thyroid cancer), small intestine (duodenal and ampullary adenomas/carcinoma), bones (osteoma), and skin/connective tissue (desmoids) [3•]. In the case of AFAP, duodenal polyposis is common while the other extra-intestinal manifestations occur less frequently [12].

According to NCCN guidelines [2], testing for *APC* germline mutations should be considered when (1) 20 or more cumulative colon adenomas diagnosed in a patient or greater than 10 adenomas are identified on a single colonoscopy and/or (2) a family member with known FAP diagnosis. Furthermore, consider testing if extra-colonic manifestations like bilateral/multifocal congenital hypertrophy of the retinal pigmented epithelium (CHRPE), desmoid tumors, personal history of hepatoblastoma, or cribriform morular variant of papillary thyroid cancer are identified.

Management

Classic FAP patients should begin CRC screening around age 10 to 12 years with flexible sigmoidoscopy or colonoscopy. If adenomas are detected, a full colonoscopy should be performed. Even in the absence of adenomas, CRC screening should be repeated annually. In first-degree relatives of affected individuals from families without an identified pathogenic *APC* mutation, intensive screening can be discontinued at age 40 years if no adenomas have been detected on prior examinations [13]. Since AFAP patients present at a later age and the lesions can be proximal, colonoscopy is the preferred test and it can be started at a later age than FAP. These recommendations are summarized in Table 2.

Indications for colorectal surgery in FAP and AFAP include documented or suspected cancer, presence of multiple adenomas > 6 mm, adenoma with high-grade dysplasia, and inability to adequately survey the colon because of multiple diminutive polyps [3•].

Elective colectomy can be deferred to the late teens or early twenties in patients with classic FAP who are in the second decade of life with only sparse (< 10) or small (< 5 mm) adenomas. The decision to perform ileorectal anastomosis, end ileostomy with total proctocolectomy, or ileal pouch anal anastomosis (IPAA) is dependent on disease-related factors and joint decision-making between the patient and the surgeon [3•]. Colectomy with ileorectal

anastomosis (IRA) to preserve the rectum may be preferred in patients with low risk of rectal cancer or female patients who wish to have children. IRA can be considered if there are less than 20 rectal adenomas, none larger than 1 cm, and none with high-grade dysplasia. Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is a preferable option in patients with personal or family history of desmoids or germline mutation predisposing to desmoids as future conversion of IRA to IPAA might be difficult due to mesenteric desmoid tumors and shortening of the mesentery [13]. A detailed endoscopic exam of the rectum documenting the number and extent of polyps is essential for preoperative work up in these patients. Unfortunately, even after colectomy there is a small risk of adenoma and carcinoma in the ileal pouch, rectal cuff, or even the ileostomy site. These patients should undergo endoscopic surveillance (with retroflexion) every year of the residual rectum or the pouch [14, 15]. End ileostomy should be examined every other year with ileoscopy.

Upper gastrointestinal lesions: duodenal polyps

The lifetime risk of development of duodenal adenomas in FAP approaches almost 100%, similar to the risk of colorectal polyp development. However, the lifetime risk of duodenal cancer development is only 2–5% [3•, 16•]; furthermore, duodenal cancer is the most common cause of mortality in FAP patients who have undergone colectomy [3•, 9]. The Spigelman staging system of duodenal polyposis [17] determines the severity of polyposis based on number of polyps, polyp size, histology, and degree of dysplasia and is associated with the risk of cancer development; it is incorporated by guidelines [2, 3•] to determine surveillance intervals (ranging from 3 months to every 4 years) by esophagogastroduodenoscopy (EGD).

The ESGE does not recommend random routine biopsies of either small, benign appearing duodenal polyps in the absence of suspicious gross appearance or a normal appearing ampulla due to risk of fibrosis, pancreatitis, and interference with future endoscopic resection and optical diagnosis [4•]. Endoscopic resection of duodenal/ampullary adenoma 10 mm or greater in size should be considered. Patients meeting criteria for the most severe degree of polyposis (i.e., Spigelman stage IV) are recommended to undergo surgical evaluation for duodenotomy, pancreas preserving duodenectomy, or a Whipple pancreatico-duodenectomy. Pancreaticoduodenectomy (Whipple procedure) is appropriate for patients with invasive cancer or with severe adenomatous disease not amenable to endoscopic therapy. A pancreas preserving total duodenectomy (PPTD) is a technically demanding procedure that requires experienced surgeons. It is preferred when there are endoscopically unresectable adenomas in the duodenum that cannot be removed via duodenotomy due to location, size, or multicentricity of lesions. Malignancy must be definitively excluded prior to PPTD as it is not an oncological procedure. The major benefit from this procedure includes lower rates of exocrine or endocrine insufficiency as well as easier endoscopic surveillance and fewer anastomoses [16•].

There are limitations to the Spigelman classification, such as the lack of incorporation of patient age and pathology at the ampulla. Risk factors for duodenal cancer development include Spigelman stage IV at first endoscopy, large duodenal polyps (10 ml or greater) or polyps with high-grade dysplasia on histology as well as ampullary adenomas with high-grade dysplasia or a villous

component on histology [18•]. Surveillance intervals should thus incorporate all of these factors and may need adjustment based on specific factors identified in the patient [4•].

The ampulla should be visualized during every surveillance exam with a side-viewing duodenoscope to assess for pathology at the ampulla, as shown in Fig. 1a. However, recent studies have found that cap-assisted forward-viewing endoscopy may be a cost- and time-saving alternative that allows adequate visualization of this region [16•]. A recent study [19•] also found that dye-based chromoendoscopy could improve duodenal surveillance in patients with MAP and FAP with improved detection of adenomas and resulted in a clinically significant upstaging in Spigelman score in FAP and MAP patients. Current guidelines do not recommend regular assessment of small intestinal polyps distal to the duodenum in FAP/MAP in the absence of any suggestive symptoms.

UGI lesions: gastric polyps

While fundic gland polyps are found in the stomach of the majority of FAP patients (Fig. 1b) and commonly have focal low-grade dysplasia on histological examination, the risk of gastric cancer has not been found to be elevated in the Western population with a risk less than 1% [9]. Surveillance of the stomach with EGD should begin at the age of 25–30 years, since development of upper gastrointestinal (UGI) malignancy is extremely rare before the age of 30 years. A recently described [20] gastric polyposis syndrome known as gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is included on the differential diagnosis along with FAP in patients with gastric polyposis. Endoscopically, GAPPS is characterized by extensive fundic gland polyposis of the fundus and body of the stomach with characteristic sparing of the antrum and lesser curvature, the latter being a pathognomonic finding that distinguishes it from FAP [21]. GAPPS is autosomal dominant and caused by mutations in *APC* promoter 1B, making it a part of *APC*-related conditions. Gastrectomy is the intervention of choice in the presence of intramucosal or invasive cancer. Due to rarity of this disease and limited understanding of the natural history, there are no consensus guidelines on screening, timing of prophylactic gastrectomy, or endoscopic surveillance in GAPPS yet.

Unlike Spigelman staging for duodenal polyps, no clear consensus guidelines exist for the staging and surveillance of gastric polyps in FAP. As a result, EGD surveillance intervals are driven by the most severe/high-risk findings in either the stomach or duodenum [16•]. In general, gastric polyps 10 ml or greater in size and those with an unusual appearance (ulcerated, mucosal depression, etc.) should be removed endoscopically and random biopsies should be taken from the polyps from the proximal, mid, and distal stomach per the ACG guidelines. Contrary to the ACG guidelines, the ESGE does not recommend routine random sampling of fundic gland polyps [4•]. Baseline magnetic resonance imaging (MRI) or computed tomography (CT) scan should also be considered in patients with polypoid masses as there have been reports of identifying metastatic disease in such patients.

Chemoprevention

Several trials with chemoprophylaxis agents to delay or prevent cancer development have had mixed results. Sulindac, a nonsteroidal anti-inflammatory

agent, has been shown to reduce colorectal adenoma burden [22–24] though the impact on cancer development is less certain and is not recommended in patients who would otherwise require colectomy. It may have some role in patients who have residual rectum after surgery as a means to prevent polyp development but not recommended routinely for use in these patients.

In one short-term, six-month study, a combination of sulindac and erlotinib, the latter an epidermal growth factor inhibitor, reduced duodenal polyposis dramatically by 70% [25]; however, the side effect profile of this combination was limiting including development of an acne-like rash in 87% of participants. Multicenter studies evaluating longer term follow-up and safety profiles are under way. Overall, there are no current guidelines for universal administration of these chemopreventative agents in FAP patients.

MUTYH-associated polyposis

Overview

MUTYH-associated polyposis (MAP) is an autosomal recessive disease characterized by an attenuated polyposis phenotype caused by germline mutations (homozygous or compound heterozygous) in the *MUTYH* gene [3•, 8]. MAP is a relatively newly established syndrome, formally identified in 2002.

The risk of CRC by age 50 years is 19% and by age 60 years is 43%, with an average age of onset of 48 years. Although the predominant polyp type in MAP is an adenoma, multiple hyperplastic or sessile serrated polyps can also be found [3•].

Monoallelic (single gene) *MUTYH* mutations are common and present in 1–2% of the general population [26]. These patients do not develop polyposis and are thought to have a slightly higher than average CRC risk, though this is a point of ongoing debate. ACG guidelines published in 2015 recommended CRC screening starting at age 40 years and repeated every 5 years [2]. However, the latest NCCN and ESGE guidelines recommend managing patients with monoallelic *MUTYH* mutations based on their family history rather than their *MUTYH* mutation status. Individuals unaffected by CRC and no first-degree relative with CRC, should be managed the same as the general population [3•, 4•].

Clinical presentation and diagnosis

Patients classically have 20–99 colorectal adenomas and duodenal polyposis is the main extra-colonic manifestation seen [3•, 9]. The indications for genetic testing for MAP are the same as for AFAP.

Management

Patients with MAP are managed like those with AFAP—colonoscopy is performed every 1–2 years, beginning at the age of 20–25 years, and surgery is recommended when polyp progression is beyond the control of endoscopic surveillance. Duodenal adenomas occur less frequently and at a later age in MAP compared with FAP. EGD should be initiated at the age of 30–35 years with surveillance intervals based on endoscopic findings and Spigelman score [2]; similar to FAP/AFAP, ampulla should be thoroughly examined during each surveillance EGD in MAP. Rarely extra-colonic malignancy has been reported

with MAP (ovarian, bladder, skin, and breast cancers); however, no routine surveillance is recommended for extra-intestinal malignancies in MAP [26].

Hamartomatous polyposis syndromes

Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and PTEN hamartoma tumor syndrome (PHTS) are three GI hamartomatous syndromes with an approximate prevalence of 1 in 100,000. A hamartoma is disorganized growth of normal appearing cells in native tissue and is generally considered benign with very rare progression to cancer.

Lack of family history or negative genetic test results do not rule out the diagnosis of hamartoma syndrome as 25% patients have a de novo mutation, and 10% of patients will have negative genetic test results despite having a hamartoma syndrome. There are no clinically useful genotype-phenotype correlations, so genetic testing results do not change management [9]. Solitary juvenile hamartomatous polyp is the most common type of polyp encountered in children and accounts for 70% of polyps. Mesiya et al. [27] reported that 0.15% of adult patients had a single sporadic colonic hamartomatous polyp. Sporadic, singular GI hamartomatous polyps are not thought to increase the risk of cancer, but removal should still be considered [28]. There are no proven chemopreventive medications for use in clinical practice for the hamartomatous syndromes.

Peutz-Jeghers syndrome

Overview

PJS is an autosomal dominant condition characterized by distinctive mucocutaneous pigmentation and characteristic hamartomatous polyps [29–31] and is caused by germline mutations of the *STK11* (previously known as *LKB1*) tumor suppressor gene, which is found in 80–94% of PJS patients (Table 1). It has an estimated incidence ranging between 1:50,000 and 1:200,000 births [32–34]. The age of initial presentation varies from a few months to the fifth decade of life [32, 35].

Clinical presentation and diagnosis

Mucocutaneous pigmentation is often the first clinical sign of PJS and is classically seen in the perioral region (lips, gums, hard palate, and buccal mucosa). The perioral pigmentation around the lips is distinctive and classically crosses the vermillion border. Though not pathognomonic, almost all patients with PJS have these macules and while most of the spots often fade with age, the buccal mucosa pigmentation often persists longer [3•, 30].

Hamartomatous polyps in PJS have distinctive histological features in which the cystic spaces are filled with mucin, and smooth muscle proliferation is ubiquitous and often widespread [34]. The polyps occur most frequently in the small intestine (60–90%) followed by the colon (25–50%), stomach, and rectum [3•, 9, 33]. Larger polyps are more prone to ulceration, bleeding, and intussusception [36–38].

Patients with PJS have increased risks for GI and non-GI malignancies, including cancers of the stomach, small intestine, colorectum, pancreas, breast, testes, uterus, and ovaries [3•, 31, 37–41].

A clinical diagnosis of PJS can be made by the presence of any two of the following: (1) Two or more Peutz-Jeghers-type hamartomatous polyps of the GI tract or (2) typical hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers or (3) family history of PJS. Patients meeting these criteria warrant germline testing for pathogenic variants in the *STK11* gene [33].

Management

EGD, colonoscopy, and video capsule endoscopy should be considered beginning as early as 8 years, and no later than the early teenage years [3•, 33] as shown in Table 2. If polyps are detected, surveillance should be performed every 1–3 years. If no polyps are detected on the index exams, then surveillance exam should be done at 18 years of age. However, capsule endoscopy should be performed every 1–3 years starting at 8 years. Polyps greater than 10 ml in size should be endoscopically resected [3•, 33].

Screening for pancreas cancer should start at 30 years of age and be performed every 1–3 years with either MRI or endoscopic ultrasound (EUS) [3•, 41]. Screening for extra-intestinal cancer (breast, ovarian, endometrial, cervical, and sex cord tumors) is important, but beyond the scope of this review.

Everolimus and rapamycin have been explored as chemoprevention agents, but no effective pharmacological agent has found a role for use in clinical practice as yet [3•, 42].

Juvenile polyposis syndrome

Overview

JPS is a rare, autosomal dominant disease [42] with an estimated incidence between 1:100,000 and 1:160,000 and typically presents within the first two decades of life. Roughly half of patients with JPS have mutations that can be identified in the *SMAD4* gene or *BMPR1A* gene [9].

Clinical presentation and diagnosis

Unlike the other hamartomatous polyposis syndromes, patients with JPS usually do not have physical examination findings of the disease, although hereditary hemorrhagic telangiectasias can be seen with a *SMAD4* mutation [9]. The most common presenting features are anemia in the setting of overt hematochezia, followed by abdominal pain, diarrhea, and intussusception [3•, 43]. Extra-intestinal manifestations of JPS vary widely and can include cardiac anomalies (i.e., mitral valve prolapse, ventricular septal defect, pulmonary stenosis), aneurysms of the splenic and iliac arteries, and ocular defects. Cranial defects such as macrocephaly, hydrocephalus, and cleft palate as well as disorders like epilepsy, undescended testes, and autism are also associated with JPS [44].

The most common location of juvenile polyps is in the colon (98%), but these can also be seen in the stomach and small intestine. The polyps in JPS are typically large, exophytic, often bleed, and, on histology, demonstrate an

inflamed lamina propria along with cystic glands, frequently filled with thick mucin. In contrast to the polyps seen in PJS, the degree of smooth muscle proliferation is much lower [37]. Notably, the term "juvenile" refers to the histology of the polyp rather than the age of onset of patient as the polyp can be diagnosed at all ages [43].

Clinical diagnosis of JPS can be made if one of the following three criteria are met: (1) Individuals with five or more juvenile polyps in the colorectum; (2) any juvenile polyp outside of the colorectum (Fig. 1c); or (3) any number of juvenile polyps and a family history of JPS [3•, 43].

The cancer risk in JPS is presumed to arise from the adenomatous tissue within the juvenile polyp [3•]. Patients with JPS mutation are at very high risk of colon cancer (39–68%) and increased risk of gastric, duodenal, and pancreatic cancer [2, 45].

Management

The ACG guideline recommends that endoscopic assessment for polyps in JPS should be undertaken with EGD and colonoscopy starting at 12–15 years of age [2, 3•]. The ESGE has similar recommendations for colonoscopy but recommends performing an EGD at 18 years in patients with *SMAD4* mutation and at 25 years in the presence of a *BMPR1A* mutation. Depending on the number and size of polyps, surveillance intervals vary from 1 to 3 years.

PTEN hamartoma tumor syndromes (PHTS)

PHTS encompass several disorders which occur due to mutations in the *PTEN* (*phosphatase and tensin homolog*) tumor suppressor gene. These disorders, such as Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome, are characterized by the development of hamartomas in multiple organs and an increased risk of cancer [46]. Cowden syndrome, an autosomal dominant disorder with an estimated prevalence of 1:200,000, is the most common condition with a *PTEN* mutation [46, 47]. Individuals with multiple GI hamartomas or ganglioneuromas should be evaluated for Cowden syndrome and related conditions [3•].

Clinical presentation and diagnosis

NCCN diagnostic criteria for Cowden syndrome include a combination of several major and minor criteria and it can be accessed at NCCN Clinical Practice Guidelines in Oncology [46]. Interestingly, diffuse esophageal glycogenic acanthosis, though rare, combined with colonic polyposis is considered pathognomonic for Cowden syndrome [3•].

The polyps in Cowden syndrome are characteristically colonic, sessile, small, and few to numerous (even hundreds) without surface erosion, and, on histology, show mildly inflamed fibrotic lamina propria with smooth muscle proliferation and lymphoid follicles. They demonstrate the least degree of cystic glands and have no thick mucin, unlike juvenile polyps and those seen in PJS [34]. However, patients may have multiple polyp types including traditional adenomas, hamartomas (Fig. 1d), hyperplastic polyps, lipomas, and ganglioneuromas [3•, 46]. Risk of CRC is generally 9–16%, much lower

compared with other hamartomatous syndromes. Breast cancer is the most common malignancy in Cowden syndrome.

Management

There is wide variability in GI surveillance recommendations in PTEN hamartomatous syndrome. The ACG recommends surveillance with EGD and colonoscopy starting at 15 years and repeated at 2–3-year intervals [3•]. However, the NCCN [2] recommends starting colonoscopy at 35 years and repeating every 5 years or 10 years before the earliest known CRC in the family but does not recommend EGD surveillance.

Newly described polyposis genes

In recent years, several newly discovered genes and hereditary polyposis syndromes have been described [48]. The polymerase proofreading–associated polyposis (PPAP) is caused by germline variants in *POLE* and *POLD1* (replicative and repair DNA polymerases), inherited in an autosomal dominant manner and characterized by multiple colorectal adenomas and carcinomas [48, 49]. Biallelic germline mutations in *NTHL1* (a base excision repair gene) have been shown to be associated with attenuated colonic polyposis and CRC as well as duodenal, basal cell, and endometrial cancer [48, 50]. Biallelic pathogenic variants in *MSH3* (a mismatch repair gene not associated with Lynch syndrome) cause a colonic adenomatous polyposis syndrome resembling AFAP [48]. Hereditary mixed polyposis syndrome (HMPS), caused by mutations in the *GREM1* gene, presents with multiple polyps of more than one histologic type and/or polyps with overlapping histologic features within the individual polyp [48]. Lastly, *RNF43*, *ATM*, *AXIN2*, and *GALNT12* have been identified as few other genes with some preliminary evidence of increased colon polyposis and CRC susceptibility. Currently, the NCCN guidelines recommend colonoscopy at age 25–30 years and every 2–3 years if negative and every 1–2 years if polyps are found; surgical referral is recommended if polyp burden is not manageable endoscopically for all of these syndromes. As more data becomes available, more specific guidelines will likely be available based on cancer risk. Also, *CHEK2* as well as *APC* I1307K variant within the Ashkenazic Jewish population have shown moderately increased risk of CRC. The NCCN recommends colonoscopy starting at age 40 or 10 years prior to age of first-degree relative's age at CRC diagnosis and repeating every 5 years for these patients.

Conclusion

Hereditary polyposis syndrome is a conglomerate of conditions associated with significantly increased risk for development of GI cancers. Increased awareness, early recognition, and implementation of an active surveillance strategy for the gastrointestinal polyposis syndrome is the key to reducing morbidity and mortality in this patient population. Most of these patients benefit from a multidisciplinary approach at specialized centers with high-quality endoscopy and organized endoscopic follow-up system.

Compliance with Ethical Standards

Conflict of Interest
Trilokesh D Kidambi, Divyanshoo R Kohli, N Jewel Samadder, and Aparajita Singh declare no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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