Review

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Genotypic and Phenotypic Characteristics of Hereditary Colorectal Cancer

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The genomic causes and clinical manifestations of hereditary colorectal cancer (HCRC) might be stratified into 2 groups, namely, familial (FCRC) and a limited sense of HCRC, respectively. Otherwise, FCRC is canonically classified into 2 major categories; Lynch syndrome (LS) or associated spectra and inherited polyposis syndrome. By contrast, despite an increasing body of genotypic and phenotypic traits, some FCRC cannot be clearly differentiated as definitively single type, and the situation has become more complex as additional causative genes have been discovered. This review provides an overview of HCRC, including 6 LS or associated spectra and 8 inherited polyposis syndromes, according to molecular pathogenesis. Variants and newly-identified FCRC are particularly emphasized, including *MUTYH* (or *MYH*)-associated polyposis, Muir-Torre syndrome, constitutional mismatch repair deficiency, *EPCAM*-associated LS, polymerase proofreading-associated polyposis, *RNF43*- or *NTHL1*-associated serrated polyposis syndrome, *PTEN* hamartoma tumor syndrome, and hereditary mixed polyposis syndrome. We also comment on the clinical utility of multigene panel tests, focusing on comprehensive cancer panels that include HCRC. Finally, HCRC surveillance strategies are recommended, based on revised or notable concepts underpinned by competent validation and clinical implications, and favoring major guidelines. As hereditary syndromes are mainly attributable to genomic constitutions of distinctive ancestral groups, an integrative national HCRC registry and guideline is an urgent priority.

Keywords: *Hereditary neoplastic syndrome; Colorectal neoplasms; Lynch syndrome; Adenomatous polyposis coli; Interstitnal polyposis*

INTRODUCTION

Malignant neoplasms are multifaceted, comprising various clones, and comprehensive understanding of carcinogenesis requires detailed information, not confined to a specific disease stage. The ongoing process involved in carcinogenesis is conveyed by the word "neoplasm" meaning "forever fresh." Tumor formation essentially constitutes a sequential stepwise accumulation of alterations, as evidenced by serial histopathological and molecular changes. Mutation analysis of 189 genes in 13 samples of primary colorectal cancer (CRC) and matched metastases revealed an overall concordance rate of 78%, while exclusion of rare mutations (potential passenger mutations) raised the rate to 90% [1]. By contrast, genomic profiling of 349 individual glands from 15 colorectal tumors revealed the absence of selective sweeps, and instead detected a uniformly high level of intratumoral heterogeneity and subclonal mixture in distant regions, supporting the so-called "Big Bang" model of tumor development [2]. Accordingly, the majority of private mutations occur early after transition to the advanced tumor stage, rather than as a result of the subsequent selection of *de novo* clones. The 2 most prevalent routes of colorectal carcinogenesis were determined by study of Lynch syndrome (LS) and familial adenomatous polyposis (FAP), as representative familial CRC (FCRC). Hereditary CRC (HCRC) occur via a number of oncogenic pathways, which involve various relevant genes and their interactions. Here, we described molecular pathogenesis and ge-

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Table 1. Causative genes and clinical manifestations of Lynch syndrome and associated spectra

Syndrome	Causative gene/clinical manifestation	Lifetime risk of associate neoplasms[a] (%)									
		Colon	Stomach	Small bowel	Pancreas	Breast	Endometrial	Ovary	Urinary	Thyroid	Others
LS	MMR genes (AD): *MLH*, *MSH2*, *MSH6*, *PMS2*	40–70	6–13	1–4	1–4		32–45	4–12	5–21		
Muir-Torre[b]	MMR genes (65%, AD), *MUTYH* (35%, AR)	40–70	6–13	1–4	1–4		15	4–12	5–21		Skin
Turcot[b]	MMR genes (AR)/LS, GB *APC* (AR), FAP, MB	40–70	6–13	1–4	1–4		32–45	4–12	5–21	5–20	GB/MB
CMMRD	MMR genes (AD): particularly PMS2, MSH6/café au lait	32 (colon+stomach+SB)									GB, H
EALS	EPCAM, MSH2 silencing/congenital tufting enteropathy	40–70	6–13	Moderately increase risk of CRC/lower risk of extracolonic cancer							
FCCTX	Unidentified genes/site-specific distal CRC with later age onset	Moderately increase risk of CRC/lower risk of extracolonic cancer									

LS, Lynch syndrome; MMR, mismatch repair genes; AD, autosomal dominant; AR, autosomal recessive; GB, glioblastoma; FAP, familial adenomatous polyposis; MB, medulloblastoma; CMMRD, constitutional MMR deficiency; SB, small bowel; H, hematological malignancy; EALS, *EPCAM*-associated LS; CRC, colorectal cancer; FCCTX, famili-al colorectal cancer type X.
[a]Lifetime syndrome risks mostly based on the American College of Gastroenterology Guideline of Hereditary Gastrointestinal Cancer Syndromes (2015; https://gi.org/guidelines/) and included references. [b]Predicted on the basis of LS with additional FAP in Turcot syndrome.

nomic alterations in HCRC and their clinical application, including genetic testing, and surveillance.

A SPECTRUM OF HEREDITARY COLORECTAL CANCER

CRC was among the first solid tumors to be molecularly characterized, and several genes and pathways are implicated in CRC tumor initiation and growth [3]. Bodmer et al. [4] explored gene alterations causative of FAP localized to chromosome 5q21-q22 as determined by linkage analysis of DNA markers from 124 subjects in 13 different FAP families, with further analysis showing that this locus was located at chromosome 5q22.2. The stepwise "adenoma-carcinoma" continuum is a principal CRC progression model first proposed by Fearon and Vogelstein [5] as a process that initiates with the formation of benign tumors (adenomas and sessile serrated polyps), followed by sequential steps of progression to more histologically invasive cancer. Molecular alterations underlying CRC progression are generally acquired early in the carcinogenic process, and there is substantial inter-connectivity among genomic drivers, transcriptomic subtypes, and immune signatures [3, 6].

Approximately 25% of all CRCs have been found to be FCRC (5%) and a limited sense of HCRC (20%), respectively (HCRC in this review includes both FCRC and a limited sense of HCRC) [7, 8]. The former category includes a variety of genetically verified syndromes with high penetrance of CRC, whereas the latter can include any familial occurrences of CRC due to mostly multigenic variants, each with low-level effects on the basis of an analysis of polygenic risk scores [9]. FCRC is canonically stratified into 2 categories; LS or LS-associated spectra and inherited polyposis syndrome. The former includes classical LS, Muir-Torre syndrome, Turcot syndrome, constitutional mismatch repair deficiency (CMMRD) syndrome, *EPCAM*-associated LS, and transiently called FCRC type X (FCCTX) (Table 1). The latter comprises a broad spectrum associated with multiple polyposis, including FAP, *MUTYH*-associated polyposis (MAP), polymerase proofreading-associated polyposis (PPAP), serrated polyposis syndrome (SPS), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), *PTEN* hamartoma tumor syndrome (PHTS), and hereditary mixed polyposis syndrome (HMPS) (Table 2).

LYNCH SYNDROME AND ASSOCIATED SPECTRA

Lynch syndrome

LS, previously known as a conventional hereditary nonpolyposis colorectal cancer, carries estimated lifetime CRC risk rates of 70% and 40% for males and females, respectively (range, 22%–75%) [10]. The term "nonpolyposis" is a misnomer, as almost all colorectal polyps can be LS precursor lesions, which typically present with villous growth and high-grade dysplasia [11]. Endometrial adenocarcinoma is the most common extracolonic cancer in LS, with a lifetime risk of 32% to 45%, followed by ovarian, small bowel, gastric, urinary tract, pancreas, and brain cancers. Almost all LS CRCs exhibit a defective DNA mismatch repair (MMR) phenotype, and can be distinguished from sporadic high microsatellite instability (MSI) CRCs in that LS tumors lack somatic *BRAF* mutations and *MLH1* promoter hypermethylation, which are hallmarks of the serrated route to CRC [10]. Among the >3,000 unique germline sequence variants in the 4 LS-associated MMR genes deposited in the InSiGHT locus-specific database, 40%, 34%, 18%, and 8% are alterations of *MLH1*, *MSH2*, *MSH6*, and *PMS2*, respectively [12]. Although total lifetime risk for CRC in *MSH6*

Table 2. Causative genes and clinical manifestations of inherited polyposis syndrome

Syndrome	Causative gene	Clinical manifestations	Lifetime syndrome risk of associate neoplasms[a] (%)									
			Colon	Stomach	Small bowel	Pancreas	Breast	Endometrial	Ovary	Urinary	Thyroid	Others
FAP	*APC* (AD)	Benign soft tissue tumor, CHRPE	90 (69[b])	2–5	5–20	2–5					5–20	Desmoid, MB
MAP	*MUTYH* (AD)	CRC-proximal colon, mucin, LC infiltration	43–63	Less common than those in FAP, otherwise similar spectrum to LS								
PPAP	*POLE*, *POLD1* (AD)	LS-like phenotype in a minority	70		9.5			12	IR			
Sessile polyposis	*RNF43* (AD)	≥5, >rectum (≥2, ≥10 mm), ≥20 (≥5, >rectum)	20	Undetermined								
Peutz-Jeghers	*STK11* (AD)	Mucocutaneous pigmented macules	40	5–20	2–5	5–20	50	10	20			
JP	*SMAD4*, *BMPR1A* (AD)	≥5, extrabowel JP, family history	20–40	5–20								
PHTS	*PTEN*, *PTCH* (AD)	Including BRRS, CS, GS, PS; Upper GI[c]	9				85	28		34	35	Melanoma
HMPS	*SCG5/GREM1* (AD)	Adenoma, serrated/ inflammatory polyp	Undetermined									

FAP, familial adenomatous polyposis; AD, autosomal dominant; CHRPE, congenital hypertrophy of retinal pigment epithelium; MB, medulloblastoma; MAP, *MUTYH*-associated polyposis; CRC, colorectal cancer; LC, lymphocyte; LS, Lynch syndrome; PPAP, polymerase-proofreading-associated polyposis; IR, increased rate; JP, Juvenile polyposis; PHTS, *PTEN* hamartoma tumor syndrome; BRRS, Bannayan-Riley-Ruvalcaba syndrome; CS, Cowden syndrome; GS, Gorlin syndrome; PS, Proteus-like syndromes; GI, gastrointestinal; HMPS, hereditary mixed polyposis.
[a]Lifetime syndrome risks mostly based on the American College of Gastroenterology Guideline of Hereditary Gastrointestinal Cancer Syndromes (2015; https://gi.org/guidelines/) and included refer-ences; PPAP based on the National Study of Colorectal Cancer Genetics (2013), UK; PHTS based on the International Cowden Consortium (2012). [b]Risk in the parenthesis indicates lifetime risk (%) in attenuated FAP. [c]The most common upper GI lesions are esophageal glycogenic acanthosis (37%), gastric hamartomatous polyps (47%), and duodenal hamartomatous polyps (20%).

mutation carriers is similar to that associated with *MSH2* and *MLH1*, tumors tend to occur in the elderly in these patients, similar to sporadic CRCs [13, 14].

The MSH2/MSH6 protein complex, MutS, recognizes single-nucleotide base-pair mismatches, while a second heterodimer complex, comprising MLH1 and PMS2, MutL, binds to MutS and triggers "long-patch excision" of newly-synthesized DNA. Loss of DNA MMR activity results in the rapid accumulation of mutations, generating a hypermutated genomic environment thought to accelerate carcinogenesis [10]. LS-associated tumors exhibit accelerated transition from adenoma to carcinoma, with frequent reports of "interval" cancers developing within 1- to 2-year intervals after colonoscopy [15, 16]; however, LS-related CRCs are less prone to nodal and distant metastatic spread compared with sporadic CRC, despite their apparently high-risk histologic features [7].

Muir-Torre syndrome

The hallmark features of Muir-Torre syndrome are sebaceous neoplasms of the skin and colonic carcinoma, which are the most common visceral malignancies [17]. Additionally, all LS-associated extracolonic tumors can also occur in Muir-Torre syndrome, as well as hematologic malignancies and lung cancer. Some autosomal recessive cases of Muir-Torre syndrome have been described without MSI and are caused by defects in base excision repair (BER) genes, such as *MUTYH* [18]; such cases account for approximately 35% of Muir-Torre syndrome, and are referred to as Muir-Torre syndrome II. Three histologic variants of dermatologic lesions occur in Muir-Torre syndrome; solid, cystic, and keratoacanthoma-like. Lesions can be sebaceous adenomas, sebaceous epitheliomas, sebaceous carcinomas, cystic sebaceous tumors, basal cell carcinomas with sebaceous differentiation, or keratoacanthomas.

Turcot syndrome

Turcot syndrome is LS associated with primary brain tumors. Notably, either LS or FAP can co-segregate with Turcot syndrome, and are referred to as Turcot syndrome 1 and 2, respectively [19]. Turcot syndrome is mostly inherited by autosomal recessive transmission of biallelic MMR and *APC* mutations, and rarely as an autosomal dominant condition, with pleiotropic effects and variable expressivity. Glioblastoma may be caused by MMR gene mutations, specifically in *MLH1*, whereas medulloblastomas are associated with mutations of *APC* [20]. Patients with Turcot syndrome 1 present with hematologic malignancies, café au lait spots, and glioma, particularly glioblastoma multiforme, while those with Turcot syndrome 2 who express the colonic polyposis phenotype tend to manifest the disease after 17 years of age (later than classical FAP), and those who do not express the colonic phenotype develop cerebellar medulloblastoma by 10 years of age [21]. FAP

traits may also be accompanied by congenital hypertrophy of retinal pigment epithelium (CHRPE), subcutaneous or soft tissue benign tumors, and more critical duodenal neoplasms. Paraf et al. [21] attempted to reclassify Turcot syndrome into brain-tumor polyposis syndrome 1 and 2, referring to patients without and with FAP syndrome, respectively; however, patients with brain-tumor polyposis syndrome 2 may develop polyposis later, or may simply not survive long enough for it to emerge.

Constitutional mismatch repair deficiency

CMMRD is a highly-penetrant cancer predisposition syndrome caused by alterations of biallelic MMR genes and can be effectively detected using an *in vitro* G-T repair assay to assess MSH2-MSH6 and MLH1-PMS2 activity [22]. In contrast to the relatively low prevalence of tumors in the first 2 decades of life in patients with LS, individuals harboring homozygous or biallelic MMR gene mutations exhibit a distinct childhood cancer predisposition syndrome [23]. Similarly, the *MSH2* mutations most commonly found in LS are less frequent or absent in CMMRD, while *PMS2* and *MSH6* mutations are more frequent in CMMRD. Specifically, *PMS2* is the gene most frequently mutated in CMMRD, with other MMR genes contributing up to 40% of cases [24].

All children with CMMRD have café au lait spots and most are from consanguineous families. Brain tumors are the most common cancers reported (48%), followed by gastrointestinal (32%), and hematological (15%) malignancies. Fortunately, solid tumors are mostly low grade and resectable [23]. Tumor immunohistochemistry (IHC) assays provide 100% sensitivity and specificity for diagnosis of MMR deficiency, while MSI analysis is neither sensitive nor specific. Screening of normal tissue by IHC can also assist in genetic confirmation of CMMRD.

***EPCAM*-associated Lunch syndrome**

The epithelial cell adhesion molecule gene, *EPCAM*, maps 17 kb upstream of *MSH2* on the short arm of chromosome 2. *EPCAM* alteration was described in patients from Dutch and Chinese families with MSH2-deficient tumors carrying heterozygous germline deletions of the last exons of *TACSTD1*, a gene directly upstream of *MSH2* encoding EPCAM [25]. Biallelic mutations in *EPCAM* cause congenital tufting enteropathy, a rare chronic diarrhea disorder, during infancy, whereas monoallelic deletions of the last exons of *EPCAM* cause LS in 1% to 3% of affected families [26]. Some studies have suggested that the frequency of *EPCAM* deletions causing LS is approximately 30% in patients with *MSH2*-mutation-negative tumors or around 20% in LS patients without MMR mutations [26]. *EPCAM*-associated LS carries a risk of CRC, similar to those of tumors with *MLH1* and *MSH2* mutations, whereas the cumulative risk of endometrial cancer in patients with *EPCAM*-associated LS is much lower [27, 28]. In other words, *EPCAM*-associated LS, epigenetic silencing of *MSH2* is tissue specific, leading to mosaic inactivation of MSH2, a high risk of CRC, and a low risk of endometrial cancer.

Familial colorectal cancer type X

As many as 40% of CRCs fulfilling the LS clinical criteria are microsatellite stable (MSS) and transiently designated FCCTX. Patients with FCCTX have a moderately increased risk of CRC, with a low risk of extracolonic cancers [29]; the risk of CRC is lower than that in LS (relative risk, 0.5), but higher than that of the general population (standardized incidence ratio, 2.3) [30]. FCCTX appears to be associated with site-specific CRC (mainly distal) diagnosed at somewhat later ages compared with LS [12]. Causative genes for FCCTX remain poorly defined, although several candidates have been proposed via next generation sequencing (NGS)-based assays, including *BCR*, *BLM*, *BRF1*, *CHEK2*, *FAN1*, *GABBR2*, *GALNT12*, *HABP4*, *KIF24*, *OGG1*, *RPS20*, *SEMA4A*, and *ZNF367*. By contrast, some genes suggested to carry mutations causing FCCTX are known to cause inherited polyposis syndrome; for example, *BMPR1A*, *MUTYH*, and *POLD1*. One multigene panel (MGP) study of FCCTX found >1 high-penetrant non-LS gene mutation for every 5 LS mutations identified, suggesting that unexpected actionable genomic alterations may occur in patients with LS-like phenotypes [31]. To date, even for those few FCCTX families with plausible gene candidates, the true nature and penetrance of specific gene variants have yet to be proven.

INHERITED POLYPOSIS SYNDROME

Familial adenomatous polyposis

FAP occurs in 1 in 8,300 to 14,000 individuals, approximately one-half of whom develop colorectal adenomas by the age of 16 years [32, 33]. Patients with the classical FAP phenotype carry germline mutations in *APC*; and in >90% of individuals, the lifetime risk for CRC exceeds 90% in the absence of proctocolectomy, along with increased risks of duodenal cancer, pancreatic cancer, medulloblastoma, and papillary thyroid cancer, as well as hepatoblastoma in children aged <5 years [10]. Desmoid tumors occur in 15% to 20% of patients during the second and third decades of life and are more frequent in patients with prior abdominal surgery and relevant family history [6]. Other benign lesions include osteomas (approximately 20%), lipomas, epidermoid cysts, fibromas, dental abnormalities, and CHRPE, which is pathognomonic for FAP diagnosis.

Although FAP is associated with autosomal dominant inheritance, approximately 30% of affected individuals with germline *APC* mutations have no family history, and presumably, index patients have new mutations [34]. FAP can be classified according to the number of colonic adenomas detected as profuse (≥1,000), classic (100–999), or attenuated (<100). The attenuated FAP (AFAP) is conventionally indicated by adenomatous polyposis with ≤100 colorectal adenomas and characterized by later onset polyposis and fewer extracolonic manifestations [35].

Multivariable analyses of 7,225 individuals, including 1,457 with classic polyposis and 3,253 with attenuated polyposis, showed that adenoma count is strongly associated with pathogenic *APC* muta-

tions [36]. That study demonstrated prevalence rates of pathogenic *APC* and biallelic *MUTYH* mutations of 80% and 2% among individuals with ≥1,000 or more adenomas, 56% and 7% in those with 100 to 999 adenomas, 10% and 7% among those with 20 to 99 adenomas, and 5% and 4% among those with 10 to 19 adenomas, respectively. Germline *APC* mutations around codon 1,300 (codons 1,286–1,513, designated the mutation cluster region [MCR]) are thought to result in severe colorectal polyposis [37]; patients tend to acquire somatic mutations as well as normal allelic loss, otherwise incurring truncating second hits. Somatic mutations in upper gastrointestinal polyps, including severe duodenal polyposis, occur between codons 1,400 and 1,580, retaining only one of the 20-amino acid β-catenin-binding degradation repeats [38]. *APC* mutations at the 3′ and 5′ termini of the gene are generally associated with an attenuated phenotype, consisting of fewer polyps and later onset [10]. Further, pathogenic mutations in the promoter 1B region (60 kb upstream of the transcription start site) were also reported in a pedigree from the Swedish polyposis registry without germline *APC* mutations [39].

MUTYH-associated polyposis

MAP tends to present later in life (>25 years) compared with FAP and may predominantly develop in the proximal colon. MAP is characterized by mucin-rich histology and abundant lymphocyte infiltration, and patients have a better prognosis than those with sporadic CRCs [40]. Other common extracolonic features of FAP, such as gastric fundic gland polyps, are less commonly observed in the absence of desmoid tumor [32]. Additionally, some case reports have indicated that the spectrum of extraintestinal lesions in *MUTYH*-associated disease differs greatly from that observed in FAP, and is rather more similar to that in LS, with significantly increased risk for ovarian, endometrial, bladder, and skin tumors [32].

MUTYH maps to the chromosome 1 locus, lp34, and contributes to the DNA BER system. The 2 most common *MUTYH* founder mutations, Y179C and G396D (previously referred to as Y165C and G382D), account for 70% to 80% of MAP cases among individuals of Northwestern European ancestry and are inherited by autosomal recessive transmission [10]. Approximately 1/3 of persons with biallelic *MUTYH* mutations develop CRC in the absence of polyposis, suggesting incomplete penetrance [32]. Interestingly, 10% of Korean patients and their relatives with AFAP carried another heterozygous mutation in the BER gene, *OGG1* (c.1-18G>T), with some heterozygous for the *MUYTH A359V* mutation, suggesting that there may be minor allele mutations in areas devoid of *MUYTH* founder mutations [41]. Another study identified heterozygous loss-of-function *MSH3* mutations (e.g., c.1148delA, c.2319-1G>A, c.2760delC, and c.3001-2A>C) in a subgroup of patients with colorectal adenomatous polyposis [42].

Polymerase-proofreading-associated polyposis

Germline pathogenic variants affecting the exonuclease domain of the polymerases, POLE and POLD1, predispose to PPAP. According to a United Kingdom national study that screened 2,349 probands, the cumulative incidence rates of CRCs in heterozygotes for *POLE* and *POLD1* variants are estimated as approximately 90% and 50%, respectively [43]. Most patients have AFAPs, with few polyps; however, a minority of cases have an LS-like phenotype, with early-onset CRC and increased risks for endometrial and ovarian cancers [44]. Most *POLE* variant heterozygotes exhibit a colorectal tumor phenotype, with median ages at diagnosis of polyposis and CRCs of 36 and 44 years, respectively [43]. Duodenal tumors are the next most frequent lesions in *POLE* variant heterozygotes, occurring in 9.5%, most frequently duodenal carcinoma, with 15% of patients developing ≥1 duodenal adenoma. By contrast, endometrial and ovarian cancers are the most common malignancy in female *POLD1* variant heterozygotes aged <50 years.

Serrated polyposis syndrome

SPS is characterized by the development of numerous serrated polyps throughout the entire colon, with an increased risk of CRCs [45]. The updated criteria for SPS diagnosis (World Health Organization, 2019) include individuals with ≥5 serrated polyps proximal to the rectum that are ≥5 mm in size, with at least two being ≥10 mm in size, or individuals with ≥20 serrated polyps of any size throughout the colon with ≥5 proximal to the rectum [46]. CRCs arising from the serrated route are characterized by mutations of either *KRAS* or *BRAF*, leading to disruption of the WNT signaling pathway and widespread methylation of CpG islands, respectively. Along with *BRAF* mutation in both MSI and MSS CRCs, nonsynonymous mutations in *RNF43* have been identified in affected siblings of patients with SPS, but not in an unaffected sibling, hence *RNF43* mutations are considered causative gene variants [47]. RNF43, an E3 ubiquitin-protein ligase, functions as a negative regulator of WNT signaling by mediating the ubiquitination, endocytosis, and subsequent degradation of the WNT receptor component, Frizzled.

An additional novel disease entity, possibly categorized as SPS, *NTHL1* (catalyzing the first step in BER) tumor syndrome, is caused by germline biallelic pathogenic variants in *NTHL1*, and characterized by an increased lifetime risk for colorectal polyposis, CRC, breast cancer, and variable occurrence of LS- and FAP-associated extracolonic tumors [48]. The cumulative lifetime risk of developing extracolonic cancer by 60 years of age has been estimated to be as much as 35% to 78% in patients with *NTHL1* tumor syndrome.

Peutz-Jeghers syndrome

PJS is a hereditary syndrome manifesting in early childhood and characterized by gastrointestinal hamartomatous polyposis, mucocutaneous pigmented macules, and predisposition to various cancers [49]. Patients with PJS are at an increased risk of gastrointestinal cancers including of the colon, small bowel, biliary tract,

pancreas, stomach, and esophagus, in addition to a wide variety of extraintestinal malignancies, including breast, uterine, cervical, lung, ovarian, and testicular cancers [49]. The overall risks of developing any cancer at ages of < 30, 40, 50, 60, and 70 years are 1% to 3%, 19%, 32%, 63%, and 81%, respectively. Among various malignancies, CRC is the most common, with a lifetime risk of 39%, followed by breast cancer in females with a lifetime risk of 32% to 54%. A pathognomonic feature of intestinal hamartoma is the proliferation of smooth muscle cells derived from the underlying muscularis mucosae, growing in an arborizing pattern to displace the surface epithelium into the submucosa and muscularis propria, and featuring pseudoinvasion [50]. Mucocutaneous presentation includes pigmented dark blue, brown, to black macules distributed on the lips, perioral areas, buccal mucosa, eyes, nostrils, fingertips, palms, soles, and perianal areas, without malignant transformation [49]. The PJS phenotype manifests when germline serine/threonine protein kinase (*LKB1*) mutations are accompanied by an acquired defect/second hit in the other allele in somatic cells, and is transmitted by autosomal dominant inheritance [51]. Loss-of-function mutations of *STK11* can be oncogenic because they lead to disruption of the AMPK pathway, aberrant activation of the mammalian target of rapamycin (mTOR) pathway, and increased metabolic glucose and glutamine use via the hypoxia-inducible factor 1-α (HIF-1-α) pathway. The hamartoma-carcinoma sequence can be explained by 3 potential cellular and molecular pathogenic pathways (including mothers against decapentaplegic homolog 4 [SMAD4] and *STK11*): dysplastic transformation; altered turnover rate of stem cells, resulting in expanded progenitors; or hamartoma-adenoma transition [52-54].

Juvenile polyposis syndrome

JPS is an uncommon hamartomatous disorder with significant gastrointestinal malignant potential. JPS can be diagnosed when any of the following clinical criteria are met; more than 5 juvenile polyps in the entire colon, extraintestinal juvenile polyps, or any number of juvenile polyps with family history [55]. JPS is accompanied by hereditary hemorrhagic telangiectasia (HHT), malrotation of the midgut, cardiac and cranial abnormalities, cleft palate, polydactyly, and genitourinary defects [50]. Höfting et al. [56] reviewed 272 JPS cases and described affected sites in order of frequency as the colon (98%), stomach (14%), jejunum and ileum (7%), and duodenum (2%). JPS polyps are generally relatively large, often exhibit surface erosion, and are unlikely to spread *via* smooth muscle proliferation. JPS must be distinguished from solitary juvenile polyps, which develop in 2% of children and adolescents without any malignant transformation [50]. In contrast to PHTS, JPS has significant gastrointestinal malignant potential; however, extraintestinal cancers are uncommon [57]. There is a risk of malignancy from 20 years old, which reaches 68% by 60 years [50].

JPS is caused by *SMAD4* and *BMPR1A* (*ALK3*) mutations, with autosomal dominant transmission and incomplete penetrance; reported collective incidence rates are 23% and 21% to 38%, respectively [57, 58]. Mutations of *BMPR1A* affect BMP receptors lacking a serine-threonine kinase domain that are upstream of SMAD4 in the transforming growth factor-β pathway, and result in loss of BMP intracellular signaling through SMAD4 [50]. The landscaper-defect hypothesis was proposed by Kinzler and Vogelstein [59] to explain how stromal overgrowth in JPS predisposes to epithelial malignancy; however, a subsequent cytogenetic study found that epithelial malignancies are likely to develop in JPS through direct progression in epithelial cells, suggesting that SMAD4 acts as a gatekeeper to JPS development [60]. Juvenile polyps should be distinguished from syndrome-specific features of other diseases caused by *PTEN* mutations; for example, Cronkhite-Canada syndrome is also characterized by gastrointestinal hamartomatous polyposis and was erroneously classified as a hereditary polyposis, but is rather caused by autoimmune inflammation or idiopathic traits [61].

***PTEN* hamartoma tumor syndrome**

Patients with PHTS, including Bannayan-Riley-Ruvalcaba (BRRS), Cowden (CS), Gorlin (GS), and Proteus-like syndromes, are at increased risk of developing cancer [62]. The reported cumulative lifetime cancer risk (CLTR) for any cancer varies from 81% to 90% in patients with PHTS, with a median age at diagnosis of 36 years [62]. The tumor spectrum includes female breast cancer (CLTR, 25%–50%), endometrial cancer (19%–28%), thyroid cancer (6%–38%), CRC (9%–32%), renal cell cancer (2%–24%), and melanoma (≤ 6%). There is evidence that some autism spectrum disorders can be classified within PHTS, and these are characterized by CRC, esophageal glycogenic acanthosis, penile macules, testicular lipomatosis, and vascular anomalies [63]. CS features multiple hamartomas, macrocephaly, or Lhermitte-Duclos disease (LDD; accompanied by hamartomatous dysplastic gangliocytoma of the cerebellum), trichilemmomas, and a high risk of benign and malignant neoplasms of the thyroid, breast, uterus, and skin. BRRS features macrocephaly, mental retardation, esophageal glycogenic acanthosis, lipomatosis, hemangiomas, and genital pigmentation, whereas GS presents as multiple nevoid basal cell carcinomas, skeletal abnormalities, odontogenic keratinocytes, macrocephaly, intracranial calcification, and craniofacial abnormalities [64]. Mutations in *PTEN* (10q23.3) and *PTCH* (9q31) can rule out almost all patients with JPS, who are exclusively considered in the context of PHTS [57].

PTEN contributes to apoptosis and the cell cycle by affecting the PI3K/AKT/mTOR pathway. Patients with CS or a CS-like phenotype may also have associated hypermethylation of the *KLLN* promoter, leading to deregulation of p53-induced apoptosis [65]. Despite initial reports that colonic polyps were found in 40% of patients with CS, recent data demonstrate that polyps are found in up to 95% of adults with *PTEN* mutations [66]. A wide range of polyps have been detected in PHTS, including adenomas, ganglioneuromas, hamartomas, inflammatory polyps, leiomyomas,

lipomas, and lymphoid polyps [4]. To date, multiple trichilemmomas are most strongly indicative of *PTEN* mutations and can be seen on the face, including the eyes, mouth, nose, and forehead, as well as the neck, axillae, and hands, along with acral keratosis.

Hereditary mixed polyposis syndrome

Robust diagnostic criteria for HMPS have yet to be firmly established. HMPS is characterized by few polyps per endoscopy, with a mixture of phenotypes, most commonly adenoma and non-dysplastic mixed serrated/inflammatory polyps. More than 50% of polyps demonstrate variable amounts of smooth muscle bands interdigitating between the epithelial crypts, a feature common in hamartomatous polyps, but do not contain large bands of arborizing smooth muscle or compartmentalize the colonic crypts, reminiscent of PJS polyps [67]. Gene variants causative of HMPS were previously mapped to the 10q23 chromosomal region, which includes *BMPR1A* [68]. Among confirmed causative genetic alterations, a 40 kb duplication including the 3′ end of *SCG5* (Ashkenazi Jewish founder mutation) results in aberrant epithelial expression of the mesenchymal BMP antagonist, gremlin1 (GREM1), and is transmitted *via* autosomal dominant inheritance. Mutations in *KRAS* or *BRAF*, *APC*, or *CTNNB1*, a CpG island methylator phenotype, and/or p16 loss drive further neoplastic progression [67]. Further, a Korean family with HMPS carrying 2 missense mutations in the *APC* MCR, affecting codons 1,304 and 1,309, was initially reported as JPS [69]. Epithelial expression of GREM1 may occur in classical serrated adenomas and sporadic premalignant lesions with a hitherto unknown CRC pathogenesis, similar to HMPS polyps [68]. Crypt base stem cells form ectopic crypts and proliferate on accumulation of somatic mutations, enabling initiation of intestinal neoplasia, indicating that these cells may not be the sole cell-of-origin in CRC associated with HMPS polyps.

GENETIC TESTS

Overview

Mechanistic knowledge derived from genome-based diagnosis applied using systems biology approaches can accelerate discovery of useful biomarkers and therapeutics [3]. MGPs, comprising a comprehensive cancer panels including HCRC genes, have been developed for this purpose. MGPs can be broadly categorized according to their manufacturers and purposes; for example, institutional or commercial, and syndrome-specific or comprehensive cancer-diagnostic panels. Comprehensive panels have mostly adopted NGS tools designed for efficient identification of pathogenic single or multiple gene variants; however, gene discovery via MGPs generates considerable numbers of variants of unknown significance (VUS) and clinically questionable or nonactionable alterations [70]. Actionable CRC gene variants that have been identified using MGPs include mutations/alterations in *APC* (the I1307K polymorphism), *AXIN2*, *CHEK2*, *GREM1*, *GALANT12*, *MSH3*, *MUTYH* (monoallelic), *NTHL1*, *POLE*, and *POLD1* [71]. The reproducibility of established MGP platforms is consistent, with minimal variation in designated mutation subsets, although there are different thresholds for variant calling, particularly of variants with low allele frequency ($\leq 1\%$) [72]. Herein, new approaches to find rare variants need to consider the 2 criteria described by Bodmer and Bonilla [73], i.e., genes with obviously severe disruption of function with relevant familial trait and abnormal version of phenotype, and unequivocally involved in the biological phenotypes based on biochemical and physiological studies [73].

Multigene panels for novel gene discovery

According to a genome-wide association study (GWAS) of a Finnish CRC cohort, an association between single-nucleotide polymorphism (SNP) rs992157 at chromosome 2q35 (in the introns of *PNKD*/*TMBIM1*) and CRC was independently replicated in a meta-analysis of European ancestry individuals [74]. Another GWAS demonstrated that *TRIM4* and *PYGL*, which encode proteins that influence redox homeostasis and cellular metabolic reprogramming, respectively, are potentially implicated in a novel CRC pathway linked to cell growth and proliferation [75]. Additionally, *CXCR1* and *CXCR2*, which encode cytokine receptors, are currently under clinical investigation as potential therapeutic targets (clinical trial No. NCT02370238). An institution-based comprehensive cancer MGP (OncoPanel; Eurofins Panlabs, Inc. , St. Charles, MO, USA) has a sensitivity of 74% to 98% for detection of SNPs, insertions-deletions, copy number variations, and structural variants across 282 genes considered to have roles as pan-cancer drivers [76]. OncoPanel was used to identify receptor tyrosine kinase (RTK) fusions occurring exclusively in *KRAS*, *NRAS*, and *BRAF* wild-type CRCs, which play critical roles in CRC oncogenesis, predicting likely response to epidermal growth factor receptor-directed therapeutics. Although MMR-deficient CRCs with RTK fusions were exclusively detected in tumors with *MLH1* promoter hypermethylation, RTK fusions were also identified in MSS CRCs, possibly providing a rare therapeutic target. Another custom-made MGP (HaloPlex; Agilent Technologies, Santa Clara, CA, USA), targeting 112 genes, including established CRC genes and candidate CRC susceptibility genes, identified 17 pathogenic gene variants in 21 samples as potential gene alterations associated with CRC susceptibility, including variants of *ATM*, *AXIN1*, *AXIN2*, *BMP4*, *BRCA1*, *CCDC18*, *CHEK2*, *MUTYH*, *NUDT7*, *PICALM*, *PTPRJ*, *SLC5A9*, *TLR2*, *TWSG1*, *UBAP2*, *USP6N*L, and *ZFP14* [77].

Chip on a bed

Clinicians can currently choose 4 types of MGP tests to identify the cause of inherited cancer susceptibility: (1) syndrome-specific, (2) cancer-specific high-penetrance MGPs, (3) cancer-specific moderate-penetrance MGPs, and (4) comprehensive cancer, including genes associated with multiple cancers or hereditary cancer syndromes [70]. Genes analyzed using MGPs are categorized

as high- or moderate-penetrance, based on the expected lifetime cancer risk (graded as ≥40%, <40%, or unknown) associated with respective cancer predisposition syndromes [31]. Genes associated with LS (MMR genes), adenomatous polyposis (*APC* and *MUTYH*), and hamartomatous polyposis (*BMPR1A*, *PTEN*, *SMAD4*, and *STK11*) syndromes, breast and ovarian cancer (*BRCA1/2*), familial atypical multiple mole melanoma syndrome (*CDKN2A* and *CDK4*), hereditary diffuse gastric cancer (*CDH1*), and Li-Fraumeni syndrome (*TP53*) are classified as high penetrance, whereas the remaining 8 genes (*ATM*, *BARD1*, *BRIP1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, and *RAD51D*) are considered moderate-penetrant HCRC.

An assay for *SEPT9* DNA methylation has also been assessed for use in CRC screening, shown to have clinical sensitivity of 68% and adjusted specificity 80%, and is currently approved as an alternative for individuals who refuse colonoscopy [78].

Aberrant methylation of exon-1 sequences within the non-transcribed vimentin gene (*VIM*) may be a molecular biomarker of CRC, detected in fecal DNA to identify nearly half of individuals with CRC [79]. Multitarget stool-based tests have been developed for noninvasive screening for CRC and its precursors. A multitarget stool DNA test (Cologuard, Exact Sciences, Madison, WI, USA) that combines screening for *KRAS* mutations and abnormal *NDRG4* and *BMP3* promoter region methylation was approved by the U.S. Food and Drug Administration, as well as a fecal IHC test for CRC screening [80]. Unlike the *SEPT9* DNA methylation test, the National Comprehensive Cancer Network (NCCN) guideline for CRC screening recommends the use of multitarget stool DNA testing as a potential screening modality in average-risk individuals; however, data determining an appropriate interval for longitudinal screening and how the multitarget stool DNA test should fit within an overall screening program are lacking.

Liquid biopsy stool DNA assays also represent potential tools for early detection of recurrence and monitoring therapeutic response, although important issues have yet to be overcome; for example, epigenetic plasticity in normal non-cancerous cells and epigenomic flexibility [81,82]. Another strong argument for MGP testing is that there is considerable overlap among hereditary cancer syndromes and their associated phenotypes [70]. Moreover, evidence supporting clinical recommendations based on mutations in moderate-penetrance genes is lacking. Although rigorous cost-effectiveness analyses are beyond the scope of this review, MGP testing offers a lower cost per gene by facilitating parallel, rather than sequential, gene analysis, thereby reducing ancillary costs, including specialist consultations [70].

SURVEILLANCE APPROACHES

Overview

Many recently described HCRC surveillance schemes appear to be either too complex or too stringent for application in clinical practice. In this section, we primarily focus on recently revised and notable HCRC surveillance approaches, based on competent validation or likely impact (Table 3). Major determining factors for HCRC surveillance include cancer risk, age at diagnosis, family history, and phenotypic expression. Current strategies are mainly based on guidelines from the American College of Gastroenterology, Gastroenterology/Association of Coloproctology of Great Britain and Ireland (BSG/ACPGBI, 2020), the NCCN (ver. 1-2021), and the American Society of Colon and Rectal Surgeons [83-86]. Generally, mutation carriers and individuals at risk of well-known HCRCs, particularly those with a family history, require intensive surveillance and prophylactic surgery if necessary, as well as family counseling and management tailored according to the particular syndrome.

Surveillance approaches for Lynch syndrome and associated spectra

Screening for CRC by colonoscopy should be performed at least biennially, beginning at age of 20 to 25 years in individuals at risk based on the Amsterdam criteria II, or affected with LS. Colectomy with ileorectal anastomosis (IRA) is the preferred treatment for patients with LS who develop CRC, while less extensive surgery may be considered in patients aged >60 to 65 years. A decision regarding whether segmental or total/near total colectomy is preferred should balance the risks of metachronous cancer, the functional consequences, and patient age and/or wishes. Parry et al. [87] reported that the risk of metachronous CRC is reduced by 31% for every 10 cm of large bowel excision. Annual colonoscopy should be considered in confirmed MMR mutation carriers, along with annual screening for endometrial and ovarian cancer in females by Pap-smear/endometrial biopsy and transvaginal ultrasound, starting at age of 30 to 35 years. Risk management for gastric, small bowel, or pancreatic surveillance in patients with LS is generally recommended within the scope of a clinical trial. Cancer risk in extracolonic viscera may be increased in carriers of pathogenic variants in *MLH1* and *MSH2*. Screening for gastric and duodenal cancer by baseline esophagogastroduodenoscopy (EGD) at age of 30 to 35 years may be considered in at-risk patients with LS or in endemic countries, with treatment of *Helicobacter pylori* when detected. Patients with LS can be advised to take aspirin daily to reduce CRC risk, regardless of surgical intervention. The benefits of regular aspirin intake take at least 3 to 5 years to become evident; however, taking aspirin for <2 years does not appear to confer any benefit in reducing risk or increasing survival. LS-associated spectra can be managed in accordance with the principles set out for LS, or based on the patient's phenotypic traits. In particular, in patients with eligible MMR-deficient CRCs between the ages of 30 and 50 years at diagnosis of CRC, MGP testing may be applicable on the basis of FCCTX, or other clinical parameters that alter the threshold for genetic testing, while a balance between clinical requirements and ethical considerations must be ensured.

Table 3. Surveillance recommendations for hereditary colorectal cancer syndrome

Syndrome	Organ	Start age (yr)	Interval (yr)	Procedure	GRADE[a]
LS and LS-spectrum[b]	Colon	20–25	1–2	Colonoscopy	High
	EM, cervix, ovary	30–35	1–2	Biopsy, USG, PS	Moderate
	Stomach, duodenum	30–35	1–3	EGD	Moderate
	Urinary tract	20–35	1	Urinalysis	Very low
	Pancreas	35–40	1–3	MRI, ERCP	Low
EALS	Colon	20–25	1–2	Colonoscopy	High
	Stomach, duodenum	30–35	1–3	EGD	Moderate
FCCTX	Colon	20–25	1–2	Colonoscopy	Moderate
FAP	Colon	12–14	1–2	Colonoscopy	High
	Stomach, duodenum	25–30	1–3	EGD	Moderate
	Thyroid	15–20	1–2	PE and USG	Low
Attenuated FAP	Colon	18–20	1–3	Colonoscopy	High
	Stomach, duodenum	25–30	1–3	EGD	Moderate
MAP	Colon	18–20	1–2	Colonoscopy	High
	Stomach, duodenum	25–30	1–3	EGD	Moderate
PPAP	Colon	25–30	1–3	Colonoscopy	Moderate
	Stomach, duodenum	25–30	1–3	EGD	Low
	EM, cervix, ovary	25–30	1–2	Biopsy, USG, PS	Low
SPS	Colon	Undetermined	1–3	Colonoscopy	Moderate
PJS	Colon	10, 18[c]	3	Colonoscopy	High
	Upper GI	10, 18[c]	3	EGD, enteroscopy	High
	Pancreas	30	1–3	MRI, ERCP	Moderate
	Breast	25	1	PE, MG, USG	Moderate
	EM, cervix, ovary	25	1–2	Biopsy, USG, PS	Low
	Testis	Birth–teenage	1	PE, USG	Low
JPS	Colon	12–15	1–3	Colonoscopy	Moderate
	Stomach, duodenum	12–15	1–3	EGD	Low
PTHS	Colon	15	1–3	Colonoscopy	High
	Stomach, duodenum	15	1–3	EGD	Moderate
	Breast	25–35	1	PE, MG, USG	Moderate
	EM, cervix, ovary	30–35	1–2	Biopsy, USG, PS	Low
	Thyroid	15–20	1	PE and USG	Low
	Kidney (renal cell)	18	1	Urinalysis, USG	Low
	Skin (melanoma)	By 18	1	PE	Low
HMPS	Colon	Undetermined	1–3	Colonoscopy	Low

LS, Lynch syndrome; EM, endometrium; USG, ultrasonography; PS, Pap smear; EGD, esophagoduodenoscopy; MRI, magnetic resonance imaging; ERCP, endoscopic retrograde cholangiopancreatography; EALS, *EPCAM*-associated LS; FCCTX, familial colorectal cancer type X; FAP, familial adenomatous polyposis; PE, physical examination; MAP, *MUTYH*-associated polyposis; PPAP, polymerase-proofreading-associated polyposis; SPS, sessile polyposis syndrome; PJS, Peutz-Jeghers syndrome; GI, gastrointestinal; MG, mammography; JPS, juvenile polyposis syndrome; PTHS, PTEN hamartoma syndrome; HMPS, hereditary mixed polyposis syndrome.
[a]GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to grade the strength of recommendations and the quality of evidence. [b]LS-spectrum includes Muir-Torre syndrome, Turcot syndrome, and constitutional mismatch repair deficiency. [c]At age of 8 years, if present every 3 years; if no polyps, repeat at age of 18 years, then every 3 years or earlier on symptom.

Surveillance approaches in patients with inherited polyposis syndrome

General colon screening for children at risk for classical FAP starts at age of 12 to 14 years with follow-up sigmoidoscopy every 1 to 2 years, while those initially diagnosed at an older age should undergo colonoscopy at first examination. Individuals with bilateral and multiple CHRPE should be referred for FAP screening, including genetic testing of *APC* variants and colonoscopy. Total proctocolectomy with ileal-pouch-anal anastomosis (IPAA) must be offered to patients with FAP, particularly those with rectal cancer, a large and significant rectal polyp burden (> 20 synchronous adenomas, high-grade dysplasia, and > 30-mm adenomas), and a profuse polyp phenotype. Pouch polyposis can generally be treated by polypectomy or chemoprevention with sulindac, which leads to considerable regression and prevention of colorectal adenomas but has uncertain value for cancer prevention. Screening for gastric and proximal small bowel tumors should be conducted by EGD, starting at age of 25 to 30 years. Gastric polyps occur in 23% to 100% of patients with FAP, mostly presenting as fundic gland polyps and rarely progressing to cancer. FAP is accompanied by duodenal adenoma in > 50% of patients and duodenal adenocarcinoma in up to 12% of patients. Duodenal surveillance by EGD should be repeated according to Spigelman staging, as follows; every 5 years for stage 0–I, every 3 years for stage II, annually for stage III, and every 0.5–1 year for stage IV [88]. For desmoid tumors, surgical resection is not generally recommended and is strictly reserved for small and well-defined tumors with clear margins. First-line treatment includes high-dose selective estrogen receptor modulators and sulindac, and leads to regression in 85% of patients with stable desmoid size, while chemotherapy or radiotherapy can be considered for patients with intractable disease.

Colorectal screening should commence at age of 18 to 20 years in patients with MAP and biallelic *MUTYH* variants; however, in monoallelic *MUTYH* pathogenic variant carriers, the risk of CRC is not sufficiently different from the population risk, hence routine colonoscopy is not recommended. Timing and type of surgery in patients with biallelic *MUTYH* mutations depend on the ability to maintain clearance of polyps, and otherwise follows the principles for FAP. The observed frequency of duodenal adenomas is much lower than that observed in FAP but greater than that in the general population, hence EGD is recommended from age of 25 to 30 years. AFAP is inherited in an autosomal dominant manner, exclusive of MAP. The emergence of adenomas and cancer is usually delayed by 10 to 20 years compared with typical FAP. In a large study of 276 patients with MAP, 17% had extracolonic lesions, with an estimated 38% lifetime risk of extracolonic malignancy, which is approximately double the risk in the general population. Surgical treatment conforms to that used for MAP and is reserved for patients without colonoscopic clearance or associated CRC. Annual thyroid screening by ultrasound may be recommended, but is not obligatory, for individuals affected with FAP, MAP, and AFAP.

As SPS does not yet have a clear genetic etiology, genetic testing is not routinely recommended. A strong association between smoking and SPS has been reported, with 60% current or past smokers [89]. Patients with serrated polyposis require colonoscopy every 1 to 3 years, with removal of all polyps of > 5 mm. The majority of index individuals exhibit a pancolonic polyp distribution (89%–96%) and presence of adenomas (78%–80%), with mean age at diagnosis of CRC 48 years. Surgery is advised when polyps cannot be controlled by endoscopy and subtotal colectomy with IRA is a reasonable option, given the risks of metachronous CRC.

Once a disease-causing mutation is identified in a patient with PJS, other family members should undergo *STK11* mutation-specific testing to determine appropriate surveillance. The risk of malignancy in PJS includes colorectal, breast, pancreatic, gynecological, small bowel, lung, and gastroesophageal cancers, in that order. Patients with PJS develop gastrointestinal polyposis as early as 10 years old, with the small intestine the most common site; hence, it is imperative to evaluate the small intestine by enteroscopy, in addition to colonoscopy, beginning in early adolescence. More recent data reveal that gastrointestinal cancers are less of a clinical problem than pancreatic and breast cancers, which are the most commonly diagnosed malignancies in PJS. Endoscopic clearance of all polyps is preferable, but not always possible; therefore, colectomy is often required to control colonic polyps and neoplastic changes, as well as the accompanying intussusception that occurs in 69% of patients. PJS polyps overexpress COX-2, suggesting that COX-2 inhibitors may be useful in reducing polyps, and everolimus (an mTOR inhibitor) is under clinical investigation.

JPS most frequently presents as hamartomatous polyps in the colon. The average age at diagnosis is 18 years but can be older, and rectal bleeding with anemia is the most common presenting symptom. Cardiovascular examination and evaluation for HHT should be considered for *SMAD4* mutation carriers. Patients with a *SMAD4* pathogenic variant should be evaluated for HHT and appropriately managed in conjunction with a specialist center. Colonoscopy, preferably with EGD and enteroscopy, is recommended beginning at age of 12 to 15 years, or earlier if symptoms occur, and should be repeated every 1 to 3 years. Total colectomy with IRA or proctocolectomy and IPAA is indicated for endoscopically unmanageable or malignant lesions.

PHTS can be diagnosed by the presence of 3 or more major criteria, 1 of which must include macrocephaly, LDD, or gastrointestinal hamartomas, otherwise 2 major and 3 minor criteria are required [63]. Patients with PHTS are prone to exhibit a severe form of juvenile polyposis, with onset in early childhood and increased risk of extraintestinal manifestations, including breast, follicular thyroid, and endometrial cancers. Individuals with multiple gastrointestinal hamartomas or ganglioneuromas should also be evaluated for CS and related conditions. The esophagus frequently develops diffuse glycogenic acanthosis, which is observed in ≥ 80% of individuals with PHTS. Surveillance of affected or at-risk pa-

tients should include colon screening every 1 to 3 years, starting from age of 15 years, with advised consideration of extracolonic malignancies, including stomach, small bowel, thyroid, breast, uterus, kidney, and skin (melanoma).

HMPS was originally described in a large Ashkenazi Jewish family with multiple colorectal polyps and cancer. Affected patients exhibit mixed juvenile-adenomatous polyps, serrated adenomas, and even inflammatory polyps and adenocarcinomas, with a mean age of polyp detection of 28 years. Annual or biennial colonoscopy is recommended and surgery is reserved for unmanageable polyp burden.

CONCLUSIONS

HCRC enlightens principal routes of colorectal carcinogenesis, although the hereditary nature of a subset of serrated, hamartomatous, and mixed polyposis remains uncertain. Unidentified HCRC requires exploration, even through a straight gate, given that established routes in LS and FAP, identified MSI and chromosome instability, respectively, as drivers of carcinogenesis. The field of gene panel testing for inherited cancer risk assessment is rapidly evolving and has significant potential to provide valuable information. NGS-based MGPs should enable definition of HCRC where the causative gene is unknown; for example, by identification of FCCTX. At present, rare genes or VUS generally exhibit low penetrance and await further validation of related familial traits, as well as biochemical and physiological implications. Such variants are otherwise overlooked in family-based studies, due to incomplete co-segregation, similar to findings from various GWAS trials even with large sample sizes reaching statistical significance. As hereditary syndromes are mainly attributable to genomic constitutions, that is, distinctive ancestral traits segregating in populations of a specific ethnicity, an integrative national HCRC registry and guideline are urgently required, and the idea that it is now "too late" for such an approach should be resisted.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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