

Hereditary Colorectal Cancer: An Updated Review

Part 1: Hereditary Polyposis Syndromes

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Abstract: Hereditary colorectal cancer (CRC) is a major public health problem by virtue of its relatively high frequency in the general population. Approximately 15–20% of all CRCs are familial, while 5–10% are hereditary. Hereditary CRCs include the Lynch syndrome—the most common hereditary CRC-prone syndrome, which accounts for about 2–7% of the total CRC burden and is caused by a mutation in 1 of the mismatch repair genes (*MSH2*, *MLH1*, *MSH6*, *PMS2*)—and familial adenomatous polyposis, which is caused by germline mutations in the adenomatous polyposis coli gene and accounts for approximately 1%. Recent research has elucidated the molecular-genetic bases for other hereditary polyposis syndromes, which account for a relatively small percentage of hereditary CRCs. This review focuses on the clinical, pathologic, molecular-genetic, surveillance, and management aspects of these various forms of hereditary CRC, based upon our current understanding of these and other hereditary cancer-predisposing syndromes.

During the past decade there has been a sea change with respect to insights into the hereditary etiology of an increasing number of gastrointestinal (GI) cancers; this change has been heralded by prodigious advances in molecular genetics, enabling greater precision in hereditary cancer syndrome identification. These advances have led to a greater sense of certainty about patients' hereditary predisposition to cancer, limited only by the penetrance of the particular deleterious mutation.^{1,2} In certain diseases, such as familial adenomatous polyposis (FAP), the penetrance for colonic adenomas and colorectal cancer (CRC) in the adenomatous polyposis coli (*APC*) mutation approaches 100% over the patient's lifetime. This likelihood contrasts with the 70–85% penetrance for CRC in hereditary nonpolyposis colorectal cancer (HNPCC; the Lynch syndrome), due to a germline mutation in 1 of the DNA mismatch repair (MMR) genes, most frequently *MSH2* or *MLH1*, and the extremely low penetrance, perhaps in the range of only 10–15%, for CRC in Ashkenazi I1307K germline mutation carriers.^{3,4}

The challenge to the clinician in this new age of molecular genetics is to understand how a hereditary cancer syndrome's natural history and molecular genetics can be effectively translated into highly targeted surveillance and management strategies. To accomplish this goal, it is necessary to compile a thorough family history. Knowledge about cancer phenotypes peculiar to hereditary cancer-prone

Keywords

Colorectal cancer, hereditary cancer, familial adenomatous polyposis, colonic polyposis, hamartomatous polyps, adenomatous polyps

Table 1. Clinical Findings Suggestive of a Hereditary CRC–Predisposing Syndrome

Endoscopic/Histologic Findings (including immunohistochemical findings)
<ul style="list-style-type: none"> • Adenomatous polyp(s) before the age of 30 • Juvenile polyp(s) with adenomatous features • >5 Juvenile hamartomatous (retention) polyps • Gastric/small intestinal adenomatous or hamartomatous polyps at any age. • Numerous gastric fundic gland polyps at any age. • HNPCC: MMR mutations (<i>MSH2</i>, <i>MLH1</i>, <i>MSH6</i>), MSI, IHC
Extraintestinal Features
<ul style="list-style-type: none"> • Multiple lipomata at a young age, lipofibroma, fibroma • Osteoma (especially skull osteomas involving the mandibular angle in FAP) • Skin <ul style="list-style-type: none"> - mucocutaneous pigmentation (Peutz-Jeghers syndrome) - freckling of the glans penis (BRRS/CS) - keratoacanthoma (Muir-Torre syndrome) - papilloma, trichilemmoma (<i>PTEN</i> hamartoma syndrome)
Pedigree Characteristics
Autosomal dominant inheritance pattern

BRRS = Bannayan-Riley-Ruvalcaba syndrome; CRC = colorectal cancer; CS = Cowden syndrome; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal carcinoma; IHC = immunohistochemistry; MMR = mismatch repair; MSI = microsatellite instability.

disorders and their variable expression within families will enable the initiation of clinical and/or research programs dealing with cancer genetics.^{1,2} It is also essential to keep in mind that cancer-causing mutations do not act in a vacuum; rather, environmental perturbations may play an extremely important role in modifying molecular genetic susceptibility to cancer. *Helicobacter pylori* and its association with gastric cancer provides an excellent example of genetic-environmental interaction.⁵⁻⁷

Hereditary disorders of the GI tract are not rare. On occasion, however, they may fail to be identified, due to an insufficiently detailed family history⁸ or limited physician knowledge of syndromal phenotypic features and their differential diagnosis; consequently, available molecular genetic knowledge, particularly those germline mutations that predispose to these disorders, may not be effectively identified and employed for diagnostic benefit.⁹ For example, in certain syndromes—such as FAP with its *APC* mutation,¹⁰ the Lynch syndrome with mutations in MMR genes (*MSH2*, *MLH1*, *MSH6*),¹¹⁻¹⁴ and hereditary diffuse gastric carcinoma (HDGC) and the germline

mutation *CDH1*^{15,16}—the presence of such a deleterious germline mutation in the patient or family will enable an extremely high level of diagnostic certainty.

But how do we go about this? A classical example would be the discovery of a patient with a phenotype of hundreds to thousands of colonic adenomas, which should immediately signify the diagnosis of FAP; few risk missing such a glaring phenotype, but the index of suspicion must be heightened to include far less obvious presentations. On the other hand it would not, of course, be cost-effective to extensively evaluate every patient with an adenoma for CRC. A compromise needs to be reached whereby certain red flags (Table 1) should alert the clinician to the possibility of a syndrome predisposing the patient to hereditary CRC.

In the absence of such a striking premonitory cancer phenotype, recognition of a pattern of early age of onset of CRC with proximal colonic predilection, and an increase in synchronous and metachronous CRC, would provide clues for considering a diagnosis of the Lynch syndrome. The index of suspicion for this diagnosis would be heightened by the presence of 1 or more extracolonic cancers that are part of the expanding tumor spectrum of the syndrome (discussed in Part 2).^{1,2} The finding of a germline mutation in an MMR gene will then be the sine qua non for the Lynch syndrome diagnosis.

Pathology findings may also provide powerful diagnostic clues to a hereditary cancer syndrome. For example, early age of onset of submucosal carcinoma of the stomach with prominent signet cell pathology and a positive family history should, particularly in the presence of the *CDH1* mutation, clinch the diagnosis of HDGC.¹⁷

In each of these hereditary cancer syndromes, diagnosis and cancer control can be clinically expedited through genetic counseling. The patient must be fully informed about the availability of DNA testing, its pros and cons with particular respect to knowledge of potential insurance or employment discrimination, and the availability of targeted surveillance and management opportunities including surgical prophylaxis, as indicated in FAP with prophylactic colectomy,¹⁸ and prophylactic gastrectomy in individuals with HDGC and the *CDH1* mutation.^{17,19}

Familial Adenomatous Polyposis Coli

History of FAP

Perhaps the first evidence in support of a hereditary GI cancer syndrome was FAP. The following historical review of FAP has been aided significantly by detailed descriptions provided by Bussey.¹⁸ It begins with observations by Menzelio²⁰ who, in 1721, reported what may have been the first example of a patient with a large number of polyps in the GI tract. It was not until many decades later, however,

that there began to emerge a more refined understanding of histology, incidence, and location of polyps and associated lesions in the colon, and their possible familial incidence. The discipline of histopathology, initiated in the early 1860s, aided in the recognition of the clinical importance of intestinal polyps. In 1881, Woodward²¹ divided polyposis into "primary" (no apparent antecedent disease), and "secondary" (when polyps followed previous inflammation and ulcers of the colon).

In 1882, Cripps²² reported polyposis coli in a brother and sister. This was likely the first indication that the disease was familial and possibly of genetic origin. Bussey¹⁸ believes that this important observation marks the point at which the history of FAP started. In 1887, Smith²³ mentioned the presence of "adenocarcinoma" of the colon when describing 3 members of a family with multiple polyps. In 1890, Bickersteth²⁴ reported a family with affected members in 2 generations (mother and son), which strengthened the issue of FAP's inheritance.

At the end of the 1800s, 3 of the 4 most prominent features of FAP had been recognized: large number of polyps that were histologically adenomatous and inherited. The fourth feature, the association with CRC, had been mentioned in 1887 by Smith.²³

St. Mark's Hospital and Cancer Registry

The first register of polyposis families, which contributed significantly to the number of patients available for clinical and pathology investigation, was initiated by Cuthbert Dukes, consultant pathologist at St. Mark's Hospital, London, England, in 1925. He pioneered family studies and the importance of the family pedigree. The FAP registry at St. Mark's Hospital was then established. As of 1990, the registry contained more than 510 families, 63 of which showed the adenomatous type of polyposis; 1,238 members of these families were found to have polyposis. Other families in the polyposis registry include 37 with Peutz-Jeghers syndrome (PJS), 64 with juvenile polyposis (JP), and 46 with miscellaneous types.

New technology employing the sigmoidoscope with self-contained illumination was introduced at the beginning of the 20th century. Barium enema was subsequently improved by the double-contrast technique.

It is noteworthy that prior to World War II, about 65% of FAP patients were diagnosed with CRC on their first examination; this number has fallen to about 5%. Soberingly, Arvanitis et al²⁵ at the Cleveland Clinic Foundation showed in 1990 that 59% of patients with FAP were dying of metastatic CRC.

By World War II, Dukes decided that puberty was the right time to commence regular annual sigmoidoscopic examination of the children of a polyposis patient. Hill et al²⁶ and Morson et al²⁷ subsequently described the natural

history of FAP (number of adenomas, age-range of onset, adenoma-carcinoma sequence).

Prophylactic Colectomy in FAP

Bussey¹⁸ noted that through the advent of safe surgical treatment, patients in the benign stage of FAP could benefit from cancer prevention by total removal of their colon and rectum. Two views emerged: one advocated total proctocolectomy and ileostomy, while the other argued that an ileostomy posed a severe handicap to the patient. It was also reasoned that the risk of rectal cancer following colectomy and ileorectal anastomosis would be minimal when rectal examinations were carried out every 6 months. It then became a policy at St. Mark's Hospital to retain the rectum. Therein, the first ileorectal anastomosis was conducted in 1948. Many surgical innovations have been adopted since, including abdominal perineal resection, mucosectomy, and ileal pouch reservoir, to protect against rectal carcinoma.

Associated Extracolonic Lesions

In 1953, Gardner and Richards²⁸ reported on a large Utah family with polyposis in which affected members also exhibited multiple osteomas of the cranium and mandible, multiple epidermoid cysts, and fibromas of the skin, which was subsequently given the eponym Gardner syndrome. Further study of the family added dental abnormalities (supranumerary teeth), desmoid tumors of the abdominal wall, and extension of osteomas to any part of the skeletal system.²⁹ Desmoids, while not strictly cancerous, cause a high rate of morbidity and mortality through their propensity to extend to and obstruct vital anatomic structures. The very surgery for control of CRC may provoke desmoid formation.³⁰ Desmoid tumors have become an extremely vexing problem in FAP.³⁰⁻³² Figure 1 is the pedigree of an FAP family that, along with CRC, manifests desmoids and extracolonic cancers.

In 1975, Utsunomiya and Nakamura³³ reported that x-rays of the mandibles of more than 90% of Japanese polyposis patients they examined showed occult osteomas, a finding that was subsequently confirmed at other centers. Lewis et al³⁴ in 1984 added congenital hypertrophy of the retinal pigment epithelium. In 1985, Bulow and colleagues³⁵ showed that about one third of FAP patients also had gastric polyps, mainly of 2 types: adenomas and fundic gland polyps. Carcinomas, in addition to CRC, include stomach, duodenum, jejunum, pancreas, bile ducts, and papillary thyroid carcinomas, hepatoblastoma, and brain tumors in so-called Turcot's syndrome.³⁶

Chromosome 5 and the APC Mutation

In 1986, Herrera and colleagues¹⁰ reported on a patient with multiple developmental abnormalities as well as

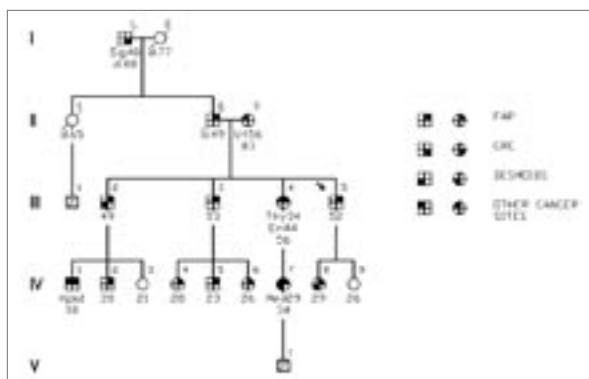


Figure 1. Pedigree of a family with familial adenomatous polyposis (FAP), showing instances of desmoid tumors.

CRC = colorectal cancer; En = Endometrium; Hpb = Hepatoblastoma; Med = Medulloblastoma; Sig = Sigmoid Colon; Thy = Thyroid; Ut = Uterus.

multiple colonic polyps. Cytogenetic studies revealed an interstitial deletion of chromosome 5. In 1987, Bodmer et al³⁷ provided evidence that the FAP gene, now known as *APC*, was on chromosome 5. Since then, there have been abundant advances in the understanding of the genotypic and phenotypic heterogeneity of this *APC* mutation.^{38,39}

Attenuated FAP

In 1988, our group described a colon cancer-prone family with few adenomas (1–50 and, rarely, up to 100).⁴⁰ Because this early report showed the adenoma morphology to be similar to the “flat adenoma” of Muto et al,⁴¹ the term “hereditary flat adenoma syndrome” was proposed.⁴² Because CRC had a later age of onset (average age, 55 years) in this syndrome compared to patients with classical FAP (average age of CRC onset, 39 years), and because of the relative paucity of colonic adenomas, the term “attenuated FAP” was later considered to be a more appropriate name for the condition. Spirio et al^{43,44} subsequently linked this family, and others with similar phenotypes, to chromosome 5q and characterized the proximal mutations at the *APC* locus.⁴³⁻⁴⁵ A mutation at the 3′ location was subsequently identified.^{38,39,46} This FAP variant may be exceedingly difficult to diagnose given its limited polyposis phenotype that, incidentally, shows a predilection to the proximal colon. Herein, a well described family history is essential for diagnosis.⁴⁷

Genotype–phenotype correlation studies in patients with FAP have shown a variety of clinical variants resulting from mutations at specific sites within the *APC* gene. Van der Luijt et al⁴⁸ studied a large family with FAP wherein a frameshift mutation was located in the alterna-

tively spliced region of exon 9; phenotypic investigation of affected family members showed a delayed clinical course for FAP; compared with classical FAP, GI symptoms occurred an average of 25 years later and death from CRC occurred an average of 20 years later. The number of colorectal adenomas differed markedly among individuals, and CRC was frequently located in the proximal colon. These findings appear to implicate the exon 9 mutation in the pedigree as being responsible for later onset of FAP, wherein the *APC* protein product indicated that the exon 9 mutation did not result in a detectable truncated *APC* protein. The authors concluded that, given the location of the mutation within an alternatively spliced exon of *APC*, it is conceivable that normal *APC* proteins are produced from the mutant allele by alternative splicing.

Friedl et al³⁹ also identified germline mutations in a large number of families with FAP, thereby enabling the study of several genotype–phenotype relationships that were interpreted in concert with the structure and functional domains of the *APC* protein. The attenuated phenotype was found to be associated with mutations at the 5′ end of the protein. In contrast, they identified a severe clinical expression in patients, with the most common mutation at codon 1309. Furthermore, they identified 2 families “with a rather mild phenotype due to a frameshift mutation at codon 1597.” The authors then proposed a model to discern the relationship between the severity of the disease and the size of the mutant *APC* protein.

I1307K, Ashkenazi Mutation

A variant of the *APC* gene was described by Laken et al⁴⁹ and features a missense mutation (T to A transversion) that causes a substitution of lysine for isoleucine at codon 1307 (I1307K). This change is believed to be silent—that is, it does not alter the function of the *APC* protein; hence it may be called both a mutation and a polymorphism. Although protein function is not affected, the transversion changes the base sequence from (A)3T(A)4 to (A)8, resulting in an unstable tract at risk for somatic mutations.

Approximately 6% of Ashkenazi Jews and a lower proportion of non-Ashkenazi Jews are carriers of the I1307K mutation/polymorphism. Ten percent of Ashkenazi Jews with CRC and 28% with familial clustering of CRC were found to have the I1307K alteration.⁴⁹ It has not been seen in non-Jews.^{3,49,50} Carriers have an approximately 2-fold risk of CRC compared with noncarriers.⁴⁹ It is believed that the T to A change results in a stretch of 8 adenosines (A’s), which are predisposed to somatic mutations due to slippage at replication.^{49,51} The investigation of the phenotype in this disorder is still in its early stages; however, because of the relatively low increased risk of CRC in I1307K mutation carriers, its public health implications appear to be limited.³

MYH Mutations

Eliason et al⁵² call attention to *MYH* mutations as representing an important component of comprehensive genetic testing for colonic polyposis and CRC. The *MYH* mutation is implicated in recessive inheritance of colorectal adenomas and carcinomas.⁵³ The majority of subjects that have been screened for *MYH* are from the United Kingdom, and 2 missense variants—Y165C and G382D—were the most prevalent mutations in the white population. Eliason et al⁵² note that the carrier frequency for these 2 mutations is approximately 2% in the British population.

MYH-associated polyposis is characterized by multiple colorectal adenomas and an autosomal recessive pattern of inheritance. In their study, Wang et al⁵⁴ did not find biallelic mutations in *MYH* in the following settings: 1) *APC*(-) patients with less than 20 adenomatous polyps, 2) patients older than 50 years of age with CRC, or 3) patients undergoing screening with 0–3 polyps. The presence of biallelic germline *MYH* mutations was found to correlate with the presence of 20 or more adenomatous polyps.

Screening of *MYH* should be considered not only in patients with multiple colonic polyps but also in patients with early-onset CRC.⁵⁴

Hereditary Breast and Colorectal Cancer Phenotype

The *CHEK2*-Breast Cancer Consortium⁵⁵ noted that *BRCA1* and *BRCA2*, while conferring a high risk of hereditary breast and ovarian cancer, nevertheless account for only a small fraction of breast cancer susceptibility. It is therefore important to identify additional genes that confer susceptibility to breast cancer, and they investigated *CHEK2*, which is known to encode a cell-cycle checkpoint kinase “that is implicated in DNA repair processes involving *BRCA1* and p53.” They found that *CHEK2**1100delC, a truncating variant “that abrogates the kinase activity, has a frequency of 1.1% in healthy individuals. However, this variant is present in 5.1% of individuals with breast cancer from 718 families that do not carry mutations in *BRCA1* or *BRCA2*,” including 13.5% of patients who are members of families with male breast cancer. Furthermore, this variant shows an approximately 2-fold increase in breast cancer risk in women and a 10-fold increase of risk in men.

This *CHEK2**1100delC mutation is highly pertinent to this review in that, in addition to carcinoma of the breast, it also predisposes to CRC. Specifically, Meijers-Heijboer et al⁵⁶ found that the *CHEK2* low-penetrance breast cancer susceptibility allele was absent in 95 families with FAP but was present in 2.6% of 234 HNPCC and HNPCC-like families, compared to a 1% population frequency ($P=.07$, nonsignificant). When non-*BRCA1/BRCA2* families were defined as hereditary breast and

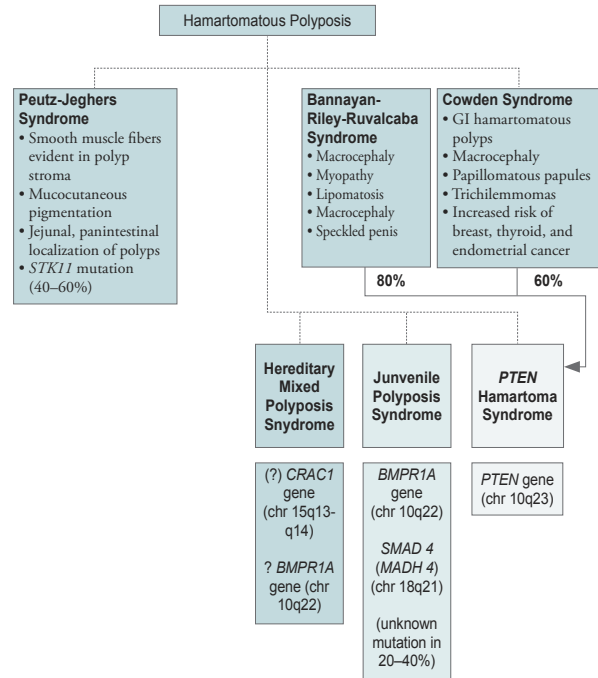


Figure 2. Hamartomatous polyposis syndromes, classification based on gene mutation analysis.

chr = chromosome; GI = gastrointestinal.

colorectal cancer (HBCC) phenotype, *CHEK2**1100delC was identified in 18.2% of 52 of these families compared with 4.0% of 380 non-HBCC families ($P<.001$).

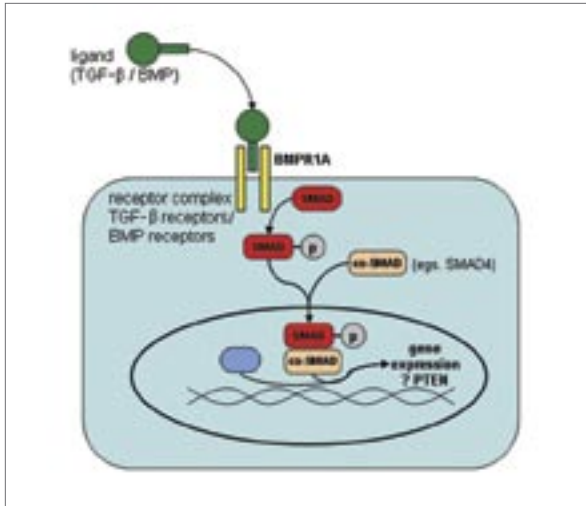
Meijers-Heijboer et al⁵⁶ concluded that this mutation provides conclusive genetic evidence for the existence of an HBCC subtype of familial breast cancer. Furthermore, this *CHEK2**1100delC mutation is not the major predisposing factor for HBCC phenotype, but instead appeared to act in synergy with one or more as-yet-unknown susceptibility genes. Finally, definition of the HBCC phenotype opens new avenues to search for this putative susceptibility gene.

Hamartomatous Polyposis Syndromes

Historically, apart from the clear phenotype and comparatively straightforward gene mutation findings in PJS (described below), our understanding of hamartomatous polyposis syndromes has undergone a transition similar to the evolution in understanding FAP (Figure 2). Seemingly separate syndromes like Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Cowden syndrome (CS) have coalesced in the crucible of a common gene mutation with phenotypic characteristics in part affected by the specific mutation in the *PTEN* gene; this in turn overlaps with the phenotypic classification for JP (Table 2). This conceptual

Table 2. Diagnostic Criteria for Juvenile Polyposis⁸⁷

- More than 5 polyps of the colon and rectum.
- Polyps throughout the gastrointestinal tract.
- Any number of polyps involving the gastrointestinal tract with a family history of juvenile polyposis.

**Figure 3.** Interplay of *BMPRIA* and *SMAD* in the transforming growth factor (TGF)- β signaling pathway.

Adapted from: Eng C. *Nat Genet.* 2001;28:105-107 and Merg A, Howe JR. *Am J Med Genet C Semin Med Genet.* 2004;129:44-55.

BMP = bone morphogenetic protein.

definition has been frustrated by both the rarity of hamartomatous polyposis syndromes in general and, in the case of JP, by the difficulty in distinguishing between common sporadic juvenile polyps and their syndromic counterparts that entail a risk of malignant transformation.

Juvenile Polyposis

Since its initial recognition as a separate, probably hereditary, polyposis syndrome (described by McColl and colleagues in 1964⁵⁷), the association of JP with CRC has been a foremost concern. Based on the hamartomatous nature of the polyps, McColl et al opined that malignant transformation would be unlikely; histopathologically, however, syndromic juvenile polyps may exhibit adenomatous foci that may predispose to malignant transformation. In the 1960s, Veale et al,⁵⁸ Smilow et al,⁵⁹ and Haggitt and Pitcock⁶⁰ noted the autosomal dominant pattern of inheritance and increased risk of CRC in families with JP, which has proven difficult to quantify but

is generally accepted to be 22% in the fourth decade of life and 68% by 60 years of age. The diagnosis of JP has also evolved to a definition based more on polyp number and distribution and family history, with the exclusion of other rare hamartomatous polyposis syndromes (Table 2). The current definition is unclear as to whether it is the one-time or cumulative number of polyps following either sigmoidoscopy or complete colonoscopy that needs to be factored in the diagnosis of JP. This and other considerations make a gene mutation-based definition of JP attractive but as yet unattainable.

Our molecular-genetic understanding of JP has seen several recent strides; insight into the genetic associations of JP started with the report by Jacoby et al⁶¹ of a patient with JP and chromosome 10q22–24 deletion. Shortly after its description as a susceptibility gene for CS by Nelen and coworkers in 1996,⁶² *PTEN* gene (chromosome 10q23) mutations were described in patients diagnosed with JP by Olschwang et al⁶³ and Lynch et al.⁶⁴ These observations were, however, questioned by Eng and Peacocke,⁶⁵ who suggested that the *PTEN* mutation-positive patients were indeed patients with CS or BRRS. The next breakthrough in JP genetics came from Howe et al, first with their description of *SMAD4* gene mutations on chromosome 18 in 21–40% of JP patients,⁶⁶ followed by their report of *BMPRIA* gene mutations on chromosome 10 in as many as 37% of patients with JP.⁶⁷ Like several other groups, they could not detect *PTEN* gene mutations in their patients with JP.

A model of *SMAD4* gene and *BMPRIA* gene products in the signal transduction pathway transforming growth factor (TGF)- β pathway now channels together the 2 abnormalities noted in JP patients in a common pathway involved in transcriptional regulation and, therefore, cytologic growth and replication (Figure 3).

Screening and surveillance of individuals with JP includes colonoscopy and polypectomy every 1–3 years from age 15 onward and earlier if they are symptomatic; if polyps are present, surveillance should be annual until the patient is polyp-free or has a colectomy. Upper GI small-bowel contrast studies are indicated every 3–5 years from the time of diagnosis.

The emerging concepts in JP include the recognition of new gene mutations but also the association of recognized mutations with clinical phenotype; thus *SMAD4* carriers are recognized to be more likely to harbor gastric polyps than either *BMPRIA* mutation carriers or individuals in whom no mutation is yet recognized. In addition, individuals without detectable mutation tend to present earlier but are less likely to have a family history of either CRC or polyposis, suggesting some degree of overlap between this subgroup and individuals with multiple but sporadic juvenile polyps.⁶⁸

PTEN Hamartoma Syndrome

Considerable overlap exists between JP and both CS and BRRS. All include hamartomatous polyps in the GI tract. CS and BRRS share several phenotypic characteristics, including macrocephaly, high arched palate, pectus excavatum, hypotonia, mild to severe mental retardation, and characteristic skin lesions. JP and CS may be associated with *BMPRIA* gene mutations, whereas the majority of cases of CS and BRRS are associated with mutations in the *PTEN* gene on chromosome 10q23. Marsh and colleagues⁶⁹ suggested that BRRS and CS are different presentations of a single syndrome and further suggested genotype–phenotype correlations between the clinical features of BRRS, namely lipomatosis, cancer or breast fibroadenoma, and *PTEN* mutation. They therefore proposed the encompassing term *PTEN* hamartoma syndrome to include both entities. Waite and Eng⁷⁰ have discussed the differences between JP and *PTEN* hamartoma syndrome, emphasizing the different cancer predisposition of the latter, which necessitates a broader approach to surveillance, including breast examination and mammography in both males and females from an early age, thyroid examination and neck ultrasound, and endoscopy.⁷¹ Although broadly supported, these general recommendations have not been proven to affect the course of the disease or even result in early detection of neoplastic complications.

Hereditary Mixed Polyposis Syndrome

Thomas and colleagues reported on an autosomally dominant inherited trait in an Ashkenazi Jewish family characterized by atypical juvenile polyps, inflammatory polyps, hyperplastic polyps, colonic adenomas, serrated adenomas, and tubular adenomas. Affected individuals tended to have fewer than 15 polyps on colonoscopy, and no extraintestinal manifestations were evident.^{72,73} The initial linkage analysis pointed toward a locus on chromosome 6q⁷²; however, subsequent analysis including new family members followed through the St. Mark's Registry identified the putative gene locus as 15q13–14 (*CRAC1*).⁷³

Peutz-Jeghers Syndrome

Following the initial description of the association of intestinal polyposis and pigmented abnormalities in the skin and mucous membranes by Peutz in 1921,⁷⁴ PJS was defined by the presence of hamartomatous polyps in the jejunum, although they could also be in other parts of the GI tract—notably the colorectum—raising the question of an association with CRC. Indeed, although an increased risk of GI cancer was suspected by Williams and Knudsen as early as 1965, the impact of both GI and extraintestinal malignancy in this syndrome could be proven only on close scrutiny of pedigrees with PJS

Table 3. Screening and Surveillance Recommendations in Pediatric Patients With Peutz-Jeghers Syndrome

EGD/EGD + enteroscopy; small-bowel contrast study	From age 5–10: every 2–3 yr
Colonoscopy	From age 25 or earlier if symptomatic: every 2–3 yr
Pelvic ultrasound (females), testicular ultrasound	Annually in females, annually in males with gynecomastia

EGD = esophagogastroduodenoscopy.

followed over a period of time. Thus, Giardiello's group, describing their experience at Johns Hopkins through 1985,⁷⁵ and Spigelman's group, describing patients followed through the St. Mark's Registry,⁷⁶ outlined a 48% incidence of cancer and a relative risk of 13 and 9 for GI cancers and all cancers, respectively. This has subsequently been reflected in the surveillance recommendations for PJS that have evolved at various institutions (Table 3) and which emphasize both GI and genitourinary tumor surveillance. Gastrointestinal tract surveillance in PJS is more challenging than in other polyposis syndromes; although small-bowel series are widely accessible, their sensitivity is probably inferior to enteroscopy and capsule endoscopy, which are less widely available.⁷⁷ When present, a strategy geared toward removal of all detectable polyps through intraoperative enteroscopy and endoscopic polypectomy appears to decrease the overall need for surgery in these patients.⁷⁸ Hinds et al⁷⁹ recently reported on the practice at the St. Mark's Registry wherein all polyps, including asymptomatic polyps, greater than 1 cm in diameter in children are removed.

Recently, linkage analysis by Jenne et al identified the gene mutation responsible for PJS as a serine threonine kinase (*STK11/LTKB1*) on chromosome 19p13.⁸⁰ The protein product of *STK11* is involved in a variety of intracellular processes, including cell cycle arrest, cell polarity, and chromatin remodeling. When detectable, the mutation in unrelated affected families and individuals with de novo PJS involve disruption of the kinase activity through either truncation or missense mutation. However, 40–60% of individuals with PJS do not appear to harbor a mutation in *STK11*; it appears that individuals with a truncating mutation of *STK11* or no detectable mutation have a more severe Peutz-Jeghers phenotype than those with a missense mutation.⁸¹

Other Syndromes Associated with Hamartomatous GI Polyposis

Gastrointestinal involvement with ganglioneuromatosis is observed in up to 40% of individuals with mucosal neu-

Table 4. Colorectal Polyp Pathology in Familial Syndromes Predisposing to Multiple Polyps or CRC

<p>Familial Adenomatous Polyposis (FAP)/Gardner Syndrome⁸⁸</p> <p>Polyp pathology: Mainly tubular adenomas Polyp numbers: 100 to >5,000 Age at presentation: Second decade CRC association: Very high; average age 39, 90% by age 50</p>	<p>Cowden Syndrome⁹⁵</p> <p>Polyp pathology: Small hamartomas with fibrous stroma (sometimes including ganglioneuromatous elements) separating mildly distorted glands Polyp numbers: Approximately 5–100 Age at presentation: Third decade CRC association: Little, if any</p>
<p>Attenuated FAP⁴⁴</p> <p>Polyp pathology: Tubular adenomas, flat adenomas, proximal colon Polyp numbers: 10–100 Age at presentation: Fourth decade CRC association: High; average age 50–55</p>	<p>Bannayan-Riley-Ruvalcaba Syndrome⁹⁶</p> <p>Polyp pathology: Hamartomas resembling juvenile polyps and ganglioneuromas Polyp numbers: Variable Age at presentation: First decade CRC association: Little, if any</p>
<p>MYH Polyposis⁸⁹</p> <p>Polyp pathology: Adenomas, few hyperplastic polyps Polyp numbers: Median 40 (range: 5–1,000) Age at presentation: 50 yr CRC association: High; after age 45, mainly left-sided</p>	<p>Bloom Syndrome⁹⁷</p> <p>Polyp pathology: Adenomas, mainly proximal Polyp numbers: 45 in one case report Age at presentation: Fourth decade CRC association: Probably significantly increased</p>
<p>Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome⁹⁰⁻⁹²</p> <p>Polyp pathology: Adenomas with predilection for proximal colon, often villous and/or with high-grade dysplasia, often with loss of expression of DNA mismatch repair protein Polyp numbers: 0–10 Age at presentation: 20–50 yr CRC association: High likelihood that individual adenoma will progress and within short time frame (aggressive adenoma)</p>	<p>Hereditary Mixed Polyposis Syndrome⁹⁸</p> <p>Polyp pathology: Tubular adenomas, hyperplastic polyps, juvenile polyps, serrated adenomas, and mixed polyps Polyp numbers: 1–15 Age at presentation: 40 yr (range: 23–65 yr) CRC association: High</p>
<p>Juvenile Polyposis^{87,93}</p> <p>Polyp pathology: Juvenile polyps, atypical (multilobated and/or foci of dysplasia) juvenile polyps, adenomas Polyp numbers: 5–200 Age at presentation: Severe forms in infancy, less severe forms in second decade or later CRC association: 10–60% lifetime risk</p>	<p>Serrated Pathway Syndrome⁹⁹</p> <p>Polyp pathology: Hyperplastic polyps, serrated adenomas, mixed polyps, adenomas Polyp numbers: 5–50, with some patients meeting criteria for hyperplastic polyposis Age at presentation: 58 yr (range: 41–79 yr) CRC association: Moderate</p>
<p>Peutz-Jeghers Syndrome⁹⁴</p> <p>Polyp pathology: Hamartomas with arborizing smooth muscle separating mucosal lobules, rare foci of dysplasia provide evidence for malignant potential Polyp numbers: Small intestine is site of predilection, but polyps are found in colon in majority of patients Age at presentation: Third decade CRC association: Increased but low risk</p>	

CRC = colorectal cancer.

roma syndrome (MEN 2B, Wagenmann-Froboese syndrome),⁸² which is usually associated with mutations in the *ret* proto-oncogene on chromosome 10q11. Affected individuals may be mistaken for having Marfan syndrome, and they may present early with failure to thrive, hypotonia, and developmental delay. Perhaps half of these individuals do not have a family history of the syndrome; the risk of CRC remains speculative but patients are at a markedly increased risk of medullary thyroid carcinoma and pheochromocytoma.⁸³

Gorlin and Goltz⁸⁴ described multiple basal cell tumors, rib abnormalities, and jaw cysts as a distinct syndrome in 1960; this was subsequently broadened to include palmar skin pits, ovarian calcification or fibroma, cerebral gigantism, astrocytoma, medulloblastoma, cardiac fibroma, cleft palate, and ophthalmic abnormalities. Schwartz described multiple gastric hamartomatous polyps in patients with basal cell nevus syndrome⁸⁵ (Gorlin syndrome); although it is rare, Desai and coworkers described 2 patients with the syndrome in a series of 22 patients followed for JP through St. Mark's Registry.⁸⁶ The CRC association also remains speculative in this disorder.

It is clear that colonic polyps of all varieties may provide powerful beacons to the diagnosis of hereditary cancer-prone syndromes, as seen in Table 4.

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