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Familial Colon Cancer Syndromes: an Update of a Rapidly Evolving Field

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Abstract

Colorectal cancer (CRC) is a major cause of morbidity and mortality in the world. Up to 30% of CRCs have evidence of a familial component and about 5% are thought to be due to well-characterized inherited mutations. This review will focus on recent developments in the understanding of the individual hereditary colorectal cancer syndromes including Lynch Syndrome, Familial Colorectal Cancer Type X, Familial Adenomatous Polyposis, *MutYH* associated polyposis, Peutz-Jeghers Syndrome, Juvenile Polyposis Syndrome, PTEN Hamartomatous Syndrome, and Serrated Polyposis Syndrome. Advances within the area of hereditary colon cancer syndromes paint a picture of a rapidly moving, rapidly maturing and increasingly collaborative field with many opportunities for ongoing research and development.

Keywords

Hereditary Colon Cancer; Lynch Syndrome; EPCAM; Familial Colorectal Cancer Type X; Familial Adenomatous Polyposis; *MutYH*; Peutz-Jegher Syndrome; Juvenile Polyposis Syndrome; PTEN Hamartomatous Syndrome; Serrated Polyposis Syndrome

Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer death in the world with >1 million cases and 600,000 deaths per year (1). In the US, CRC is the fourth most common malignancy and the second leading cause of cancer-related death (2). Up to 30% of CRCs have evidence of a familial component and about 5% are thought to be due to well-characterized inherited mutations. In this regard, Woods et al. (3) carefully classified 750 consecutive patients with CRC from Newfoundland, a region with a high rate of familial disease. Clinically, 1% had polyposis, 5% met Amsterdam criteria for Lynch Syndrome (Table 1), 45% met Bethesda criteria (Table 2) and the other 50% were deemed “low risk.” Genetically, 0.5% had FAP, 0.4% had *MutYH* associated polyposis (MAP), 2.7% had Lynch Syndrome, and 2.3% met clinical

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criteria for Familial Colorectal Cancer type X. This review will focus on recent developments in the understanding of the individual hereditary colorectal cancer syndromes.

Lynch Syndrome

Lynch Syndrome, an eponym honoring Dr. Henry Lynch, is also called hereditary non-polyposis colorectal cancer (HNPCC). Lynch Syndrome is the most common hereditary cause of CRC, accounting for up to 2%–4% of all cases. It is an autosomal dominant syndrome caused by a germline mutation in one of the mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2). Somatic events lead to inactivation of the remaining wild-type allele, resulting in genomic instability due to an inability to correct single-base mismatches or insertion-deletion loops that occur commonly during normal DNA replication. This genomic instability is the basis of the increased cancer risk in Lynch Syndrome.

Colorectal Cancer in Lynch Syndrome

The high initial estimates of CRC risk in Lynch syndrome (50%–80%) were largely derived from selected families referred to genetics clinics and were probably overestimates due to ascertainment bias (4). Several earlier small studies that have tried to correct for ascertainment bias have found lower lifetime CRC risk in mutation carriers. Bonadona et al. recently published the largest study to date estimating the age specific incidence of Lynch-associated cancers in a population-based model using a ‘genotype-restricted likelihood’ method to correct for ascertainment bias (5). They included a total of 537 families across forty centers in France and reported a cumulative risk of CRC at age 70 of 38% in males and 31% in females with substantial variability by genotype. The cumulative CRC risk was much lower in MSH6 mutation carriers (12%) than in those with MLH1 or MSH2 mutations (41% and 48%, respectively).

Extracolonic Cancers in Lynch Syndrome

The two most common extracolonic malignancies in Lynch Syndrome are endometrial and ovarian cancer. Some of the earlier estimates of extra-colonic malignancies were likely also inflated due to ascertainment bias. Bonadona et al. (5) estimated an overall 34% cumulative risk of endometrial cancer and a 20% cumulative risk of developing ovarian cancer by age 70, but the incidence did not begin to rise for either cancer until after age 40, suggesting that decisions about prophylactic gynecologic surgery might be safely deferred until that age. Endometrial cancer risk was highest in MLH1 mutation carriers (54%) versus MSH2 and MSH6 mutation carriers (21% and 16%, respectively), whereas cumulative ovarian cancer risk was very low in MSH6 mutation carriers (1%) versus MLH1 and MSH 2 mutation carriers (20% and 24%, respectively).

Genetics of Lynch Syndrome

Traditionally, mutations of MLH1 and MSH2 were thought to account for up to 90% of Lynch syndrome cases, but MLH6 and PMS2 families are likely underrepresented in high-risk registries due to their attenuated phenotype. For example, Hampel et al. (6) performed universal molecular screening on 1066 consecutive CRCs and found twenty-three patients with genetic mutations consistent with Lynch syndrome. Of these, 13% had MSH6 and 9% had PMS2 mutations.

EPCAM (Epithelial Cell Adhesion Molecule) deletions—Germline deletions of *EPCAM* are reported (7) to cause the clinical picture of Lynch syndrome with MSH2 deficient, microsatellite unstable tumors, but without detectable MSH2 mutation. These deletions involve the 3’ end of *EPCAM* leading to transcriptional read-through into, and

subsequent epigenetic silencing of, the neighboring MSH2 gene by promoter hypermethylation. This phenomenon, however, accounts for only a minority of such patients. Rumilla et al. (8) analyzed 58 patients with CRCs that had loss of MSH2 by immunohistochemistry but no MSH2 mutations and found EPCAM mutations in only 11. One patient had hypermethylation of MSH2 without EPCAM deletions, but the rest (80%) remain unexplained.

Until recently, little was known about the how the EPCAM deletion affected overall and age-specific cancer risk or the expected tumor spectrum. Kempers et al. (9) found that among 194 EPCAM deletion carriers, the cumulative risk of CRC was 75% by age 70, a rate similar to those with a combined EPCAM-MSH2 deletion (69%), MSH2 mutation (77%), or MLH1 mutation (79%), but was higher than MSH6 mutation carriers (50%). Interestingly, women with EPCAM deletions had a cumulative risk of endometrial cancer of only 12% compared to 31%–55% in the other genetic groups and the risk of endometrial cancer was restricted to deletions that extended close to the MSH2 gene promoter. Similarly, Lynch et al. (10) found no endometrial cancers in 77 gene carriers from 2 large families with the EPCAM deletions. These data suggest that intensive endometrial cancer screening may not be necessary in these families unless the *EPCAM* deletion extends close to or into the MSH2 promoter.

Diagnosis

Lynch syndrome is grossly under-recognized (6, 11) and the traditional criteria for recognition of Lynch Syndrome are dependent on obtaining an accurate 2–3 generation family history. The Amsterdam II Criteria (Table 1) identify only about half of patients with Lynch syndrome and about half of the families who meet Amsterdam Criteria do not have Lynch syndrome (12). The Bethesda criteria (Table 2) are used to identify individuals with CRC who should have their cancers tested for evidence of MMR deficiency by either immunohistochemistry (IHC) for loss MMR proteins or for microsatellite instability (MSI) (the genetic signature of Lynch cancers) using a polymerase chain reaction-based method. Those individuals with evidence of MMR deficiency would then be offered germline MMR gene testing. In a recent population-based cohort of 2,093 consecutive CRC patients who all had MSI testing, a total of 486 met Bethesda criteria including 12 of 14 patients found to have Lynch Syndrome, equating to an 86% sensitivity and 78% specificity for the Bethesda criteria (13).

IHC Tumor Testing for Lynch Syndrome—Traditionally, IHC is done for all four mismatch repair proteins: MLH1, MSH2, MSH6, and PMS2, but since PMS2 and MSH6 are obligatory dimerization partners with MLH1 and MSH2 and they are expressed in tandem, testing for only PMS2 and MSH6 would theoretically capture all mutations in MLH1 and MSH2, in addition to less common mutations in PMS2 and MSH6. This approach was initially proposed by Shia et al. (14) who found that IHC of PMS2 and MSH6 captured all of 70 CRCs with any MMR protein loss. Similarly, Hall et al. (15) reviewed the results of traditional IHC for MMR proteins on 344 CRCs and reported that the two-antibody approach detected all 104 CRCs with any MMR protein loss. Although the two-antibody approach may be less costly than traditional four-antibody IHC, its interpretation is more complex and is not widely used.

Predictive Models—Three main quantitative predictive models have emerged to help identify potential Lynch syndrome patients. They are all accessible on the internet: MMRPredict (<http://hnpccpredict/hgu.mrc.ac.uk/>), PREMM (<http://www.dfci.org/premm/>), and MMRPro (<http://www.utsouthwestern.edu/breasthealth/cagene/>). MMRPredict is designed to predict risk of gene mutation only in CRC-affected patients, whereas PREMM

1,2,6 (16) and MMRPro predict risk in unaffected individuals as well. These models all require collection of an accurate multi-generation family history and are primarily used in genetics clinics. Khan et al. (17) compared the test characteristics of these three models in 230 consecutive patients referred for genetic testing at two US centers including 113 who were found to have a germline mutation. All three models performed similarly in predicting MMR mutation carriers with area under receiver-operator characteristic curves (AUCs) between 0.76 and 0.82. All models were superior to Amsterdam II and revised Bethesda criteria (AUCs 0.68 and 0.52, respectively). Although the predictive models offer an improved sensitivity and specificity over Amsterdam/Bethesda, they do miss cases (22 missed by at least one model 2 missed by all models).

Dinh et al. (18) used the Archimedes model to estimate the cost effectiveness of using the PREMM 1,2,6 model. They found that initiating risk assessment between ages 20–30 and gene testing all individuals whose estimated risk of a MMR mutation exceeded 5% reduced CRC and endometrial cancer incidence in mutation carriers by 12.4% and 8.8%, respectively, with an acceptable cost-effectiveness ratio (\$26,000 per quality adjusted life year gained). Although this is simulated data, it supports the value of predictive testing, particularly in families that do not have CRCs available for molecular testing.

Universal MSI or IHC Testing—Recently, universal testing of all CRCs for evidence of MMR deficiency has been recommended as a means to increase the detection rate of patients with Lynch syndrome (19). Perez-Carbonell et al. (13) argued for universal testing on the basis of its higher sensitivity (100% vs 86%) and similar specificity (96% vs 98%) to molecular testing of patients who met Bethesda criteria. Interestingly, this group also found that universal MSI or IHC testing identified many more patients with MSI-high CRCs not due to MLH1 hypermethylation (62 vs 27 in those who met Bethesda criteria) and suggested that family members of this group should be followed like Lynch mutation carriers. If this group really is at high risk, this finding would argue strongly in favor of universal testing.

Universal testing of CRCs was supported by Ladabaum et al. (20) who used a Markov model to estimate the cost-effectiveness of various strategies to identify patients with Lynch syndrome. They concluded that, optimally applied, both universal molecular testing and predictive models followed by IHC could result in significant reduction in mortality from colorectal (24%–32%), endometrial (3%–4%), and ovarian (3%–4%) cancers at similar costs. For either approach, the predicted benefits were substantially greater for affected relatives than for probands with CRC, for women than for men, and are increased with increasing acceptance of prophylactic hysterectomy and bilateral salpingo-oophorectomy. The cost-effectiveness of either approach was greatly dependent on participation rates of unaffected family members in cancer prevention strategies. Genetic testing of 3–4 family members was required to bring cost estimates down to acceptable levels (<\$50,000 per quality year life gained). It is not known whether current universal screening programs can achieve this level of genetic testing within Lynch families.

Since endometrial cancer is common in women with Lynch syndrome, one could also consider universal MSI testing of endometrial cancers. Kwon et al. (21) used a Markov model and concluded that this approach was very costly (\$648,494 per year of life gained). In contrast, testing the tumors of women with a single first degree relative with a Lynch associated tumor was estimated to be very cost effective (\$9,126 per year of life gained). This approach deserves prospective evaluation.

Direct Germline Testing—A final alternative approach would be targeted or universal germline testing. Limburg et al. (22) performed genetic testing for MLH1, MHS2, and MSH6 mutations on 195 patients with early onset (before age 50) CRC and 11 (5.6%) had a

deleterious mutation. Of these 11, 6 did not meet Amsterdam II criteria and of the 7 mutation carriers with IHC data, one was normal. The cost effectiveness of this approach is not known.

Management

Screening & Surveillance—There is general agreement that colonoscopic screening should be begin around age 20–25 or 10 years prior to the earliest age of CRC in the family and that families with MSH6 mutation can start screening around age 30 given the later onset of CRC. Engel et al. (23) presented data from a prospective cohort of Lynch patients showing that the median time between diagnosis of CRC and the preceding colonoscopy was 11.3 months supporting the generally recommended screening/surveillance interval of 1 year.

Chemoprevention—Burn et al. (24) reported the post-study follow up results of Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2), a prospective trial of 861 Lynch mutation carriers randomized to 24 months of treatment with 600 mg of aspirin or placebo. At the end of treatment, aspirin had no effect on adenoma or cancer risk but after a 56-month follow up, there was a marginally lower CRC incidence (OR 0.56, 95% CI 0.32–0.99, $p=0.05$) in the aspirin-treated group. Secondary analyses suggested decreased incidence of all Lynch-associated cancers. Additional studies with long-term follow up are needed to confirm this result and to assess overall benefits and risks of this therapy.

Surgical Management—Although a total or subtotal colectomy is generally recommended in patients with Lynch syndrome who require colonic resection, there is little controlled data comparing surgical approaches. Parry et al. (25) retrospectively reviewed the outcomes of 382 MMR mutation carriers who underwent surgery for CRC. Of the 50 patients who underwent total or subtotal colectomy, none were diagnosed with metachronous CRC compared to 74 of 332 patients (22%) who underwent a segmental colectomy. Although retrospective, this data strongly supports the recommendation for a total or subtotal colectomy in these patients.

Familial Colorectal Cancer Type X (FCCTX)

The term Familial Colorectal Cancer type X was coined by Lindor et al. in 2005 (26) to describe families that meet Amsterdam I criteria (Table 1), but have microsatellite stable CRCs. Members of families that met the FCCTX criteria were found to have an increased CRC risk, but lower than that found in comparable families with MSI-H CRCs (SIR 2.3 vs 6.1) and no increased risk of other cancers (27). FCCTX families appear to have an autosomal dominant pattern of transmission but the genetic basis for FCCTX is not established. Initial studies suggest that both the histologic spectrum and the somatic mutational profile of CRCs in these families are more heterogeneous than seen in Lynch CRCs (28–30). Undoubtedly a great deal more will be learned about FCCTX families in the coming years.

Familial Adenomatous Polyposis (FAP)

FAP is a rare syndrome that accounts for less than 1% of all CRC cases. Classic FAP is characterized by hundreds to thousands of colonic adenomas beginning in adolescence. There is a near 100% lifetime risk of CRC in untreated individuals at an average age of 39 years. Attenuated FAP is a less severe form of the condition characterized by fewer adenomatous polyps, a later age of onset of adenomas and CRCs, and a lower lifetime risk of developing CRC.

Extracolonic manifestations

A variety of extracolonic lesions occur in FAP. Duodenal cancer is the second most common cancer in FAP, carrying a 4%–12% lifetime risk. Fundic gland polyps are very common but have little cancer risk, whereas gastric adenomas have a higher risk of progression to cancer but are far less common. The cumulative lifetime risk of developing gastric cancer is low ($\approx 1\%$). Other associated malignancies that carry a low ($< 1\%$ – 2%) cumulative lifetime risk include pancreatic, thyroid, hepatoblastoma, and medulloblastoma (31).

Benign conditions associated with FAP include osteomas, congenital hypertrophy of the retinal pigment epithelium (CHRPE), epidermoid cysts, fibromas, dental abnormalities, and desmoids. Although desmoid lesions are histologically benign, they carry a great deal of morbidity and even mortality due to local compression. Nieuwenhuis et al. (32) retrospectively examined 2260 patients with FAP, 387 of whom had desmoid tumors. Multivariate analysis revealed that previous abdominal surgery, APC mutations 3' of codon 1444, and a family history of desmoids were independent predictors of desmoids.

Genetics

FAP and attenuated FAP are autosomal dominant conditions that arise from germline mutations of the Adenomatous Polyposis Coli (APC) gene located on chromosome 5q21–q22. More than 1000 unique APC variants have been identified that generally cause a truncated gene product, either because of frame shifts or premature stop codons (33). Newton et al. (34) retrospectively examined phenotype/genotype relationships in 492 patients with FAP or *MutYH* associated polyposis (MAP) and confirmed many of the previously noted genotype/phenotype associations (35). They also found that the 'severe' genotype was associated with a significantly earlier onset of CRC (53 vs 61–65 years) as well as a worse survival than the other genotypes and suggested this severe group may be better served with earlier prophylactic surgery.

Management

Screening & Surveillance—Usual recommendations are to start annual flexible sigmoidoscopy or colonoscopy screening at age 10–12 for classical or severe FAP and annual colonoscopic screening starting around age 20–25 in attenuated FAP (36).

Chemoprevention—Although chemoprevention is not a substitute for properly timed colectomy, non-steroidal anti-inflammatory drugs (NSAIDs) have been extensively studied for chemoprevention in FAP. Numerous studies have shown that sulindac induces a marked reduction in polyp count and single studies of the selective COX-2 inhibitors celecoxib and rofecoxib showed similar, albeit less dramatic, results (37). Aspirin is an attractive chemopreventive agent given its cardioprotective properties. The CAPP1 (38) study randomized 206 FAP patients to 600 mg of aspirin, resistant starch, combination aspirin/resistant starch, or placebo. After a median treatment period of 17 months there was a non-significant trend towards decreased polyp count (OR 0.77, 95% CI 0.54–1.1) and size (3.8mm vs 5.5mm, $p=0.09$) in the aspirin group. Further studies are needed to clarify this finding.

Surgical Management—Surgery remains the basis of effective management of colon cancer risk in FAP, but the management of duodenal lesions in FAP is not standardized. Most practitioners perform surveillance and remove adenomatous lesions endoscopically, reserving surgery for large lesions or cancer. Parc et al. (39) performed a retrospective review of the literature from 1965 to 2009 and reported that recurrence rates did not appear to differ between endoscopic removal and transduodenal resection of duodenal adenomas.

There is significant morbidity and mortality related to extra-colonic manifestations in FAP. Gibbons et al. (40) examined cases of FAP from a single center in the UK and divided the group into two cohorts; those identified through screening program (call-ups) and those diagnosed outside of the screening program (probands). Probands were more likely to die of CRC (42.4% vs 22.5%, $p=0.025$), whereas call-ups were more likely to die of extra-colonic manifestations (30.6% vs 13.4%, $p=0.027$). This data highlights that colon surveillance and colectomy play a critical role in the early management of FAP, however over time, extra-colonic manifestations have a significant impact on morbidity and mortality.

MutYH-Associated CRC

The *MutYH* gene is a part of the base-excision repair pathway involved in the repair of oxidative DNA damage. Bi-allelic mutations in *MutYH* were originally described to cause an autosomal recessive colonic polyposis syndrome (*MutYH*-Associated Polyposis or MAP) with a clinical picture similar to attenuated FAP. It is now clear that the clinical spectrum of *MutYH* germline mutations is broad and can include CRC without polyposis (41). Although adenomatous polyps are the most common CRC precursors in this syndrome, serrated polyps have also been reported. In one series of 17 MAP patients, 8 had hyperplastic and/or sessile serrated adenomas/polyps (42).

Colorectal Cancer risk in MutYH Mutation Carriers

Cleary et al. (43) reported CRC rates in a population based case-control study of 3811 CRC patients and 2802 matched controls; 27 cases (0.7%) and 1 control subject carried homozygous or compound heterozygous *MutYH* mutations (adjusted OR, 18.1; 95% confidence interval, 2.5–132.7). Compared to patients with non-*MutYH*-associated CRCs, those with *MutYH*-related CRCs were younger, more likely to have right sided or synchronous CRCs, and were more likely to have a personal history of adenomatous polyps. Similarly, Nielson et al. (44) reported an improved five-year survival among patients with *MutYH*-associated CRCs compared to controls with sporadic cancers.

Although the increased CRC risk in patients with biallelic *MutYH* mutations is well established, there is controversy regarding individuals with monoallelic mutations (heterozygous). A meta-analysis by Theodoratou et al. (45) confirmed the increased risk for biallelic individuals, (OR 10.8, 95% CI 5.02–23.2) and reported differential risk by mutation site. In monoallelic carriers, there was a marginally increased CRC risk (*MutYH* [OR 1.16, 95% CI 1.00–1.34]).

Extracolonic manifestations in MAP

Vogt et al. (46) described the spectrum of extracolonic features of 276 patients with MAP. They reported duodenal polyposis in 17% of cases with a cumulative lifetime risk of duodenal cancer of 4% and a 38% lifetime risk of any extra-intestinal cancer. There was a significantly increased risk of ovarian, bladder and skin cancers at median ages of 51–61 years.

Peutz-Jeghers Syndrome (PJS)

PJS is an autosomal dominant syndrome that can arise from germline mutations in the serine threonine kinase gene (STK11). STK11 has multiple functions including cell cycle regulation, mediation of apoptosis, and cellular polarity among others (47)

Colorectal Cancer in PJS

Although still debated, most experts agree that hamartomas serve as precursors to CRC as adenomatous and malignant changes have been seen in hamartomas (48). Although the cancer incidence in PJS may be over-estimated by ascertainment and publication bias, there appears to be a very high cumulative risk of any cancer (up to 85%) and of CRC (over 50%) in PJS (49). Van Lier et al. (50) described a cohort of 133 PJS patients, 37% of whom had cancer; CRC was the most common malignancy (14%).

Extracolonic manifestations

There is an exceptionally high rate of extracolonic cancers in PJS, including gastric (29%), small bowel (13%), pancreatic (36%), breast (54%), ovarian (21%), lung (15%), cervical (10%), and uterine/testicular cancer (9% each) (51).

Management and Screening

Two of the main management goals in PJS are to prevent polyp-related complications that often necessitate surgery (bowel obstruction from intussusception, bleeding) and early detection of cancer. Despite a lack of controlled studies to guide screening, Beggs et al. (51) published a detailed European consensus statement recommending colonoscopy, upper endoscopy, and video capsule endoscopy starting around age 8 in patients with PJS with repeat exams every three years if polyposis is present and at age 18 if polyposis is not present on the initial exam. After age 18, they suggest luminal exams be performed every three years. At age 50, they recommend shortening surveillance intervals to 1–2 years given the sharp rise in cancer incidence with age.

In a series of 110 patients with PJS, van Lier et al. (52) reported a remarkably high (69%) intussusception rate at a median age of 16 years from polyps with a median size of 35 mm (range 15–60 mm). They recommended capsule endoscopy or MR enterography starting at age 8–10 years with removal of any polyp greater than 1 cm. You et al. (53) described a cohort of 54 PJS patients identified between 1950 and 2002 and concluded that preventing repeated surgery and aggressive screening/surveillance for cancer could have a major impact on morbidity and mortality in PJS. To this end, they recommended the use of pediatric colonoscopes for upper endoscopy to visualize additional small bowel, removal of any polyps >1–1.5 cm, the use of MR enteroscopy rather than capsule endoscopy to avoid capsule retention, and deep enteroscopy if large polyps cannot be removed by routine endoscopy.

In terms of extraintestinal cancers, Beggs et al (51) recommended that women undergo annual breast MRI or ultrasound starting at age 25 to 30 with conversion to annual x-ray mammography starting at age 50 and 2–3 annual cervical smears beginning at age 25. They recommend that males undergo annual testicular exam from birth until age 12 with testicular ultrasound for any abnormalities detected on physical examination. They did not recommend routine screening for pancreatic, endometrial, ovarian, or lung cancer. In contrast, You et al. (53) proposed annual chest radiographs and that women have annual cervical smear, annual MR of pelvis, transvaginal ultrasound, serum CA-125, and that men have annual testicular exam and ultrasound. Although there is a substantial institutional variation in screening and surveillance guidelines for PJS, most experts encourage discussion of prophylactic surgery such as mastectomy, hysterectomy and oophorectomy.

Juvenile Polyposis Syndrome (JPS)

JPS is characterized by the occurrence of juvenile polyps throughout the intestinal tract (although most typically in the colorectum) and carries an increased risk of CRC. The World

Health Organization (WHO) diagnostic criteria for JPS require one of the following: 1) more than five juvenile polyps in the colon or rectum, 2) juvenile polyps throughout the intestinal tract or 3) any number of juvenile polyps in a patient with a family history of JPS.

Genetics

JPS is autosomal dominant, associated with a germline mutation of one of three genes (SMAD4, BMPR1A, ENG), all of which are related to transforming growth factor-beta (TGF-beta). Approximately twenty percent of JPS patients have a mutation in SMAD4 and twenty percent in BMPR1A. SMAD4 mutation has also been associated with hereditary hemorrhagic telangiectasia (HHT).

Management

Screening—The consensus is that patients with known or suspected JPS should undergo upper endoscopy, small bowel imaging with capsule endoscopy or MR enterography, and colonoscopy at around age 15 years or at the time of first symptoms. Upper and lower endoscopy is then recommended every two to three years until polyps are found, when the frequency should increase to yearly.

Chemoprevention—COX-2 expression has been demonstrated to be higher in JPS polyps and also seems to correlate with polyp size and dysplasia (54). However there are no available clinical trials to support the use of NSAIDs in chemoprevention.

Surgery—Surgery is generally considered in JPS when the polyps cannot be managed endoscopically, for severe gastrointestinal bleeding, in polyps exhibiting dysplasia, or in patients with a strong family history of CRC. Although the decision between subtotal versus total proctocolectomy typically is made on the basis of the rectal polyp burden, earlier studies have reported that up to half of patients required a completion proctectomy after initial subtotal colectomy. Thus, some experts advocate an initial total colectomy. Post-operative endoscopic surveillance is required given the high recurrence rate of polyps in remaining rectal and ileal tissue.

PTEN hamartomatous tumor syndrome (PHTS)

The PHTS includes patients that clinically have Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS). CS and BRRS can both be caused by a germline mutation of the phosphatase and tensin homolog (PTEN) gene and thus are both included in the PHTS grouping. Both are rare, with BRRS generally presenting in the pediatric population and CS more commonly presenting in adults. PHTS is autosomal dominant with relatively high penetrance (estimated 80%). The PTEN tumor suppressor gene is located on 10q23.3 and encodes a dual-specificity phosphatase that can de-phosphorylate protein and phospholipid substrates.

Cancer Risks in PHTS

The genetic identification of PHTS has only recently been possible so there are few studies of the CRC risk in this setting. Heald et al. (55) reported a cohort of 127 patients with PTEN mutations; 67 of them had undergone at least one colonoscopy and 62 had colorectal polyps. They found a wide spectrum of polyps including 18 hamartomatous, 27 hyperplastic polyps, 16 adenomas, 16 ganglioneuromatous polyps, and 11 inflammatory polyps. Nine (13%) patients had CRC (adjusted SIR 224.1, 95% CI 109.3–411.3) and all were diagnosed at an age younger than 50.

Tan et al. (56) reported results from a multi-national cohort of 3,399 patients meeting relaxed International Cowden Consortium criteria, 368 of which had a PTEN germline mutation. They observed a significantly increased incidence of CRC (SIR 10.3; 95% CI 5.6–17.4). In this cohort, CS was also associated with a marked increased risk of cancers of the breast, thyroid, endometrium, kidney and melanoma.

Diagnosis

A clinical diagnosis of CS is entertained when individuals meet criteria established by the International Cowden Consortium (57). Major and minor clinical criteria have been proposed and a scoring system has been proposed to help identify such patients (57). A relaxed diagnosis of CS can be made if pathognomonic criteria are met, a single major criteria, or at least 2 minor criteria. Clinical application of these criteria is challenging as the phenotypic spectrum of CS expands. Tan et al. (58) proposed a semi-quantitative score to assess risk of PTEN mutation that provides individualized risk estimates and may simplify clinical assessment.

Management

Screening and Surveillance—Screening recommendations, based on expert opinion, include general physical examination (with attention to skin and thyroid) yearly starting at the age of 18 years, or 5 years prior to first diagnosis in the family, including careful breast and endometrial cancer screening. Although there is not a consensus about CRC screening in CS, Heald et al. (55) has proposed initial colonoscopy at age 35, with subsequent frequency of surveillance depending whether polyps are found. Discussion regarding prophylactic mastectomy and hysterectomy is recommended on a case-by-case basis.

Serrated Polyposis Syndrome (SPS)

SPS (previously called Hyperplastic Polyposis Syndrome) is likely hereditary, but its genetic basis has not yet been defined. SPS is characterized by the presence of multiple serrated polyps of the colon (59). The World Health Organization criteria for SPS include 5 or more serrated polyps proximal to the sigmoid colon with at least two being greater than 1 cm in size; or at least 1 proximal serrated polyp in an individual with a first degree relative with SPS, or 20 or more cumulative serrated polyps of any size distributed throughout the colon (60). In a recent population based screening program, out of 50,148 participants, 28 met clinical criteria for SPS resulting in an estimated overall prevalence of SPS of about 1 in 100,000 (61).

Colorectal cancer in SPS

Estimates of CRC incidence in SPS are based on limited data. Jass (62) reviewed the literature of reported cases of SPS until 2006 and concluded that 88 of 207 (43%) had CRC. However the frequency was up to 69% in a small case series and as low as 37% in a larger case series, highlighting the likely effect of ascertainment bias. Kalady et al. (63) proposed three separate phenotypes under the umbrella of SPS including those patients with relatively few large right sided polyps, those with many left sided polyps, and those with both right and left sided polyps. Although there was no significant difference in incidence of CRC between the groups, the authors found that the right-sided phenotype had more sessile serrated polyps and tended develop cancer at a younger age.

Genetics

The genetic basis of SPS has not yet been established, with both autosomal dominant and recessive inheritance patterns proposed (64). There does appear to be an increased risk of

CRC in first-degree relatives of patients with SPS; Boparai et al. (59) for example, reported a relative risk of 5.4 (95% CI 3.7–7.8, $p < 0.001$) in first-degree relatives of individuals meeting clinical criteria for SPS.

Screening & Surveillance

No uniform screening and surveillance guidelines for SPS exist at this time. However based on the data reported above, some experts recommend colonoscopy every 1 to 2 years with the use of chromoendoscopy or narrow band imaging to improve polyp detection rates. Boparai et al. (59) suggest that earlier screening of first-degree relatives is justified, however no formal recommendations are in place at this time.

Conclusions

The evidence covered in this review paint a picture of a rapidly maturing and increasingly collaborative field. The last few years have been characterized by considerable consolidation and strengthening of the genetic understanding of the hereditary CRC syndromes. The increasingly sophisticated understanding of genetic regulation has substantially expanded the spectrum of hereditary colon cancer syndromes (the characterization of EPCAM deletions is a good example). Although single institutions with well established registries and clinics as well as collaborations among a few individual registries continue to contribute substantially to the field, some of the most important new clinical information has come as dividends from investments in multi-national, multi-institutional infrastructure (The Colon Cancer Family Registry), from international, national, and regional registries (International Cowden's Consortium, French Cancer Genetics Network, European Polyposis Registries Collaboration among others) and large collaborations among many investigators and institutions (EPICOLON I and II Cohorts and CAPP1 and 2 trials). The ability to characterize large numbers of families, including population-as well as clinic-based families, has allowed more precise estimates of gene frequencies and cancer risks, more detailed examinations of genotype/phenotype correlations, comparisons of therapeutic approaches, development of consensus guidelines, and has provided large samples for validation of predictive models.

No doubt these trends will lead to continued rapid progress in the near future. The search is on for genes and genetic mechanisms responsible for FCC type X and SPS, as well as for families that appear to have Lynch or one of the polyposis syndromes, but have no identifiable mutations. It will be particularly interesting to see if the movement toward universal molecular testing of CRCs for MSI gains momentum. If it does, it would offer a unique opportunity to define the full spectrum of the most common hereditary colon cancer syndrome and challenge our clinical systems to focus on family communication and decision-making as well as public health approaches. These would seem to be fertile areas of further study for sociologists and behavioral scientists as well as clinicians, geneticists, and counselors. It is indeed an exciting time for our field.

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Table 1**Amsterdam II Criteria**

At least three relatives with a Lynch associated cancer (CRC, endometrial, small bowel, ureter, renal pelvis)
Two or more successive generations affected
One or more relatives diagnosed before the age of 50
One should be first degree relative of the other two
Familial Adenomatous Polyposis should be excluded
Tumors should be verified by pathologic examination

Adapted from Vasen HF, Watson P, Mecklin JP, et al. "New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC." *Gastroenterology* 1999; 116:1453-6.

Note: Amsterdam I criteria are identical to Amsterdam II criteria except that they are only in reference to CRC (not all Lynch associated cancers).

Table 2

Revised Bethesda Guidelines

CRC diagnosed at age 50 or younger
Presence of synchronous or metachronous Lynch associated cancer, regardless of age
CRC with Lynch-like histology (tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern) in patient younger than 60
CRC in a patient with at least 1 first degree relative with Lynch-associated cancer diagnosed at age 50 or younger
CRC in a patient with two or more first or second degree relatives with a Lynch-associated tumor, regardless of age

Tumors meeting one or more of these criteria should be tested for Microsatellite Instability. Adapted from Umar A, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch Syndrome) and microsatellite instability. J Natl Cancer Inst. 2004 Feb 18;96(4): 261-8.