Genetic Alterations in Sporadic and Hereditary Colorectal Cancer: Implementations for Screening and Follow-Up

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Key Words

Attenuated familial adenomatous polyposis • Familial adenomatous polyposis • Familial juvenile polyposis • Hereditary colorectal cancer • Hereditary non-polyposis colorectal cancer • Juvenile polyposis coli • MYH polyposis syndrome • Peutz-Jeghers syndrome • Sporadic colorectal cancer

Abstract

The genetics underlying an inherited predisposition to cancer are rapidly being uncovered. This fact may ultimately lead to the routine use of molecular tools to diagnose these disorders, and establish interventions to prevent the development of cancer. Among the multiple cancer family syndromes, several are known to be associated with the development of colon cancer. These disorders may be diagnosed during evaluation of the index patient or during screening of family members who are at risk. Although the effectiveness of screening and surveillance strategies is unproven in controlled clinical trials for any of these syndromes, the high cancer risk warrants screening, and reasonable recommendations can be made. Several other genetic syndromes are associated with gastrointestinal polyposis. The risk of colon cancer in these diseases is uncertain, and may not be increased and they are not mentioned in this review. Examples include Cowden disease, intestinal ganglioneuromatosis, Ruvalcaba-Myhre-Smith syndrome, Devon family syndrome, and Cronkite-Canada syndrome.

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Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality worldwide. CRC is the third most common cancer and the third leading cause of cancer death in both sexes, accounting for approximately 10% of cancer deaths overall [1]. The lifetime incidence for patients at average risk is 5%, with 90% of cases occurring after age 50. Approximately 1 in 3 people who develop CRC die of this disease. While early stage CRC is frequently curable with surgery, unresectable metastatic disease is a fatal disease. These facts indicate the crucial role of an effective screening and follow-up programs in order to identify the disease in early stages. Furthermore, the identification of premalignant lesions is a prerequisite to effective CRC.

The risk factors for CRC are both environmental and genetic. These different risk factors reflect the mode of presentation of CRC that follows one of the following three: sporadic, inherited, and familial. Sporadic disease, in which there is no family history, accounts for approximately 70% of all CRC. The patients are usually older than 50 years of age and dietary and environmental factors have been etiologically implicated, although genetic changes which lead to the adenoma-carcinoma sequence have been described [2]. Less than 10% of patients have an inherited predisposition to CRC, and these cases are subdivided according to whether or not colonic polyps are a major disease manifestation. The diseases with polyposis include familial adenomatous polyposis (FAP) [3], and the hamartomatous polyposis syndromes (e.g.,

Table 1. CRC predisposition genes

Gene (synonyms) ^a	Syndrome	Hereditary pattern	Second hit	Pathway ^b	Tumor types ^c
Tumor suppressor genes					
<i>APC</i>	FAP	Dominant	Inactivation of WT allele	APC	Colon, thyroid, stomach, intestine
<i>AXIN2</i>	Attenuated FAP	Dominant	Inactivation of WT allele	APC	Colon
<i>BMPR1A</i>	Juvenile polyposis	Dominant	Inactivation of WT allele	SMAD	Gastrointestinal
<i>SMAD4 (DPC4)</i>	Juvenile polyposis	Dominant	Inactivation of WT allele	SMAD	Gastrointestinal
Stability genes					
<i>MUTYH</i>	Attenuated polyposis	Recessive	?	BER	Colon
<i>MSH2, MLH1, MSH6, PMS2</i>	HNPCC	Dominant	Inactivation of WT allele	MMR	Colon, uterus
Oncogenes					

WT = Wild type.

^a Representative genes of all the major pathways and hereditary cancer predisposition types are listed. Approved gene symbols are provided for each entry, with alternative names in parentheses.

^b In many cases, the gene has been implicated in several pathways.

^c In most cases, the non-familial tumor spectrum caused by somatic mutations of the gene includes those occurring in the familial cases plus additional tumor types.

Peutz-Jeghers, juvenile polyposis) [4], while those without polyposis include hereditary non-polyposis colorectal cancer (HNPCC, Lynch syndrome I), and the cancer family syndrome (Lynch syndrome II) [5]. These conditions are associated with a high risk of developing CRC, and the genetic mutations underlying many of them have been identified. The third and least well understood pattern is known as ‘familial’ CRC. Up to 25% of affected patients have a family history of CRC, but the pattern is not consistent with one of the inherited syndromes described above. Individuals from these families are at increased risk of developing CRC, although the risk is not as high as with the inherited syndromes. It was proposed that this group of patients represents individuals with genetic changes with an autosomal recessive pattern of inheritance. Indeed the discovery that biallelic mutations of the base excision repair gene, *MYH*, resulted in an increased risk of colorectal adenomas and cancer led to the first description of an autosomal recessive cancer syndrome [6].

The revolution in cancer research has proven that cancer is a genetic disease. The elucidation of human genome sequence has made it possible to identify genetic alterations in cancer in unprecedented detail [7]. The initial genetic alterations of a cell that triggers its aberrant proliferation are followed by the accumulation of additional mutations among its progeny. Finally, a selection

process occurred by which subclones with enhanced growth properties become dominant within the tumor, a process that was called tumor progression [8]. A clear histologic and molecular genetics evolution from pre-cancerous lesions to flunky malignant and invasive cancer has been defined for the majority of cases of CRC [9–11].

Major Genetic Alterations CRC

Alterations in three types of genes are responsible for tumorigenesis in CRC as well as in the other tumor types: oncogenes, tumor suppressor genes and stability genes (tables 1, 2) [12]. The carcinogenesis in colon epithelium is a multistep process. In 1990, Fearon and Vogelstein [9] described the molecular basis for CRC as a multistep process in which each accumulated genetic event conferred a selective growth advantage to the colonic epithelial cell. According to the Vogelstein model, also known as the adenoma-carcinoma sequence, germline or somatic mutations are required for malignant transformation, and it is the accumulation of multiple genetic mutations rather than their sequence that determines the biological behavior of the tumor (fig. 1). Germline mutations underlie the common inherited syndromes (e.g., APC, HNPCC), while sporadic cancers

Table 2. Genes that are mutated somatically but not inherited in mutant form

Gene (synonyms) ^a	Somatic mutation type ^b	Cancers with mutant gene ^c	Pathway
<i>CTNNB1</i> (β -catenin)	Activating codon change	Colon, liver, medulloblastomas	APC
<i>BAX</i>	Inactivating codon change	Colon, stomach	APOP
<i>FBXW7</i> (<i>CDC4</i>)	Inactivating codon change	Colon, uterine, ovarian, breast	CIN
<i>PI3KCA</i>	Activating codon change	Colon, stomach, brain, breast	PI3K
<i>BRAF</i>	Activating codon change	Melanoma, colorectal, thyroid	RTK
<i>FES</i>	Activating codon change	Colon	RTK
<i>KRAS2</i> , <i>N-RAS</i>	Activating codon change	Colorectal, pancreatic, non-small cell lung cancer	RTK
<i>NTRK1</i> , 3	Translocation, activating codon change	Thyroid, secretory breast, colon	RTK
<i>SMAD2</i>	Inactivating codon change	Colon, breast	SMAD
<i>TGFBR1</i> , <i>TGFBR2</i>	Inactivating codon change	Colon, stomach, ovarian	SMAD
<i>HOXD11</i> , 13; <i>HOX11</i> , <i>HOX11L2</i>			
<i>MAP2K4</i> (<i>MKK4</i>)	Inactivating codon change	Pancreas, breast, colon	Unknown
<i>PTNP1</i> , 11	Activating codon change	Leukemias, colon	Unknown

^a Representative genes of all the major pathways and cancer types are listed. Approved gene symbols are provided for each entry, with alternative names in parentheses.

^b Activating codon change, intragenic mutation altering one or a small number of base pairs that activates the gene product, indicating that it is an oncogene; inactivating codon change, any mutation (point mutation, small or large deletion, etc.) that inactivates the gene product, indicating that the gene is a tumor suppressor. Amplifications and translocations generally affect oncogenes, though occasional translocations disrupt a gene rather than activate it.

^c Only representative types of cancers are listed when a gene is mutated in many tumor types.

result from the stepwise accumulation of multiple somatic mutations.

Indeed, it was well known for many years that most CRCs arise from pre-existing adenomas, usually as result of mutation in the adenomatous polyposis coli (*APC*) gene [13] and are characterized by chromosomal instability [10]. However, approximately 10–15% of CRC arise via the microsatellite instability (MSI, mutator, DNA replication error) [11, 14, 15]. These two types of colorectal carcinogenesis present a range of distinctive genetic, pathologic and clinical characteristics [16–18].

Tumors with chromosomal instability are associated with hyperploidy, allelic losses (17p, 18q, 8p, 22q), frequent tumor suppressor gene mutations (p53 and *APC*), are mainly located in the left colon and were correlated with an unfavorable outcome.

Mutations in the *APC* gene, which are a feature common to both inherited and sporadic tumors, occur early in the process, followed by mutation in the *k-ras* gene while mutations of the p53 suppressor gene generally occur late in the process [19]. *APC* represent the most critical gene in the early development of CRC is the *APC* tumor suppressor gene. Germline mutations of the *APC* gene are responsible for the F somatic mutations in both alleles are present in almost 80% of sporadic CRC. The

function of the *APC* protein and the mechanism whereby the abnormal gene promotes tumor formation are beginning to be understood [20, 21]. Loss of function mutations in the *APC* or activating mutations in the β -catenin gene result in the nuclear accumulation of β -catenin, which binds and activates the transcription factor T-cell factor (Tcf)-4 [22]. It is proposed that β -catenin/Tcf-4 acts as a switch controlling proliferation versus differentiation in the intestinal crypt epithelial cells [23].

An important clue was the observation that most sporadic CRC with normal or wild-type *APC* had mutations in β -catenin, a protein involved in the same signaling cascade as *APC*, the Wnt (wingless-type) signaling pathway [23, 24]. The recognition of the importance of the *APC* gene began with genetic studies linking inheritance of the FAP syndrome to chromosome 5q21, and the subsequent identification of germline mutations involving a gene at this locus, the *APC* gene. The earliest malignant lesions in these patients, dysplastic aberrant crypt foci (microadenomas) and small adenomatous polyps, have lost the second *APC* allele (through deletion or somatic mutation), suggesting that *APC* loss is a very early event in colorectal tumorigenesis.

A germline mutation in codon 1307 in the *APC* gene, also named as I1307K *APC* mutation, has been described

Fig. 1. Adenoma-carcinoma sequence.

in Ashkenazi Jewish individuals and has been linked with familial CRC [25, 26]. The mutation is found in 6% of all persons of Ashkenazi Jewish descent, but in a higher frequency of Ashkenazi Jews with both a personal and family history of CRC (28%) [25]. This mutation was previously thought to represent a polymorphism because it does not cause protein structure abnormalities, but creates a small hypermutable region of the gene, which predisposes to the development of carcinomas [25]. The relative risk for CRC, although elevated relative to the general population, is much lower in affected individuals compared to those with FAP.

The *ras* oncogene exists as three cellular variants: *H-ras*, *K-ras*, and *N-ras*. Although all three oncogenes, when mutated, have the ability to transform normal cells, *K-ras* is the most frequently mutated in human CRC [27]. The *ras* oncogenes encode a family of small proteins with homology to G-proteins that regulate cellular signal transduction by acting as a one-way switch for the transmission of extracellular growth signals to the nucleus [28]. *Ras* mutations are found in up to 50% of sporadic CRCs, and 50% of colonic adenomas >1 cm; they are rarely seen in smaller adenomas [2]. The lack of mutations in smaller adenomas suggests that *ras* mutations are acquired during later adenoma progression [29].

The *p53* gene on chromosome 17p is the most commonly mutated gene in human cancer. Loss of heterozygosity (LOH) in the 17p locus could be identified in up to 75% of CRCs, while they are rarely lost in adenomas

and aberrant crypt foci, suggesting that *p53* loss represents a relatively late event in colorectal tumorigenesis [2, 9, 30].

As with *p53* and the *APC* gene, the first evidence of a tumor suppressor gene on chromosome 18q came from studies of allelic loss in CRC. In an early study, one copy of 18q was lost in 73% of sporadic CRC and 47% of large adenomas with foci of invasive cancer, but in fewer than 15% of less advanced adenomas [2].

In 1989, a candidate gene termed the '*deleted in colon cancer*' (*DCC*) gene was identified at 18q21, and point mutations in the *DCC* gene have been identified in CRC [31, 32]. A second tumor suppressor gene at 18q was identified termed *SMAD*. *SMAD4* encodes a protein that may be important to the signaling pathway of the transforming growth factor- β (TGF- β) superfamily of signaling polypeptides. TGF- β suppresses the growth of most normal cells, and many cancer cells are resistant to this growth-suppressive effect [33]. Mutations in *SMAD4* or a third putative tumor suppressor gene that also maps to 18q (*SMAD2*) have been found in a subset of sporadic CRC [34]. Germline mutations in the *SMAD4* gene have been identified as the causative mutation in some affected families with familial juvenile polyposis (FJP) [35]. The *PTEN* gene coding for a phosphatase and the *BMPRI1A* gene coding for a serine-threonine kinase receptor have also been linked to FJP in some families [36]. The mechanism by which these mutations cause hamartomas is not understood, but genetic testing is now becoming available for these syndromes.

Peutz-Jeghers syndrome, another hamartomas polyposis syndrome, has been linked to germline mutations of *LKB1* (located on chromosome 19p), which encodes the serine-threonine kinase STK-11 [37]. Among their multiple functions, STK-11 can regulate p53-mediated apoptosis [38]. In addition, adenosine monophosphate-activated protein kinase has been identified as being a direct phosphorylation target for LKB1, implicating LKB1 in the control of cellular metabolism [39, 40].

On the other hand, tumors with MSI are euploid tumors without allelic losses, present infrequent tumor suppressor gene mutations (*p53* and *APC*) and more frequently mutations of the *TGB β -R11*, *BAX*, *TCF4*, *Caspase 5*, *HIF1 α* , and oncogene mutation (*BRAF* and *PI3KCA*), and are located mainly in the proximal colon, have a greater mucinous component, contain lymphocytic infiltration, and are more often poorly differentiated. Despite the latter feature, the presence of MSI is associated with longer survival in both HNPCC and sporadic cases [41].

Mismatch repair (MMR) genes are responsible for correcting the ubiquitous nucleotide base mispairs and small insertions or deletions that occur during DNA replication [42]. Several of these genes have been identified, including *hMSH2* (human *mutS* homolog 2), *hMLH1* (human *mutL* homolog 1), *hPMS1* and *hPMS2* (human post-meiotic segregation 1 and 2), *hMSH6* (human *mutS* homolog 6), and *hMLH3*, a mismatch repair gene that interacts with *MLH1*.

HNPCC is caused due to germline mutations in one of the MMR genes. MMR gene deficiencies can also be found in approximately 10–15% of sporadic CRCs [41]. However, sporadic tumors with defective MMR do not contain MMR gene mutations, instead they have epigenetic changes that silence gene expression [43].

Cells with MMR deficiency accumulate DNA errors throughout the genome [11]. The biologic ‘footprint’ of an MMR defect is the accumulation of abnormalities in short sequences of nucleotide bases that are repeated dozens to hundreds of times within the genome – these are called microsatellites [11]. Several critical growth regulatory genes (e.g., the transforming growth factor- β type II receptor, *BAX*, the insulin-like growth factor II receptor) contain microsatellites in the promoter region and are therefore susceptible to frameshift mutations. This leaves the cell vulnerable to mutations in these genes controlling cell growth. As abnormalities in the microsatellites are common with MMR deficiency, this phenomenon is termed microsatellite instability (MSI) [44].

Germline mutations in the base excision repair gene *mutY* homolog (*MYH*) have been described in a small proportion of patients with multiple colorectal adenomas and a family history of CRC [45, 46]. Sometimes (*MYH*) mutations coexist in conjunction with somatic mutations in the *APC* gene [47]. These mutations predispose patients to recessive inheritance of multiple colonic adenomas, and the phenotype of classic adenomatous polyposis. In one series of 152 patients with multiple adenomas seen at one institution, 7.5% of those without a germline *APC* mutation were found to have two separate germline *MYH* mutations [45]. More importantly, an increasing number of reports suggest that germline mutations in these *MYH* genes may account for a substantial fraction of familial CRCs that occur in the absence of a dominantly inherited familial syndrome [48–50].

The genetic changes underlying an inherited predisposition to cancer are rapidly being uncovered, which may ultimately permit the routine use of molecular tools to diagnose these disorders, and the use of screening strategies and interventions to prevent the development of cancer.

Guidelines for Screening and Follow-Up

Before deciding how to screen, clinicians should decide whether the individual patient is at average or increased risk. A few simple questions are all that is necessary: Do you have a family history of CRC? If so, in first-degree relatives, at what age of onset, and how many? Have you had a personal history of CRC or adenomatous polyps?

The patient is considered average risk if the answer to all these questions is ‘no’. Patients answering yes to any of these questions need to be evaluated further. These questions should be asked well before the patient would ordinarily begin screening (at age 50 years) if he or she were at average risk because screening should begin earlier for patients with increased risk conditions.

Familial Adenomatous Polyposis and Attenuated Familial Adenomatous Polyposis

Classic FAP is characterized by the development of multiple colonic adenomas during the early teenage years with progressive increase so that hundreds to thousands of polyps are recognized by adulthood. Colonic adenomas are observed approximately 10–15 years after the ap-

pearance of polyposis, and almost always by the age of 40 years. FAP-associated adenomas and adenocarcinomas are distributed through the entire colon and are histologically identical to those found in the sporadic CRC. Gastric polyps can develop and are typically benign fundic gland adenomas, although gastric adenocarcinomas have also been observed in FAP families from Korea and Japan [1]. Duodenal, periampullary, or ampullary adenomas eventually develop in nearly all FAP patients. Approximately 10% will develop duodenal adenocarcinoma by the age of 60, making it the second most common malignancy in FAP [2].

Extraintestinal features include desmoid tumors, epidermoid cysts, osteosarcomas, follicular and papillary thyroid tumors, congenital hypertrophy of the retinal pigmented epithelium, and rarely hepatoblastomas and retinoblastomas. Turcot's syndrome refers to familial CRC with central nervous system tumors. Medulloblastomas have been associated with FAP, whereas glioblastomas are primarily seen in HNPCC kindreds.

An attenuated version of FAP (AFAP) differs from the classic form in that there are substantially fewer colonic polyps (<100). These polyps tend to develop on the right side of the colon and the average ages at which colorectal polyps and cancer occur are delayed approximately 15 years. The features of AFAP can also overlap with HNPCC [3], and genetic testing can distinguish between two syndromes.

Germline mutations of the *APC* gene are located throughout the entire gene, and more than 90% of mutations introduce a premature stop codon that results in a truncated protein product [4]. Certain genotype-phenotype correlations have been identified. Classic FAP is seen with mutations located in the central region between codons 169 and 1393 and mutations between codons 1250 and 1464 have been associated with particularly severe polyposis [5].

Family members of patients with classic FAP, Gardner's syndrome, or Turcot's syndrome should be offered genetic counseling and testing if appropriate. At-risk children should usually be offered genetic testing around age 10–12. Genetic testing is not recommended in children prior to age 10 because it would not lead to a change in clinical care and may lead to problems with parental bonding, peer rejection, and poor self-image.

Gene carriers or at-risk family members who have not had genetic testing or are from families in whom the gene test is uninformative should be offered a flexible sigmoidoscopy or colonoscopy every 12 months starting at around age 10–12 and continuing until age 35–40 if negative.

Classic FAP almost always involves the rectosigmoid so that sigmoidoscopy alone is adequate but many pediatric gastroenterologists screen with colonoscopy.

Screening of the upper gastrointestinal tract with upper endoscopy for gastric and duodenal polyps has been recommended [6], although the benefit has not been proven in clinical trials. A baseline examination with both an end- and side-viewing endoscope is recommended upon diagnosis, and repeated every 3–5 years. The development of symptoms referable to the upper digestive tract, including pancreatitis or signs or symptoms related to biliary obstruction, should prompt a repeat investigation at an earlier interval.

The British Society of Gastroenterology recommends upper gastrointestinal surveillance every 3 years from age 30 and more frequently if there is extensive polyposis [7]. Other authorities recommend frequent surveillance and targeted endoscopic treatment (adjusted by severity of duodenal lesions), but acknowledge that these modalities alone cannot guarantee a polyp-free duodenum [8].

Adenomas identified in the duodenum or the papilla of Vater should be removed endoscopically if possible, and follow-up examination should be performed yearly [9]. An abnormal appearing papilla should be biopsied, since adenomas in the duodenum have a predilection for the papilla. Some authorities also recommend obtaining routine biopsies of the papilla, even if it appears grossly normal.

Once colonic polyposis is established in a gene carrier or an at-risk member of an FAP family, a full colonoscopy should be performed to evaluate the extent of the colonic polyposis. An initial upper endoscopic examination should also be performed and a consultation should be arranged to discuss the timing of a colectomy. The number, size, and worst histology of the colonic adenomas determine the optimal timing of colectomy.

Colectomy at the time of initial diagnosis is strongly recommended in patients with multiple large (>1 cm) adenomas or adenomas with villous histology and/or high-grade dysplasia and is the safest approach of all those with profuse polyposis at initial diagnosis. Patients in the second decade of life with only sparse, small (<5 mm) adenomas can usually be followed endoscopically with surgery scheduled to accommodate school and work schedules. Some centers try to allow such patients to finish high school if the endoscopic appearance of the colon is stable, to minimize the psychological trauma of a colectomy during adolescence. The preferred operation in children is a total proctocolectomy with ileoanal anastomosis. A subtotal colectomy with ongoing surveillance or a total

colectomy is reasonable in patients with attenuated adenomatous polyposis who have little rectal involvement. If rectum is left intact, rigorous follow-up with sigmoidectomy every 6–12 months is required.

The risk of colon adenocarcinoma in classic FAP approaches 100% by age 45. Colonoscopy is not effective for identifying polyps with advanced pathology or in detecting early cancers, because the presence of multiple polyps precludes adequate sampling. Although the non-steroidal anti-inflammatory drug sulindac can cause regression of colorectal adenomas in FAP, regression of polyps is incomplete, and the degree of protection from the development of CRC is unknown. Sulindac (75 or 150 mg twice daily) was ineffective in delaying the time of initial development of adenomas in a controlled trial involving 41 proven FAP gene carriers [12]. Thus, sulindac is unlikely to replace colectomy as primary therapy for FAP but it is being used in some centers to slow the development of adenomas prior to colectomy and to delay new polyp formation in the rectum after subtotal colectomy [13]. One of the COX-2 inhibitors (celecoxib) was approved by the FDA based upon a controlled trial involving 77 patients in which it was associated with a 28% reduction in the number of polyps [14].

Hereditary Non-Polyposis Colorectal Cancer

Among the colon cancer syndromes, HNPCC is the most common and accounts for close to 1% of the CRC in the USA [10] and nearly 2% in Europe [11]. The lifetime risk for the development of CRC in affected individuals is 80%. The average age at diagnosis of CRC is 45 years. A unique set of extracolonic tumors is associated with HNPCC (table 3).

Clinical criteria for the diagnosis of HNPCC take into account the age of diagnosis of CRC, the number of affected family members, and the presence of extracolonic tumors. The Amsterdam I criteria of 1990 [51] are considered to be highly specific for the diagnosis of HNPCC. The modified Amsterdam and Amsterdam II criteria [52] were proposed in order to provide less stringent guidelines. In 1996, the Bethesda guidelines [53] were formulated to encompass an even broader spectrum of at risk patients, thereby maximizing sensitivity but necessarily reducing specificity. These criteria were updated and simplified in 2004 [54].

A consortium of experts has developed guidelines for cancer surveillance in patients diagnosed with HNPCC. These recommendations are reasonable based upon the

Table 3. Lifetime risk for cancer associated with HNPCC

Types of cancer	Persons with HNPCC, %	General population, %
Colorectal	80–82	5–6
Endometrial	50–60	2–3
Gastric	13	1
Ovarian	12	1–2
Small bowel	1–4	1–2
Bladder	4	1–3
Brain	4	0.6
Kidney, renal, pelvis	3	1
Biliary tract	2	0.6

available evidence, but none has been validated prospectively. As such, they are based largely upon expert opinion. The following recommendations apply to individuals who have a genetic or clinical diagnosis of HNPCC or who are at increased risk for HNPCC: colonoscopy every 1–2 years beginning at age 20–25, or 10 years earlier than the youngest age of colon cancer diagnosis in the family (whichever comes first); genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited MMR gene mutation. It should also be offered when the family mutation is not already known, but one of the first three of the modified Bethesda criteria is met.

As noted above, the optimal interval for colonoscopic surveillance has not been defined in clinical trials. Some clinics recommend that colonoscopy should be performed annually in all at-risk individuals after age 40–45 since the risk of CRC increases with age. One study showed that colonoscopy on average every 3 years decreased the CRC incidence by 62% and overall mortality by 65% in 22 families with HNPCC [55]. A decision analysis estimated that colonoscopy surveillance in HNPCC family members would be associated with a gain of approximately 14 quality-adjusted life years per screened individual compared to no surveillance. This is a much greater improvement than seen with many well-accepted therapies for other diseases such as the treatment of mild hypertension. Total or subtotal colectomy with continued surveillance of the remaining rectum is recommended for patients with HNPCC who are found during surveillance to have CRC or an advanced adenoma (large, villous, or high-grade dysplasia). At present, there are no data regarding a potential role of offering primary prophylactic surgery in patients who have not yet developed an advanced lesion.

Recommendations have also been issued by other expert groups, some of which touch upon surveillance for extracolonic tumors [55]. These include: annual screening for endometrial and ovarian cancer beginning at age 25–35 years (pelvic examination and endometrial aspirate with or without transvaginal ultrasound); annual urinalysis and cytologic examination beginning at age 25; annual skin surveillance, and periodic upper endoscopy.

There have been no prospective studies to indicate how effective some of these screening programs will be, particularly those aimed at detecting gynecologic cancers. The benefits and limitations of screening were illustrated in a study involving 292 women from HNPCC or HNPCC-like families [56]. A surveillance strategy of annual or biennial (every 2 years) with either transvaginal (when available) or transabdominal ultrasound failed to detect the only 2 cases of endometrial cancer that developed during a 13-year observation period [56]. Surveillance for breast, uterine, and ovarian cancers seems warranted because of the high estimated risk. The following are recommended: breast surveillance beginning at age 25 in women with mammography beginning at age 35 is particularly important because of the markedly high risk of breast cancer; annual abdominal and pelvic ultrasound from age 25, and Papanicolaou smear every other year.

Peutz-Jeghers Syndrome

The Peutz-Jeghers syndrome (PJS) carries a 39% lifetime risk of CRC and 93% cumulative risk for the development of any type of malignancy [57]. As mentioned above, PJS has been linked to germline mutation of the *LKB1* gene. The average age of PJS diagnosis is 23–26 years, while the mean age of any cancer diagnosis is approximately 40–50 years and the mean age of CRC diagnosis is 45.8 years [57].

PJS is characterized by the presence of numerous pigmented spots on the lips and the buccal mucosa and multiple gastrointestinal hamartomatous polyps. The lip pigmentation usually appears by age 2, but may fade with age. In contrast, buccal mucosal pigmentation usually persists into adulthood. Hamartomas occur most commonly in the small intestine (65–95%), but can also occur in the colon (60%), and the stomach (50%). Patients with PJS tend to develop recurrent bouts of small bowel intussusception, obstruction and bleeding, often requiring recurrent bowel resection.

Genetic testing for PJS is not yet commercially available. Because of the risk of complications related to polyps and the risk of malignancy, screening is recommended for asymptomatic first-degree relatives of patients with known PJS. None of the screening recommendations for this disease have been validated in clinical trials, but a reasonable set of recommendations includes for *first-degree relatives* upper gastrointestinal series and small bowel follow-through or an upper endoscopy and push enteroscopy at least once during the second decade of life is recommended, and for *affected individuals*, regular surveillance for polyps and their prophylactic excision is recommended once the diagnosis of PJS is established.

Upper endoscopy every other year beginning at age 10 or sooner if clinically indicated, with biopsy of all polyps to look for adenomatous change and complete removal of any polyp >1 cm has been proposed from a surveillance study [58]. A guideline issued by the British Society of Gastroenterology recommends upper gastrointestinal surveillance at 3-year intervals beginning at age 25 [59]. Colonoscopy every 3 years beginning at age 25 or sooner if clinically indicated, with biopsy of all polyps to look for adenomatous change and complete removal of any polyp >1 cm [59]. Push enteroscopy will no doubt be used increasingly to evaluate and remove polyps of the small bowel in PJS [58]. Surveillance with endoscopic ultrasound of the pancreas deserves study because of the exceptionally high risk of pancreatic cancer in PJS.

Juvenile Polyposis Coli and Familial Juvenile Polyposis

Juvenile polyposis coli (JPC) is characterized by the development of hamartomatous intestinal polyps and is associated with a 10–38% lifetime risk of CRC [60]. The median age of CRC is 34 years. The average age at which symptoms develop is 9.5 years. Patients also have a 15–21% lifetime risk of gastric and duodenal cancer [60]. The diagnosis of JPS is made when >3–10 juvenile colonic polyps are identified; or a juvenile polyp in the gastrointestinal tract outside of the colon is discovered; or any juvenile polyp is recognized in combination with family history of JPC. Germline mutations in the *SMAD4* and *BMPR1A* genes have been identified as the causative mutation in some affected families with familial juvenile polyposis (JPC) [35].

No consensus has been established for optimal screening of asymptomatic individuals at risk for FJP or for the

surveillance and clinical management of patients with known juvenile polyposis.

Asymptomatic first-degree relatives of patients with JPC are at risk for juvenile polyposis and CRC and should be screened for the disease. As an example, in a kindred of 118 family members, 4 died of colonic malignancy between the ages of 30 and 55, and another 5 had juvenile polyps throughout the colon that included large lobulated polyps containing adenomatous tissue [61]. One reasonable screening strategy includes annual fecal occult blood testing and flexible sigmoidoscopy or colonoscopy every 3–5 years beginning at age 12 and continuing until approximately age 40. Symptomatic patients should be evaluated regardless of age.

A guideline issued by the British Society of Gastroenterology recommends screening of at-risk individuals with colonoscopy every 1–2 years beginning at age 15–18 (or earlier in patients who presented with symptoms) [1, 59]. Screening intervals can be extended at age 35.

In contrast, documented gene carriers or affected cases should undergo surveillance until age 70. Colonoscopic polypectomy with regular surveillance is probably adequate therapy if only a small number of polyps are present [62]. Prophylactic surgery can be considered for those [59]: with a large number of polyps; with multiple polyps that have adenomatous change and high-grade dysplasia; in which polyps cannot be removed endoscopically; in which complications (such as bleeding) are not easily controlled, and where CRC is a feature of the family history.

Upper gastrointestinal surveillance has been recommended every 1–2 years beginning at age 25 by upper endoscopy/enteroscopy or UGI with SBFT [59].

MYH Polyposis Syndrome

The discovery that biallelic mutations in the base excision repair gene, *MYH*, as described above, resulted in an increased risk of colorectal adenomas and cancer, led to the first description of an autosomal recessive colon cancer syndrome [6]. In the European population, 22–29% of individuals with >10 adenomatous polyps carried biallelic germline mutations of the *MYH* gene [6]. The precise CRC risk has not yet been ascertained, but is likely to approach the 100% level appreciated in FAP. The mean ages of colon polyps and cancer diagnosis is 46 and 49.7 years, respectively [46]. Genetic testing is now available, and analysis is focused on exons 7 and 13 of the *MYH* gene. Two specific mutations in these exons (Y165C and G382D) account for 87% of all *MYH* mutations in the Northern

European population [46]. Patients who display a phenotype suggestive of AFAP but have tested negative for *APC* mutations can be offered testing for germline *MYH* mutations. It is recognized that the *MYH* syndrome has important implications for genetic counseling, as the cancer risk is limited primarily to siblings but not children. Thus far, there does not appear to be an increased risk of polyps or cancer in *MYH* heterozygote carriers.

Until official guidelines are established, it is reasonable to follow the recommendations for CRC screening in AFAP. The role of chemoprevention has not yet been studied.

Closing Remarks

There is a growing accumulation of data for the role of genetic factors in the development of CRC. A wide spectrum of genes can increase the risk of the disease when altered in the germline. The introduction of genetic testing has revolutionized the field of cancer risk assessment, and cancer prevention has become a realistic goal. The next major challenge is the identification of genetic alterations (mutations, polymorphism, imprinting loss due to epigenetic alterations) that may have low penetrance but high prevalence, as these are the genetic alterations that are likely to have an even greater impact on colon cancer risk in the population as a whole.

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