

# Genetics and Inherited Syndromes of Colorectal Cancer

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**Abstract:** The genetic pathogenesis of colorectal cancer is now well understood: it is a multistep process that causes a normal cell to acquire features of adenomatous change and, finally, malignancy as mutations in specific genes accumulate. Stool tests for identifying the presence of these mutations are now available as a colorectal cancer screening tool but are not widely used. Inheritance is an important factor in up to one third of colorectal cancer cases. The genetic etiology for most of these cases is not yet known, and screening is based upon the severity of familial risk. A small fraction of colorectal cancer cases belong to one of the single gene inherited syndromes with high colorectal cancer risks. The most important of these syndromes are familial adenomatous polyposis, which arises from inherited mutations of the *adenomatosis polyposis coli* gene, and hereditary nonpolyposis colorectal cancer (or Lynch syndrome), which occurs when one of the mismatch repair genes is inherited with a mutation. There are also several hamartomatous polyposis syndromes associated with colorectal and other cancers. The genetic etiology of these syndromes is now also known. Genetic testing is available for the diagnosis of each of the inherited syndromes, and surveillance and management guidelines have been given.

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality in the United States, with 149,000 new cases and 77,000 deaths annually. The lifetime risk for CRC is approximately 6% in both men and women.<sup>1</sup> The causes of CRC include environmental and inherited factors and a combination of each. Approximately one third of CRCs arise from inheritable factors, and up to 3% belong to one of the well-characterized inherited syndromes. The genetics of these syndromes are now well understood and have helped to define the pathogenesis of all CRCs. This understanding has, in turn, provided stool tests for the diagnosis of CRC and genetic tests for diagnosis of the syndromes and is expected to lead to better preventive and therapeutic approaches to this malignancy.

## Keywords

Colon cancer, familial colon cancer, FAP, HNPCC, Lynch syndrome, juvenile polyposis syndrome, Peutz-Jeghers syndrome, Cowden syndrome

**Table 1.** Colorectal Cancer Screening Recommendations for Persons With Nonsyndromic Familial Risk

Familial risk category	Risk compared to average population risk	Recommendation
Second- or third-degree relative with colorectal cancer	1.5-fold increased	Same as average risk
First-degree relative with colorectal cancer or advanced adenomatous polyps diagnosed $\geq 60$ years of age	2- to 3-fold increased	Same as average risk, but begin at 40 years of age
Two or more first-degree relatives with colorectal cancer or a single first-degree relative with colorectal cancer or advanced adenomatous polyps diagnosed at <60 years of age	3- to 4-fold increased	Colonoscopy every 5 years,* beginning at 40 years of age or 10 years younger than the earliest diagnosis in the family, whichever comes earlier

\*An interval of 3 years may be appropriate in some families with very strong family history.

### Molecular Pathogenesis of Colorectal Cancer and DNA Stool Screening

All CRCs arise from abnormal DNA expression, from either somatic (acquired) or inherited genetic abnormalities. Familial adenomatous polyposis (FAP) is caused by inherited mutations of the *adenomatous polyposis coli* (APC) gene, whereas hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome, derives from inherited mutations of one of four mismatch repair (MMR) genes. Interestingly, up to 85% of all CRCs begin with somatic mutations of *APC*, whereas 15% of CRCs exhibit MMR gene mutations early in their pathogenesis. Mutations in genes, including *K-ras* and *p53*, often occur after *APC* is mutationally inactivated, and frequent chromosomal deletions are also observed. These events following *APC* mutation characterize the chromosomal instability pathway of CRC pathogenesis.<sup>2</sup> CRCs associated with MMR gene mutations exhibit microsatellite instability (MSI), meaning that short segments of DNA base repeats are frequently mutated. Different genes such as *TGF $\beta$ R2* are usually mutated in this type of CRC pathogenesis, which is called the MSI pathway. Other molecular genetic pathways to CRC have been suggested but are less well defined.<sup>3,4</sup>

Understanding of the genetic pathogenesis of CRC is expected to suggest better strategies for prevention and treatment and has already led to DNA stool CRC screening tests. The sensitivity and specificity of these tests are better than those of fecal occult blood tests, and stool tests are now included as a CRC screening option.<sup>5</sup> Nonetheless, the cost of DNA stool testing has, to date, prevented widespread application.

### Common Familial Colorectal Cancer

A family history of CRC is a significant risk factor for the subsequent development of this malignancy.<sup>6-10</sup> The risk for CRC is increased 2- to 3-fold if a first-degree relative is affected.<sup>7</sup> Furthermore, the risk is approximately the same at 40 years of age as it is in the general population at 50 years of age.<sup>11</sup> The CRC risk is 3-fold or higher if the first-degree relative is diagnosed under 50 years of age or if two or more first-degree relatives are affected. The risk of CRC is also increased if a relative has colonic adenomatous polyps and even higher if the adenomas are advanced.<sup>12-15</sup>

A large twin study demonstrated that approximately one third of CRCs were familial and likely, on the basis of inheritance.<sup>8</sup> Shared environmental factors accounted for less than 10% of familial cases. Etiologic heterogeneity involving gene-gene and gene-environmental interactions appears likely, and a number of candidate lower-penetrant susceptibility genes have now been identified.<sup>8,16-24</sup>

Screening approaches for persons with familial risk of CRC have been given by a number of health policy organizations and are outlined in Table 1.<sup>5,6,25-28</sup> Recommendations for CRC screening in the setting of familial CRC are primarily empiric, based upon known risk and the known effectiveness of screening modalities.

### Inherited Syndromes of Colorectal Cancer

Inherited syndromes of CRC account for 1–3% of CRC cases and include FAP, *MYH* gene-associated polyposis (MAP), HNPCC, and the hamartoma syndromes of Peutz-Jeghers syndrome (PJS), juvenile polyposis syn-



**Figure 1.** Colonic adenomatous polyposis in a patient with familial adenomatous polyposis.

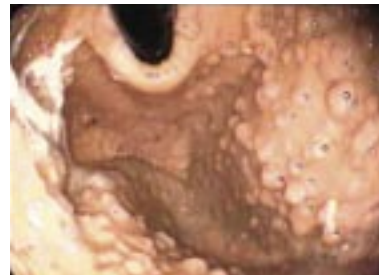
drome (JPS), and *PTEN* gene-associated polyposis. Surveillance and genetic testing guidelines have been suggested for each of these conditions. Extracolonic cancers and benign growths are present in many of these syndromes and must also be managed appropriately.

### **Familial Adenomatous Polyposis**

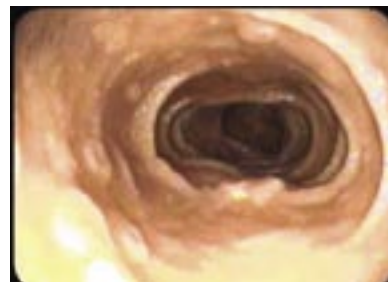
**General Characteristics.** FAP is autosomal dominantly inherited and characterized by hundreds to thousands of colonic adenomatous polyps (Figure 1) and a CRC risk approaching 100%. It occurs in approximately 1 in 10,000 persons.

FAP arises from inherited mutations in the *APC* gene.<sup>29-31</sup> Approximately one third of newly diagnosed cases arise from de novo mutations.<sup>32</sup> Mosaicism in a parent may also cause de novo cases.<sup>33</sup> The location of the mutation in the *APC* gene relates to polyp number when the condition is full blown. Mutations in the mid-portion of the gene cause dense polyposis and younger expression, whereas fewer polyps are found with mutations proximal and distal to this area.<sup>34-37</sup> Mutations in the extreme proximal or distal portion of the gene (or in certain areas of exon 9) are associated with attenuated FAP.<sup>38,39</sup> Certain extraintestinal growths also relate to mutation location, including retinal lesions, thyroid cancer, and desmoid tumors.<sup>35</sup>

Symptoms are nonspecific and often associated with CRC. Asymptomatic adenomatous polyps begin to occur in the teen years. A clinical diagnosis is made by 100 or more colonic adenomatous polyps or multiple adenomas in a first-degree relative of a known affected person. Most patients with FAP are diagnosed while asymptomatic.<sup>13,29-31</sup> Untreated FAP will inevitably lead to CRC, with an average age of occurrence of 39 years. Seven percent of affected persons will have cancer by 21 years of age and 93% by 50 years of age.



**Figure 2.** Fundic gland polyposis in the stomach of a patient with familial adenomatous polyposis.



**Figure 3.** Duodenal polyposis in a patient with familial adenomatous polyposis.

Most FAP patients exhibit gastric fundic gland polyps (Figure 2).<sup>40</sup> Dysplasia is frequently observed on the surface of these polyps, but the lifetime risk of gastric cancer is less than 1%.<sup>41</sup> Duodenal polyps occur in over 90% of FAP patients and are adenomas. They frequently occur at or around the duodenal papilla (Figure 3).<sup>42-45</sup> The lifetime risk of periampullary and duodenal cancer is 3–5%, at an average age of 45–52 years (range, 17–81 years). Cancer in this location is one of the leading causes of death in FAP patients who have had a prophylactic colectomy. Small bowel adenomas distal to the duodenum are common, but small bowel cancer is very uncommon.<sup>46</sup> Cancer may also occasionally occur in the gallbladder, biliary tree, and pancreas.

Benign extraintestinal manifestations of FAP include osteomas (20% of patients)<sup>47,48</sup> and dental abnormalities, including supernumerary teeth, unerupted teeth, dentigerous cysts, and odontomas (17%).<sup>31</sup> Cutaneous lesions in this syndrome include epidermoid cysts, sebaceous cysts, lipomas, fibromas, and pilomatricomas. Epidermoid cysts often occur before puberty and may precede the development of polyposis. Nasal angiofibromas have also been reported in FAP patients.<sup>49</sup>

Desmoid tumors are benign fibrous growths with an incidence of 3.6–20% in FAP and an average age of occurrence of 28–31 years.<sup>50</sup> Risk factors for desmoids include *APC* mutation location, family history of desmoids, female gender, and osteomas.<sup>36</sup> Although benign, desmoid tumors are a significant cause of morbidity and mortality as they impact and compress intra-abdominal structures, particularly vascular structures.<sup>51,52</sup> Mortality is 10–50%, with a 10-year survival rate of 63%. Abdominal, particularly mesenteric and abdominal wall desmoids, are the most common, though desmoids may occur in any connective tissue structure. Surgery can stimulate the development and growth of these lesions.

Congenital hypertrophy of the retinal pigment epithelium are benign pigmented lesions of the retina.<sup>53</sup> Adrenal adenomas are more common in FAP than in the general population, with an incidence of 7–13%.<sup>54</sup> Functioning adenomas and adenocarcinoma have both been reported, though the association with FAP is unclear. Nongut malignancies associated with FAP include hepatoblastoma (1.5% incidence and almost always under 5 years of age); papillary thyroid cancer (2% incidence, with an average age of diagnosis of 28 years<sup>55</sup>); and pancreatic cancer (2% incidence). A recent investigation of thyroid cancer suggested a risk of 12% and recommended periodic ultrasound in addition to palpation.<sup>55</sup>

**Variants of Familial Adenomatous Polyposis Arising From *APC* Mutations.** Attenuated FAP exhibits a lower colonic polyp burden and later age of polyp and cancer occurrence.<sup>38,39,56,57</sup> There is an average of 30 colonic polyps, with wide variation. Some affected persons have so few polyps that they are difficult to distinguish from sporadic polyp cases, whereas others have a phenotype similar to that of full-blown FAP. Polyps have a more proximal distribution in the colon. The average age of CRC diagnosis is 54 years, with a lifetime risk of 70–80%. Unlike colonic polyps, upper gastrointestinal polyps are often not attenuated.

Gardner syndrome exhibits a gastrointestinal phenotype identical to FAP, but affected persons often have clinically obvious extracolonic growths, particularly osteomas, fibromas, and epidermoid cysts. Turcot syndrome includes FAP patients who have central nervous system (CNS) tumors, particularly medulloblastoma type.<sup>31</sup> The risk of a CNS tumor in FAP is 1.5%.

**Management.** Genetic testing for hereditary syndromes allows a precise diagnosis and identification of affected family members. Laboratories offering genetic testing can be found at the GeneTests website (<http://genetests.org>).

Genetic testing for FAP should be performed to confirm the diagnosis in an individual clinically suspected of having the disease and to make a diagnosis in at-risk family members. An affected person should be tested first to identify the mutation.<sup>58</sup> The disease-causing mutation can be found in approximately 80% of clinically diagnosed patients. Other family members can then be tested for the presence or absence of that mutation with near 100% accuracy.

Appropriate management of FAP patients includes surveillance for colon polyps and CRC as well as for other potential malignancies (Tables 2 and 3) and timely referral for prophylactic colectomy.<sup>29,31,59</sup> Upper gastrointestinal endoscopy is also indicated as shown in Table 3.<sup>43-45,60</sup> Except for the colon, the screening recommendations are empirical, based upon risk, and should, therefore, be discussed with patients in that context before implementation.

Colectomy is the definitive treatment for patients with FAP and should be considered once polyps emerge, though it can often be delayed for several years with continued surveillance.<sup>31,61-63</sup> Surgical options include subtotal colectomy with ileorectal anastomosis (for attenuated FAP or low rectal polyp burden); total colectomy with mucosal proctectomy and ileal pouch anal anastomosis, where the anastomosis is at the dentate line; and restorative proctocolectomy, where 1 or 2 cm of rectal mucosa is left in place to preserve solid-liquid-gas perception. The latter procedure is usually performed when total proctocolectomy is required, unless polyps involve the rectal mucosa at the dentate line.

Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors have some utility in the management of FAP,<sup>64</sup> particularly to control polyps in a remaining rectum. The use of these drugs for primary prevention or to delay surgery is not indicated.

Duodenal adenomas may also require management and definitive therapy.<sup>43-45,60</sup> Removal should be considered when polyps are large ( $\geq 2$  cm) or exhibit advanced histology (villous architecture or high-grade dysplasia). Options for treatment include endoscopic ablation or polypectomy, surgical polypectomy, duodenectomy, or the Whipple procedure. Endoscopic papillectomy for ampullary adenomas should be performed when obstructive symptoms occur or for advanced histology.

Desmoid tumors are a particular therapeutic challenge in FAP.<sup>50,52,65-68</sup> Surgery is usually used for extra-abdominal and abdominal wall tumors. Less than half will recur with this approach. For intra-abdominal desmoid tumors, however, surgery is often difficult or impossible. Medical therapies include sulindac and tamoxifen (an antiestrogen), chemotherapy, radiation therapy, or a combination of these.

**Table 2.** Colorectal Cancer Risk and Screening Recommendations for Persons With Hereditary Syndromes

Hereditary syndrome	Lifetime colorectal cancer risk	Recommendation
Familial adenomatous polyposis (FAP)*	100% (69% in attenuated FAP)	Colonoscopy every 1–2 years, beginning at 10–12 years of age. <sup>†</sup> If there is remaining rectum or ileal pouch, screen every 6 months–2 years, depending upon polyp burden. For attenuated FAP, colonoscopy can begin in the late teens and be performed every 2–3 years, depending upon polyp burden.
Hereditary nonpolyposis colorectal cancer, <sup>‡</sup> or Lynch syndrome	80%	Colonoscopy every 1–2 years, beginning at 20–25 years of age. After surgery, sigmoidoscopy every 1–2 years if subtotal colectomy was performed, or colonoscopy if segmental resection was performed.
Peutz-Jeghers syndrome	40%	Colonoscopy beginning with symptoms or in late teens if no symptoms occur. Interval determined by number of polyps, but at least every 3 years.
Juvenile polyposis syndrome	60%	Colonoscopy beginning with symptoms or in late teens if no symptoms occur. Interval determined by number of polyps, but at least every 3 years.
Cowden syndrome	Increased	Uncertain, but interval colonoscopy every 3 years after polyps emerge would appear to be appropriate in view of newer reports of adenoma and cancer risk.

\*Includes all *adenomatous polyposis coli* gene–related syndromes.

<sup>†</sup>Sigmoidoscopy may be used in the teen years until polyps are identified. In attenuated FAP, colonoscopy should always be used because of the preponderance of proximal colonic adenomas, and screening should begin in the late teens or early twenties.

<sup>‡</sup>Includes Muir-Torre syndrome.

**MYH Gene–associated Polyposis**

MAP is phenotypically similar to attenuated FAP, with most patients exhibiting from 3 to 100 colonic adenomas.<sup>69-73</sup> MAP arises from biallelic mutations of the *MYH* gene and is, thus, recessive. Over 80% of MAP cases in the United States are accounted for by two specific mutations. MAP is present in 0.4% of CRC cases and in 0.8% of cases under 55 years of age.<sup>74-76</sup> Ten percent of FAP families with no *APC* mutations are found to have MAP, and 10–40% of patients with 15–100 adenomas and no *APC* mutations have also been found to have MAP.<sup>69-71,77</sup> Upper gastrointestinal polyps and other extraintestinal manifestations of FAP have been reported, but their association is uncertain.

The risk for CRC in MAP is substantially elevated compared to average-risk persons.<sup>74,76</sup> The age of polyp and cancer onset has not been determined, nor have specific screening and surveillance guidelines. One study did recommend colonoscopy beginning at 18 years of age for biallelic mutation carriers.<sup>73</sup> Genetic testing for attenuated FAP or *MYH* should be considered when any patient is found with 10 or more adenomas.<sup>78</sup> *MYH* mutations can be first sought if the family history is autosomal recessive.

**Hereditary Nonpolyposis Colorectal Cancer, or Lynch Syndrome**

**General Characteristics.** HNPCC, or Lynch syndrome, is an autosomal dominantly inherited syndrome with a very high risk of CRC but few colonic adenomas. It accounts for 1–3% of CRC cases.<sup>29,79</sup> A number of other cancers are also observed in this condition (see below). HNPCC is caused by germline mutations in any one of the four DNA MMR genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*.<sup>58,80</sup> *MLH1* or *MSH2* mutations account for 90% of cases, whereas 6% arise from *MSH6* and 1% from *PMS2*. When a disease-causing mutation is found, the most recent nomenclature indicates that the term “Lynch syndrome” should be used. HNPCC is then reserved for families meeting clinical criteria of the disease but not with a distinct genetic diagnosis.<sup>81</sup>

MSI is a feature of CRCs that harbor MMR gene mutations. MSI is present in almost all CRCs arising in the setting of HNPCC, but also in approximately 15% of sporadic CRCs.<sup>82</sup> Immunohistochemistry (IHC) testing for expression of MMR proteins in the cancer tissue is abnormal, depending upon the gene mutated, but as with MSI, is also abnormal in approximately 15% of sporadic CRC.

**Table 3.** Risks and Screening Recommendations for Extracolonic Cancers\*

Syndrome and cancer	Lifetime cancer risk	Screening recommendations
<b>FAP<sup>†</sup></b>		
Duodenal or periampullary cancer	5%	Upper GI endoscopy (including side-viewing examination) every 1–3 years, depending upon severity of polyposis, starting at 20–25 years of age
Pancreatic cancer	2%	Possibly periodic abdominal ultrasound or abdominal CT after 20 years of age
Thyroid cancer	2%	Annual thyroid examination and possibly ultrasound, starting at 10–12 years of age
Gastric cancer	0.5%	Same as for duodenal cancer
CNS cancer, usually cerebellar medulloblastoma (Turcot syndrome)	1.5%	Annual physical examination, possibly periodic head CT in families where CNS cancer has already occurred, or with any symptoms
Hepatoblastoma, usually occurs in the first 5 years of life	1.5%	Liver palpation, hepatic ultrasound, and $\alpha$ -fetoprotein every 3–6 months during the first 5 years. If this screening is performed, genetic testing should precede it to avoid screening children without a mutation.
<b>HNPCC</b>		
Endometrial cancer	40%	Pelvic examination, transvaginal ultrasound and/or endometrial aspirate every 1–2 years, starting at 25–35 years of age. Hysterectomy with oophorectomy should be considered after childbearing is complete.
Ovarian cancer	10%	Same as for endometrial cancer
Gastric cancer	10–20%	Upper GI endoscopy every 1–2 years, starting at 30–35 years of age
Urinary tract cancer	10%	Ultrasound and urinalysis every 1–2 years, starting at 30–35 years of age
Renal cell adenocarcinoma	<5%	Same as for urinary tract cancer
Biliary tract and gallbladder cancer	15%	Annual liver function tests and possible periodic abdominal ultrasound
CNS cancer, usually glioblastoma	<5%	Annual physical examination and head CT if any symptoms occur
Duodenal and small bowel cancer	1–2%	Upper GI endoscopy as for gastric cancer; no recommendations for small bowel cancer
<b>PJS</b>		
Stomach, duodenal cancer	25%	Upper GI endoscopy every 2 years, starting at 10 years of age
Small bowel, duodenal cancer	10–15%	Annual hemoglobin examination and small bowel radiograph every 2 years, both starting at 10 years of age <sup>‡</sup>
Breast cancer	50%	Annual breast examination and mammography, both starting at 25 years of age
Pancreatic cancer	35%	Endoscopic or abdominal ultrasound every 1–2 years, starting at 30 years of age
Lung cancer	15%	No recommendations given
Uterine cancer	10%	Annual pelvic examination with pap smear and pelvic ultrasound, both starting at 20 years of age
Ovarian cancer	20%	Same as for uterine cancer
Adenoma malignum (cervix)	10%	SCTAT tumors (females) in almost all women with PJS, same as for uterine cancer (add pap smear)
Sertoli cell tumor (males)	10%	Annual testicular examination, starting at 10 years of age; testicular ultrasound if feminizing features occur

*(Table continued on following page)*

**Table 3.** Risks and Screening Recommendations for Extracolonic Cancers\* (Continued from previous page)

Syndrome and cancer	Lifetime cancer risk	Screening recommendations
<b>Juvenile polyposis syndrome</b>		
Gastric and duodenal cancer	10%	Upper GI endoscopy every 3 years, starting in early teens (mainly to avoid complications of benign polyps)
<b>Cowden syndrome</b>		
Thyroid cancer	3–10%	Annual thyroid examination and ultrasound, starting in teens
Breast cancer	25–50%	Annual breast examination and mammography, starting at 25–30 years of age
Uterine and ovarian cancer (increased in some)	Unknown	No recommendations given

\*In general, cancer risks have usually been estimated from registries, which, by their nature, may overestimate such risks. Additionally, all of the screening guidelines given are either extrapolated from experience in other settings or have been developed by expert opinion, as there are few outcomes data regarding these recommendations. The pros and cons of screening (except for colorectal and, possibly, uterine cancer) in these diseases should, thus, be discussed with patients rather than given as only hard recommendations.

†For attenuated FAP, the relationships to extracolonic cancers are less certain, though the upper GI polyp and cancer phenotype is often similar to that of full-blown FAP.

‡Interval may be lengthened to avoid excess irradiation if polyps are not found.

CNS=central nervous system; CT=computed tomography; FAP=familial adenomatous polyposis; GI=gastrointestinal; HNPCC=hereditary nonpolyposis colorectal cancer; PJS=Peutz-Jeghers syndrome; SCTAT=sex cord tumor with annular tubules.

The lifetime risk of developing CRC in HNPCC is approximately 80%, with an average age at diagnosis of 44 years,<sup>29</sup> though some have suggested that the average age may actually be higher, perhaps over 60 years.<sup>83</sup> Patients exhibit few adenomatous polyps, and the distribution of both polyps and cancers is approximately 60% proximal to the splenic flexure. Synchronous and metachronous CRCs are common. In comparison to sporadic polyps, polyps in the setting of HNPCC develop at a younger age, are larger than age-matched controls, and tend to exhibit a more advanced histology.<sup>84,85</sup> Stage-for-stage, HNPCC patients with CRC have better survival compared to sporadic cases.<sup>29</sup>

Persons with HNPCC exhibit an increased risk for cancers of the genitourinary system, biliary system, CNS, small bowel, and stomach<sup>29,86</sup> (Table 3). The Amsterdam criteria clinically define HNPCC by the following: at least 3 relatives with CRC, 2 being first-degree relatives of the third person; at least 2 generations should be affected; and at least 1 CRC should be diagnosed before the age of 50.<sup>87</sup> Approximately 50% of families will be missed by these criteria, but more will be identified by the Amsterdam II criteria, in which any HNPCC cancer can be substituted for CRC.

The Bethesda guidelines, criteria to detect even more families, were developed to determine which patients with CRC should undergo MSI testing (Table 4).<sup>87-90</sup>

Using the Bethesda guidelines, approximately 90% of HNPCC families can be identified. Tumor IHC to look for expression of MMR proteins can be used instead of MSI. The utility of IHC testing is that it can be performed at most pathology laboratories. One should be aware, however, that IHC testing is 94% sensitive due to intricacies of the test, whereas MSI is 98% sensitive.<sup>81</sup> Furthermore, IHC for MMR protein expression is a somewhat difficult immunochemical test, requiring substantial experience for optimal performance. If there is any question regarding a negative result (eg, a family history indicative of HNPCC but normal IHC expression of MMR genes), MSI should also be performed. Genetic testing is indicated if one of the MMR proteins is not expressed. If MSI is positive, see below.

**Variants of Hereditary Nonpolyposis Colorectal Cancer.** The Muir-Torre syndrome is characterized by several different cutaneous manifestations in addition to the malignancies of HNPCC,<sup>91</sup> which mainly include sebaceous adenomas and carcinomas. This syndrome may arise from mutations in any of the four MMR genes, though it may be less common in families with *MSH6* or *PMS2* mutations. One third of Turcot syndrome families arise from mutations in the MMR genes.<sup>92,93</sup> These patients will usually manifest typical findings of HNPCC together with CNS glioblastomas.

**Table 4.** Modified Bethesda Criteria for MSI Testing in Colorectal Cancer

1. Individuals with cancer in families that meet the Amsterdam criteria
2. Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers
3. Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at <45 years of age, and the adenoma diagnosed at <40 years of age
4. Individuals with colorectal or endometrial cancer diagnosed at <45 years of age
5. Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/ciribriform) on histology diagnosed at <45 years of age
6. Individuals with signet-ring-cell-type colorectal cancer diagnosed at <45 years of age
7. Individuals with adenomas diagnosed at <40 years of age

HNPCC=hereditary nonpolyposis colorectal cancer;  
MSI=microsatellite instability.

Patients with *MSH6* mutations exhibit a somewhat lower CRC risk but a higher uterine cancer risk than HNPCC overall, suggesting a somewhat different phenotype.<sup>94</sup> However, regardless of which MMR gene is mutated, uterine cancer risk in HNPCC may be as high as 62%.<sup>95</sup> Furthermore, 9% of women with uterine cancer under 50 years of age were found to have a disease-causing MMR mutation, suggesting that women with young age onset endometrial cancer should be considered for genetic testing for HNPCC.<sup>96</sup>

Patients with *PMS2* mutations appear to have a milder phenotype of HNPCC compared to those with mutations in the other three genes and may be a more common cause of HNPCC than previously thought.<sup>97,98</sup> Many families with *PMS2*-caused Lynch syndrome do not meet the Bethesda guidelines, and the lifetime cancer risks appear to be lower than HNPCC in general: CRC, 15–20%, and endometrial cancer, 15%.<sup>98</sup>

**Management.** As HNPCC lacks a specific premalignant phenotype, genetic testing can be particularly helpful for precise diagnosis in an index case and further diagnoses in other family members.<sup>13,58,80</sup> When a family meets the Amsterdam criteria (I or II), genetic testing is indicated. The youngest person with CRC in such a family should be tested first. There is a 50–70% likelihood of finding a MMR gene mutation in the index case. If the mutation is identified in this index case, other family members can be tested for the presence

or absence of the mutation with near 100% accuracy. Genetic testing should commence in at-risk individuals at 20–25 years of age.

The Bethesda guidelines should be consulted when there is a strong family history of CRC but the Amsterdam criteria are not met. If any of these guidelines are met, tumor testing for MSI or IHC staining should be undertaken. If either is abnormal, genetic testing of peripheral blood DNA for MMR germline mutations is indicated.<sup>80</sup>

An increasingly popular approach is to perform IHC testing on all CRC tumors.<sup>80,99</sup> If the test is abnormal, DNA genetic testing should be performed. With this approach, 10–15% of persons with CRC would undergo genetic testing to find the 1–3% of those who have HNPCC. The number of patients requiring genetic testing can be reduced by half by looking for a specific mutation in the *BRAF* gene in the tumor tissue of patients with an abnormal IHC test.<sup>80,82</sup> The specific mutation in *BRAF* is indicative of increased DNA methylation. As the majority of sporadic tumors that exhibit MSI or loss of IHC expression arise from hypermethylation of the promoter region of the *MLH1* gene, the presence of this *BRAF* mutation indicates that the tumor is sporadic, and not from inherited MMR mutations. The presence of this *BRAF* mutation essentially rules out HNPCC.

It should be noted that any of these genetic approaches to the diagnosis of HNPCC requires an appropriate institutional infrastructure with knowledgeable professionals who can assist in determining optimal approaches. In addition, interpretation of results may not always be straightforward. Physicians with expertise in these genetic issues and/or genetic counselors should be available to assist in planning approaches and interpreting results, and a multidisciplinary team should be assembled to establish the infrastructure and to plan surveillance and treatment.<sup>81</sup>

Screening for syndrome cancers should be offered to persons with a disease-causing germline MMR mutation as outlined in Tables 2 and 3.<sup>28,29,81,85,100</sup> Except for CRC and uterine cancer, the surveillance guidelines outlined in these tables are empiric, based upon known risk and expert opinion. They should, therefore, be discussed with the patient in that context before proceeding.

Surgical intervention, usually subtotal colectomy, is indicated when a patient develops either CRC or an advanced adenoma that cannot be managed endoscopically.<sup>29,81,101</sup> Segmental cancer surgery is a reasonable approach if subsequent surveillance can be assured.<sup>81</sup> Hysterectomy with ovariectomy can be offered after child-bearing is finished.<sup>102</sup>

#### **Peutz-Jeghers Syndrome**

PJS includes histologically characteristic hamartomatous polyps in the gastrointestinal tract and distinctive



**Figure 4.** Duodenal polyps in a patient with Peutz-Jeghers syndrome.



**Figure 5.** Colonic juvenile polyps in a patient with juvenile polyposis syndrome.

mucocutaneous melanin pigmentation.<sup>103-107</sup> There is an associated risk of both gastrointestinal and nongastrointestinal malignancies (Tables 2 and 3). PJS is very rare, with approximately 1 in 120,000 persons being affected. It is an autosomal dominantly inherited disease that arises from a mutation in the *STK11* gene (also called *LKB1*).

The average age of diagnosis is 22 years in men and 26 years in women,<sup>108</sup> though approximately one third of patients present within the first decade of life. Typically, symptoms result from complications of gastrointestinal polyps, which occur in 88–100% of patients. Polyps can be found throughout the gastrointestinal tract, with a frequency of 24% in the stomach; 96% in the small bowel; 27% in the colon (Figure 4); and 24% in the rectum.<sup>108</sup> Polyps can ulcerate, infarct, bleed, or cause intussusception with intestinal obstruction, thereby causing much of the morbidity and surgical intervention of PJS. Areas of adenomatous and, subsequently, cancerous changes may also occur in PJS polyps.

After the age of 30, malignant complications become a major concern. By the age of 65, over 90% of PJS patients have some kind of malignancy, either intestinal or extraintestinal.<sup>104,109</sup> CRC and extracolonic cancer risks and suggested surveillance guidelines (based upon expert opinion) are given in Tables 2 and 3. All screening in PJS is empiric and based upon risk, but nonetheless provides a rational approach. Genetic testing is available for patients suspected of having PJS based upon family history or clinical presentation. Approximately 75% of families with clinical PJS will demonstrate a *STK11* germline mutation.<sup>107,110</sup>

Treatment focuses on preventing benign complications and malignancies. Removal of polyps is indicated when they are larger than 0.5 mm to 1.0 cm in size or if symptoms occur. Surgery is often necessary to remove large polyps in the small bowel. Colectomy may be necessary if polyps are sufficiently large and/or numerous for safe and effective endoscopic management.

### **Juvenile Polyposis Syndrome**

JPS is an autosomal dominantly inherited condition that affects approximately 1 in 100,000 individuals. Genes involved in the etiology of JPS include *SMAD4* (also called *DPC4*) and *BMPRIA*.<sup>103,105,111-113</sup> Mutations in one of these genes are found in approximately 50% of affected families.<sup>113</sup> JPS is characterized by multiple juvenile polyps of the gastrointestinal tract with associated colon, gastric, and duodenal cancer risk.<sup>103,105</sup> However, sporadic juvenile polyps are found in approximately 2% of children and must be distinguished from JPS because of the clinical significance of the latter.

The clinical criteria for the diagnosis of JPS includes: at least 5 juvenile polyps in the colorectum; juvenile polyps throughout the gastrointestinal tract; and any number of juvenile polyps in a person from a family with known JPS.<sup>103,105</sup> Polyps are most common in the colon (Figure 5), though they can occur anywhere in the gastrointestinal tract. Polyps usually appear in the first decade of life and can number anywhere from dozens to several hundred. Most patients will become symptomatic within the first two decades of life, presenting with rectal bleeding, abdominal pain, passage of tissue through the rectum, or intussusception.

Lifetime CRC risk is approximately 60%, with an average age of cancer diagnosis of 34 years (range, 15–68 years).<sup>103,105</sup> These cancers are thought to arise from adenomatous tissue within the juvenile polyp. Other cancers include malignancies of the stomach, duodenum, biliary tree, and pancreas.<sup>114</sup> Benign manifestations of JPS have also been found and include congenital abnormalities of the heart, gastrointestinal tract, genitourinary system, and CNS.<sup>114</sup>

Genetic testing for JPS should be performed on an index case with a clinical diagnosis and then family members once the mutation is determined. Cancer screening is outlined in Tables 2 and 3.<sup>58,103,105,111,112,115</sup> Colectomy should be considered when polyps are difficult to control endoscopically or when advanced histology is found. Likewise, partial or complete gastrectomy may be neces-

sary for large or advanced gastric lesions, which are usually associated with *SMAD4* mutations.<sup>116</sup>

### Cowden Syndrome

Cowden syndrome (CS) is an autosomal dominantly inherited disorder in which hamartomatous polyps may be found throughout the gastrointestinal tract. Facial trichilemmomas are pathognomonic of CS, and there is a high risk of breast and thyroid cancer.<sup>117</sup> There is some CRC risk in this syndrome, and adenomatous polyps may also be observed. CS arises from mutations of the *PTEN* gene, which is a tumor suppressor gene.<sup>103,118,119</sup> Up to 80% of patients fulfilling clinical criteria of CS will be found to have a mutation of the *PTEN* gene. A variant of CS, Bannayan-Riley-Ruvalcaba syndrome (BRR), also arises from mutations in *PTEN*, but only 50–60% of patients with BRR are found to have a *PTEN* mutation.<sup>93</sup> Adult onset Lhermitte-Duclos disease is considered pathognomonic of CS, though only a minority of CS patients exhibit this condition.<sup>120</sup>

Clinical manifestations include multiple gastrointestinal hamartomas with the following distribution: stomach, 75%; esophagus, 66%; colon, 66%; and duodenum, 37%.<sup>103,121</sup> Esophageal polyps are histologically glycogenic acanthosis.<sup>122</sup> The most common gastrointestinal polyps are juvenile polyps, but others have been observed, including lipomas, inflammatory polyps, ganglioneuromas, and lymphoid hyperplasia. CRC risk is elevated compared to that of the general population, but the exact risk is not known.<sup>123,124</sup> Diagnostic criteria for CS have been established,<sup>117-119</sup> and cancer risks and suggested screening recommendations (based upon expert opinion) are outlined in Tables 2 and 3.

### Summary

Substantial understanding has been gained in recent years concerning the familial risk, inherited syndromes, and genetic pathogenesis of CRC. This information has led to improved screening and management of persons with an increased risk of this malignancy. Screening guidelines for persons with a family history of CRC are appropriately more aggressive than those for average-risk persons. The precise identification of persons and families with inherited syndromes of CRC is now possible with genetic testing. Furthermore, guidelines are now also given for determining who should have genetic testing, and approaches for surveillance and management of persons with one of the syndromes have been suggested. Reduced CRC occurrence and mortality have now been demonstrated with appropriate surveillance in these increased risk settings. It is expected that the genetic and molecular understanding of CRC will further lead to better preventive and molecular approaches to this common malignancy.

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