Clinical Diagnosis and Management of Hereditary Colorectal Cancer Syndromes

By H.F.A. Vasen

COLORECTAL CANCER IS a relatively common disease of Western populations, with a typical onset at approximately 70 years. The epidemiology of the disease suggests that environmental factors, probably dietary, are the most important influences for the high prevalence of this disease in certain countries. However, in a substantial proportion of cases, genetic factors also play a significant role. The most readily distinguished form of familial risk is familial adenomatous polyposis (FAP). This autosomal dominant disease is characterized by a large number of adenomatous polyps in the colon and is responsible for 1% of all cases of colorectal cancer.[1] Another more common dominant inherited colorectal cancer syndrome is hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome, hereditary colorectal-endometrial cancer syndrome), which is characterized by the development of colorectal and endometrial cancer at an early age.[2] The disease has no antecedent clinical phenotype until cancer develops and was a controversial entity until the biology was discovered in 1993. HNPCC accounts for 1% to 5% of all cases of colorectal cancer.[3] Approximately 10% to 15% of patients with colorectal cancer have a family history of colorectal cancer, and 5% of patients have early-onset (< 45 years) colorectal cancer.[4] In the etiology of colorectal cancer in these cases, several genetic factors are likely to play a partial role, as do dietary and other environmental influences. Other rare inherited syndromes with an increased susceptibility for colorectal cancer are the hamartomatous polyposis syndromes, including Peutz-Jeghers syndrome and juvenile polyposis.

MOLECULAR GENETICS

During the last decade, great progress has been made in molecular genetics. The genes responsible for most of the inherited forms of colorectal cancer have been identified, and DNA testing has been implemented in clinical practice on a large scale. Some advantages of DNA testing are that the hereditary nature of the disease can be confirmed and that, in families with an identified mutation, the carriers of a mutated gene can be differentiated from noncarriers. The latter can be reassured and refrain from further screening. Along with the development of techniques to identify mutated genes, new diagnostic tools such as microsatellite instability (MSI) analysis and immunohistochemistry have also been introduced; these may be helpful in the differential diagnosis of hereditary colorectal cancer.

SECONDARY PREVENTION

The risk of developing colorectal cancer in the subgroups of familial or hereditary colorectal cancer varies from 15% risk in relatives of patients with colorectal cancer diagnosed before age 45 years, through 20% for family members with two first-degree relatives with colorectal cancer, to approximately 70% to 95% in patients with familial adenomatous polyposis and HNPCC.[5-7] In view of these substantial cancer risks, the identification of people predisposed to colorectal cancer is important, as it makes it possible for us to target effective preventative measures on bringing about a reduction in the substantial cancer-related mortality. Recognition of hereditary forms of colorectal cancer is also important because the treatment of hereditary cases varies from that of nonhereditary cases. A detailed family history is the simplest and most cost-effective way to identify hereditary colorectal cancer. Because cancer is a common disease, the occurrence of colorectal cancer in several members of one family might be due to clustering by chance. Characteristics of hereditary forms of colorectal cancer that might be helpful in the differential diagnosis from nonhereditary cases are an unusual early age of onset, the occurrence of multiple colorectal cancers, the combined occurrence of colorectal cancer with endometrial cancer (in an individual or family), and the finding of multiple adenomatous or hamartomatous polyps in the colorectum.

CLASSIFICATION AND NOMENCLATURE

Two main groups of the hereditary form of colorectal cancer are commonly distinguished: polyposis types with multiple colorectal polyps and nonpolyposis types without multiple polyps. The term nonpolyposis denotes the presence of only a few polyps and was introduced to allow distinction from the polyposis types. Nonpolyposis colorectal cancer can be subclassified into HNPCC characterized by early-onset colorectal cancer and endometrial cancer and

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0732-183X/00/1821s-81s

Table 1. Classification of Hereditary Colorectal Cancer Syndromes

Hereditary Colorectal Cancer Syndromes	Gene Defect
Nonpolyposis syndromes	
HNPCC, Lynch syndrome, hereditary colorectal/endometrial cancer syndrome	*MSH2, MLH1, MSH6, PMS1, PMS2*
Familial clustering of late-onset colorectal cancer, inherited predisposition of colorectal neoplasms	*I1307KAPC, TGFbeta RII*
Polyposis syndromes	
FAP	*APC*
Hamartomatous syndromes	
Peutz-Jeghers syndrome	*STK11*
Juvenile polyposis	*SMAD4, PTEN*
Other polyposis syndromes	

families with clustering of colorectal cancer at an advanced age. Within the polyposis types, a further distinction is made between adenomatous, hamartomatous, hyperplastic, and polyposis with mixed pathology (Table 1).

Most of the hereditary colorectal cancer syndromes are associated with a wide spectrum of benign and malignant lesions. When the various hereditary cancer syndromes were discovered, several names were introduced to refer to specific combinations of cancers. For example, the combination of HNPCC with specific skin (sebaceous) tumors was designated as the Muir-Torre syndrome.[8] Since the identification of the genes responsible, it became clear that diseases referred to by separate names had the same genetic background. Therefore, in this review, which provides an update of the clinical features, diagnosis, prevention, and treatment of the various inherited forms of colorectal cancer, we avoid the use of such terminology.

HNPCC

HNPCC is transmitted as an autosomal dominant trait. It is associated with germline mutations in five genes with verified or putative DNA mismatch repair (MMR) function, ie, *MSH2*, *MLH1*, *PMS1*, *PMS2*, and *MSH6*.[9,10] The incidence of carriers of a mutated mismatch repair gene is approximately one in 1,000.[3]

The protein products of HNPCC genes are key players in the correction of mismatches that arise during DNA replication. Two different MutS-related heterodimeric complexes are responsible for mismatch recognition: MSH2-MSH3 and MSH2-MSH6. After mismatch binding, a heterodimeric complex of MutL-related proteins, MLH1-PMS2, is recruited, and this larger complex, together with numerous other proteins, accomplishes mismatch repair. The DNA mismatch repair system is also able to recognize lesions caused by exogenous mutagens and has been shown to participate in transcription-coupled repair.

Mismatch repair deficiency gives rise to MSI. Microsatellites are repetitive noncoding DNA sequences of unknown function found throughout the genome. However, microsatellites can also be found in the protein encoding regions of many genes. Loss of MMR function results in mutations in the coding regions of genes involved in tumor initiation and progression, eg, *APC*, *KRAS*, *p53*, and *TGFbRII*. Because more than 90% of colorectal cancers from patients with HNPCC express a high level of MSI (termed MSI-high tumors), MSI may aid in the diagnosis of this syndrome.[3] However, MSI is not specific to HNPCC, as it also occurs in 15% of apparently sporadic colorectal and other tumors.

Clinical Features

Predisposed individuals from HNPCC families have a high lifetime risk of developing colorectal cancer (70% to 85%), endometrial cancer (50%), and certain other cancers ($<$ 15%).[6,7] Colorectal cancer is often diagnosed at an early age (mean, 45 years), is multiple (with synchronous or metachronous colorectal cancer present in 35% of patients), and, in approximately two thirds of the cases, is located in the proximal part of the colon.[11] Several studies have shown a better prognosis of patients with HNPCC-related colorectal cancer compared with nonhereditary colorectal cancer. The adenomas that occur in HNPCC tend to develop at an early age, have villous components, and be more dysplastic than adenomas detected in the general population. Although multiple adenomas may be observed in HNPCC, florid polyposis is not a feature. Extracolonic cancers include cancer of the endometrium, renal pelvis/ureter, stomach, small bowel, ovary, brain, and hepatobiliary tract; sebaceous tumors are also included. No individual microscopic feature is specific to HNPCC, but particular groups of features are diagnostically useful.[12] Three groups based on site and microscopic criteria are recognized: (1) proximally located well- or moderately differentiated mucinous carcinomas, occasionally with tumor-infiltrating (intraepithelial) lymphocytes (TIL) in nonmucinous areas; (2) proximally located poorly differentiated adenocarcinomas, in some cases with TIL and a Crohn's-like lymphocytic reaction; and (3) any colorectal cancer showing TIL and/or a Crohn's-like lymphocytic reaction.[12]

Table 2. ICG-HNPCC Criteria

Classic ICG-HNPCC Criteria (Amsterdam criteria I)
There should be at least three relatives with colorectal cancer (CRC); all the following criteria should be present: • one should be a first-degree relative of the other two; • at least two successive generations should be affected; • at least one CRC should be diagnosed before age 50 years; • FAP should be excluded; • tumors should be verified by pathologic examination.
Revised ICG-HNPCC Criteria (Amsterdam criteria II)
There should be at least three relatives with an HNPCC-associated cancer (CRC; cancer of the endometrium, small bowel, ureter, or renal pelvis); all of the following criteria should be present: • one should be a first-degree relative of the other two; • at least two successive generations should be affected; • at least one should be diagnosed before age 50 years; • FAP should be excluded in the CRC case(s) (if any); • tumors should be verified by pathologic examination.

Table 3. ICG Definition of HNPCC (Lynch syndrome)

- Familial clustering of colorectal and/or endometrial cancer
- Associated cancers: cancer of the stomach, ovary, ureter/renal pelvis, brain, small bowel, hepatobiliary tract, and skin (sebaceous tumours)
- Development of cancer at an early age
- Development of multiple cancers
- Features of colorectal cancer: (1) predeliction for proximal colon location, (2) improved survival, (3) multiple colorectal cancer, (4) increased proportion of mucinous tumors, poorly differentiated tumors, and tumors with marked host-lymphocytic infiltration and lymphoid aggregation at the tumor margin
- Features of colorectal adenoma: (1) the numbers vary from one to a few, (2) increased proportion of adenomas with a villous growth pattern, (3) high degree of dysplasia, (4) probably rapid progression from adenoma to carcinoma
- High frequency of MSI
- Immunohistochemistry: loss of MLH1, MSH2, or MSH6 protein expression
- Germline mutation in mismatch repair genes (*MSH2, MLH1, MSH6, PMS1, PMS2*)

Diagnostic Criteria

The diagnosis of HNPCC is hampered by the absence of specific diagnostic features, such as the presence of hundreds of polyps in FAP, which is pathognomic for FAP. Therefore, in 1990, the International Collaborative Group (ICG) on HNPCC proposed a set of clinical diagnostic criteria (the Amsterdam criteria, Table 2) to provide uniformity in the clinical diagnosis of HNPCC.[13] Since then, many studies have provided evidence that HNPCC is also associated with several other extracolonic cancers. That was the reason to propose a new set of criteria (the Amsterdam II criteria) that include various extracolonic cancers[14] (Table 2). It should be noted that the proposed criteria are not intended for use as exclusion criteria: in other words, families initially suspected of HNPCC but not meeting the criteria should not be falsely reassured and excluded from genetic counselling, DNA testing, or surveillance. The ICG has recently proposed a definition of HNPCC (Table 3) that comprises all typical features of HNPCC.[14] The higher the number of these features observed in a given family, the higher the suspicion of HNPCC.

Molecular Genetic Studies

Mutation detection rate and predictive factors. Because of the heterogeneity of the mutation spectrum in DNA mismatch repair genes, screening for mutations is both time-consuming and expensive. To evaluate the clinical risk factors that best predict the presence of *MLH1* or *MSH2* mutations, we analyzed the *MSH2* and *MLH1* genes by density-gradient gel electrophoresis in a large series of kindreds (n = 187) featuring familial clustering of colorectal and other cancers.[15] Pathogenic mutations were identified in 26% of the families. Multivariate analysis showed that the age at diagnosis of colorectal cancer, fulfillment of the Amsterdam criteria, and presence of endometrial cancer in the kindred were independent predictors of germline mutations of *MSH2* or *MLH1*. Using these findings, we created a logistic model that can be used to estimate the probability of detecting a germline mutation on the basis of the clinical features of a kindred with familial clustering of colorectal and other HNPCC-related tumors. If the predicted probability is low (eg, $< 20\%$), one might consider performing MSI analysis of the DNA of the colon tumor, which gives an indication of the presence of a mutated mismatch repair gene. Recently, we extended the search for mutations in the *MMR* genes (including *MSH6*) in a series of 287 families. Mutations were found in 30% of the families: 13% harbored an *MSH2* mutation, 14% an *MLH1* mutation, and 3% an *MSH6* mutation. The mutation detection rates in families meeting the Amsterdam criteria I and those meeting the Amsterdam criteria II were the same (50%). However, the sensitivity of the Amsterdam criteria II was higher (88%) than that of the Amsterdam criteria I (77%).

The use of MSI as a marker of HNPCC. Recently, various studies evaluated the usefulness of MSI to select families for mutation analysis. Aaltonen et al[3] assessed the prevalence of HNPCC in Finland by screening a population-based series of 509 colorectal tumors for MSI and by performing mutation analysis of the patients with MSI positive tumors. Sixty-three tumors (12%) showed MSI, and 10 of these patients had a germline mutation in *MSH2* or *MLH1*. Nine of the mutation carriers had a first-degree relative with colorectal or endometrial cancer, seven were

younger than 50 years of age, and four had had colorectal or endometrial cancer previously. On the basis of these findings, the authors recommend MSI analysis in all patients with colorectal cancer who meet one or more of the following criteria: a family history of colorectal or endometrial cancer, an age at diagnosis of less than 50 years, and a history of multiple colorectal or endometrial cancer.[3] Two research groups reported the yield of MSI analysis and mutation analysis in a population-based series of patients with early-onset colorectal cancer.[16,17] They found that 50% to 60% of colorectal tumors in patients younger than 30 years were MSI-high, compared with only 12% in patients older than 35 years. Approximately one half of the patients with MSI-high tumors were shown to be carriers of a germline mutation. In conclusion, these studies indicate that MSI is a cost-effective way to select families suspected of HNPCC for genetic testing.

The role of immunohistochemistry. There is some evidence that a low percentage (15%) of tumors associated with *MLH1* or *MSH2* mutations are MSI-low or MSI-stable.[16] Moreover, Dutch investigators reported *MSH6* mutations in four of 18 families with suspected HNPCC with MSI-low or MSI-stable tumors.[18] We recently identified 10 families with an *MSH6* mutation and performed MSI analysis in 16 tumors (of various types) diagnosed in these families.[19] Only nine of the 16 tumors showed an MSI-high phenotype (although instability was found at *MSH6* in all *MSH6*-related tumors). These findings suggest that an MSI-stable or MSI-low phenotype cannot be considered as an exclusion criterion for mutation analysis (especially of *MSH6*). Another recently introduced rapid and inexpensive technique to identify mismatch repair deficiency is immunohistochemistry. Previous studies have shown that loss of protein expression detected by this technique correlates well with an *MSH2* and *MSH6* gene defect.[20-22] However, its sensitivity to *MLH1* mutations is rather low.[22] The best approach is therefore to combine MSI analysis and immunohistochemistry in families suspected of HNPCC.

Presymptomatic Diagnosis

Detailed information and good psychosocial guidance are prerequisites for presymptomatic diagnosis based on DNA testing. The recommended protocol for genetic testing involves three sessions. The issues discussed during the first session include the reasons for testing, the clinical features of the hereditary cancer syndrome, the mode of inheritance, the consequences of the test results, the options for treatment in the event of a positive result, and the DNA testing procedure. In the second session, blood samples are taken. The results of the DNA test are disclosed during the third session.

Recent studies[23,24] showed that the uptake of genetic testing in families with HNPCC varied widely, from 43% in the United States to 75% in Finland. Reasons for the differences might be differences in the study setting. The Finnish family members were counselled individually and allowed a period of reflection, whereas in the United States, the relatives were informed at group family information sessions.[24] Other reasons might be fundamental differences between the health care and social security systems in the United States and Europe. In Europe, where thus far private health insurance has played a minor role, a predictive test for a treatable disease might be more readily accepted.

Phenotype/Genotype Correlation

Knowledge about a possible difference in risk between carriers of the various mutations might be important to a decision on surveillance programs. Only a few studies have been performed on the cancer risk estimated in proven mutation carriers. The studies indicate that there was no difference in risk of colorectal and endometrial cancer between *MSH2* and *MLH1* carriers.[6] However, Danish investigators have reported that the risk of endometrial cancer is significantly lower in families with a specific *MLH1* mutation,[25] and a recent study by our group suggested that families with *MSH6* mutations seemed to have a higher risk of developing endometrial cancer than families with *MSH2* and *MLH1* mutations.[19] Moreover, studies have shown that colorectal cancer associated with *MSH6* mutations develop at a more advanced age than in *MSH2* and *MLH1* carriers. There is also evidence for intragenic associations. At the second joint meeting of the International Collaborative Group on HNPCC and the Leeds Castle Polyposis Group in Lorne, Australia, in 1999, Wijnen reported that families with mutations in the first five exons of *MSH2* have a lower risk of developing endometrial cancer than families with mutations elsewhere. Regarding the less common extracolonic cancers, one study suggested that patients with *MSH2* mutations have a higher relative risk of developing extracolonic cancers than patients with *MLH1* mutations.[6]

The majority of kindreds selected for mutation analysis have been selected specifically because of multiple affected cases of colorectal cancer; therefore, lifetime penetrance of these mutations is correspondingly high (80%). Population-based studies are needed to confirm the risks of developing colorectal cancer that have been reported thus far. To date, the only study that used a population-based approach reported the same penetrance of colorectal cancer for men (70%) as in families fulfilling the Amsterdam criteria; the risk for women was significantly lower (30%).[26]

Periodic Examination

A surveillance program for carriers of a mutated gene has been recommended by the ICG and other experts groups. The

Table 4. Surveillance Protocol in Hereditary (familial) Colorectal Cancer Syndromes

Disorder	Lower Age Limit (years)	Examination	Interval (years)
HNPCC	20-25	Colonoscopy	2
	30-35	Gynecologic examination, transvaginal ultrasound	1-2
	30-35	Gastroduodenoscopy*	1-2
	30-35	Abdominal ultrasound, cytology urine†	1-2
Familial clustering of common CRC, relatives with one first-degree relative with CRC < 45 years or 2 relatives with CRC at any age	45-50	Colonoscopy	5
FAP	10-12	Sigmoidoscopy	2
	30	Duodenoscopy	1-5§
Atypical FAP	15-20‡	Colonoscopy	2
Peutz-Jeghers syndrome	15-20	Gastroduodenoscopy, small bowel follow-through	2-5
	25-30	Colonoscopy, mammography, gynecologic examination	1-2
Juvenile polyposis	25 (?)	Colonoscopy	3-5

*If gastric cancer runs in the family.
†If urinary tract cancer runs in the family.
‡Depending on the age of onset of FAP in the family.
§Depending on the severity of the duodenal polyposis.

program of colorectal surveillance (ICG) includes biennial colonoscopy starting from age 20 to 25 years. There is ample evidence that endoscopic surveillance leads to the detection of colorectal tumors at an earlier stage.[27] Moreover, a study in Finland indicated that surveillance of 22 families with a follow-up duration of 10 years led to a 62% reduction of colorectal cancer[28]; a recent update of this study also reported a significant reduction in the rate of death due to colorectal cancer after a 15-year follow-up period.[29] A Dutch study showed a surprisingly high number of interval cancers, defined as cancers detected after a recent negative colonoscopy.[30] To date, 27 cases have been identified in approximately 140 families. The substantial risk of developing colorectal cancer in mutation carriers and the observation that surveillance is not completely safe are arguments for considering prophylactic colectomy (for example, in patients with adenomas with advanced pathology).

Cost-effectiveness analysis of colorectal screening of HNPCC gene carriers revealed that surveillance of carriers of a mutated *MMR* gene would lead to an increase in life expectancy of approximately 7 years. In addition, the costs of surveillance were much less than the costs of the no-surveillance strategy.[31] Another study that examined the life expectancy benefit from endoscopic surveillance and prophylactic surgery showed an increase in life expectancy ranging from 13.5 years for surveillance and 15.6 years for prophylactic surgery.[32] Other surveillance protocols recommended for the early detection of extracolonic cancers associated with HNPCC are listed in Table 4. The effectiveness of these protocols is not yet known.

Treatment

Total colectomy with an ileorectal anastomosis is recommended for patients with colorectal cancer associated with HNPCC. The rationale for this advice is the high incidence of metachronous cancers (25% to 40%) in patients who have undergone segmental colectomy.

In experimental systems, MMR-deficient cells seemed to be tolerant to several chemotherapeutic agents, such as fluorouracil, procarbazine, temozolomide, busulfan, cisplatin, carboplatin, 6-thioguanine, etoposide, and doxorubicin. These drugs are therefore expected to be less effective on MMR-deficient tumors in humans. The loss of MMR and the consequence of drug resistance seems to relate directly to the impairment of the ability of the cell to detect DNA damage and thereby to activate apoptosis.[33,34]

FAMILIAL CLUSTERING OF LATE-ONSET COLORECTAL NEOPLASMS

In 1985, Burt et al[35] reported a large family with many cases of colorectal cancer but without a recognizable Mendelian inheritance pattern. The age distribution and tumor localization was similar to those found in the general population. When patients with colorectal adenomas (detected after screening of all first-degree relatives) were considered as having the same disorder as the patients with colorectal cancer, there was evidence for an autosomal dominant inheritance pattern. These findings were later confirmed in a second study that included an additional 33 families.[36]

In 1994, we described eight families that met each of the Amsterdam criteria except the age criterion.[37] All colorectal

cancer cases were diagnosed at ages greater than 50 years. These families were characterized by a preponderance of distal tumors, a low incidence of multiple primary colon cancers, and a high incidence of adenomas associated with colorectal cancer. Moreover, other cancers frequently encountered in HNPCC, such as endometrial cancer, did not occur in these families. So far, mutation analysis in 20 such families has not revealed any mutation in the *MMR* genes.

Jass et al[38] reported eight similar families with a relatively late onset of colorectal cancer (mean age, 57 years). As in the Dutch study, the majority of cancers developed in the left colon and rectum (80%), only one subject had multiple colorectal cancers, and the at-risk relatives had more adenomas than at-risk relatives in genuine HNPCC. The overall tumor burden in the eight families included 38 colorectal cancers and one ovarian cancer but no uterine, gastric, pancreatic, small intestinal, or upper urinary tract cancers. Analysis of the colorectal tumors for MSI was negative. The data provided by these studies suggest that there may be autosomal dominantly inherited colorectal cancer syndromes caused by genes other than the *MMR* genes and *APC* gene.

Recently, Laken et al[39] reported an unusual mutation in the *APC* (adenomatous polyposis coli) gene (I1307K) responsible for familial clustering of late-onset colorectal cancer among Ashkenazi Jews. The mutation has been found in 6% of Jews with an Ashkenazi background, in 10% of Ashkenazim affected with colorectal cancer, and 28% of Ashkenazim with colorectal cancer and a family history of colorectal cancer. To date, it has not been found in non-Jewish populations. Lu et al[40] reported the identification of a germline mutation in the transforming growth factor-beta type II receptor gene in a family with late-onset colorectal cancer without MSI. Similarly mutated genes might also be responsible for a proportion of the above-mentioned families. The surveillance program recommended for such families include colonoscopy once every 3 to 5 years starting from age 45 to 50 years (Table 4).

FAP

FAP is an autosomal dominant disease caused by inactivating mutations at the *APC* gene. The disease is characterized by numerous adenomas in the colorectum and various other manifestations.[1] The *APC* gene plays a role in cell adhesion, differentiation, apoptosis, regulation of the cell cycle, and transmission of signals to the nucleus. The incidence of FAP is approximately one per 8,000 of the population.[41]

Clinical Features

Most patients with FAP develop hundreds to thousands of colorectal adenomas during their second and third decades of life. Without surgical intervention, the patients almost inevitably develop colorectal carcinoma by the age of 45 years. The first symptoms occur between the ages of 25 and 35 years. By the time the patients present with symptoms, colorectal cancer is present in approximately one half of the cases. The majority of the patients also develop polyps in the upper gastrointestinal tract, including fundic gland polyposis (40%), gastric adenomas (5% to 10%), or adenomas in the duodenum (50% to 90%).[42] In contrast with the duodenal adenomas, the gastric polyps do not have malignant potential. The risk of developing duodenal cancer is substantially lower ($<$ 5%) than the risk of colorectal cancer.[43] Other extraintestinal features associated with FAP include desmoid tumors (10% to 15%), osteoma (75% to 90%), dental abnormalities (17%), epidermoid cysts (50%), and retinal lesions (congenital retinal pigmented epithelium [CHRPE]; 75%). As is typical with hereditary cancer syndromes, there is an increased risk for other malignancies, including thyroid cancer, hepatoblastoma, and brain tumors. A small proportion of families ($<$ 10%) have an atypical form of polyposis, which is characterized by the development of a smaller number ($<$ 100) of polyps, with colorectal cancer occurring at a more advanced age. This variant is termed attenuated or atypical familial adenomatous polyposis.

Clinical and Molecular Diagnosis

A clinical diagnosis of polyposis can be made when more than 100 adenomas are identified in the colorectum.[1] The diagnosis can be confirmed by mutation analysis. A pathogenic *APC* mutation can be identified in approximately 70% to 80% of the families. If the mutation has been identified in the family or linkage analysis has given high lod scores, then children and siblings of FAP-affected patients should be offered presymptomatic DNA testing from age 12.

Several studies have reported specific genotype-phenotype correlations. Families with FAP caused by mutations located at the extreme ends of the gene and at exon 9 are associated with a mild phenotype of the disease.[44] On the other hand, families with FAP caused by mutations between codons 1250 and 1464 often show a severe colorectal phenotype presenting with profuse polyposis.[45] In addition, several studies indicated that CHRPE is associated with mutations located between 541 and 1445[46] and desmoid tumors with mutations between 1309 and 1578.[47] Finally, multiple extracolonic lesions are more frequently observed in families with mutations between 1445 and 1578.[48]

The established geno/phenotypic correlations might have implications for clinical practice. For example, the finding of CHPRE in a family might direct mutation analysis to the exons associated with these lesions. Moreover, the geno/

phenotype correlation regarding desmoids might have implication for prophylactic surgery.[49] Because desmoids often arise as a consequence of tissue trauma, a delay of surgery should be considered in patients at high risk of developing desmoids, at least in those with smaller number of polyps and expected later onset of disease. Finally, the use of molecular genetic testing has been suggested as an aid in decision making with respect to the type of surgery.[50,51] It should be noted that the correlations are not 100%. Phenotypic variation might be observed even within families carrying identical mutations, possibly as a consequence of the effect of modifier genes or environmental influences

Periodic Examination

If DNA testing proves the carrier status of the at-risk family member or the results of DNA testing are uninformative (ie, mutation is not identified in the family), then it is recommended that regular sigmoidoscopy start from the age of 12 years and continue at 2-year intervals.[52,53] Total colonoscopy should be considered in families with an atypical form of polyposis, as adenomas may only be located in the proximal part of the colon. In such families, the endoscopic examinations may be started at a later age, eg, from age 18 to 20 years (Table 4).

The screening protocol of the duodenum should start by the age of 30 years. There would be no clinical benefit in starting at an earlier age, as reports of duodenal cancer before this age are extremely rare. Depending on the findings, the recommended interval between examinations is 1 to 5 years. The Spigelman classification might be used to follow the course of the disease.[54]

Treatment

Colonic polyposis. Until a decade ago, colectomy with an ileorectal anastomosis (IRA) was the most frequently applied surgical procedure for the treatment of FAP. This surgical option is attractive because it is a relatively simple procedure with good functional results. Major disadvantages, however, are the need for continuous endoscopic follow-up and the remaining risk of rectal cancer that increases over time.[50,55] In addition, a secondary proctectomy is needed in approximately one half of the cases because of uncontrollable polyposis.[50] These disadvantages might be the reason that an increasing number of patients are treated with the alternative surgical option, ie, a proctocolectomy and ileal-pouch-anal anastomosis (IPAA). However, this surgical procedure also has various disadvantages, including (in the worst case) a risk of severe postoperative complications necessitating removal of the pouch and construction of an ileostomy ($< 5\%$). Another disadvantage is the worse functional outcome compared with that of IRA, although the quality of life after IRA and IPAA seemed to be the same.[56,57]

An IPAA seems the procedure of first choice in patients with a large number of rectal adenomas or rectal cancer and in patients who will not comply with follow-up examinations after IRA. However, with regard to patients with a limited number of rectal adenomas, there is no agreement about the best surgical option. Although the risk of developing rectal cancer after IRA is important when deciding between the two procedures, the risk of death from rectal cancer is even more crucial. A recent study involving more than 600 FAP patients with an IRA showed that the risk of dying from rectal cancer after IRA was 12.5% by 65 years. Noncompliance was not the explanation for this finding, as most patients had their endoscopic examination within 1 year of the last screening examination. On the basis of these findings, an IPAA seemed to be the most attractive option for most patients. Only patients with a few rectal polyps from families with a similar mild phenotype might be selected for IRA. The results of molecular genetic testing might be used to identify such patients.

Several studies have shown that treatment of FAP patients with nonsteroidal anti-inflammatory drugs leads to reduction in the number and size of the colonic adenomas.[58] However, the fact that usually not all polyps disappear and the fact that rectal cancer has been reported after prolonged sulindac chemoprevention make clear that this treatment does not replace the surgical management of colonic polyposis.

Duodenal polyposis. The treatment of duodenal adenomas is limited by a number of factors. Because of the presence of large number of polyps or by the usual sessile nature of the polyps, endoscopic snaring may be impossible. Endoscopic electrocoagulation, if repeated very often, will lead to considerable scarring, which might cause strictures in the periampullary area. Laser ablation of polyps via the endoscope can be used but carries the risk of duodenal perforation. Polyp removal by (surgical) duodenotomy, consisting of submucosal infiltration and local excision of all polyps, is not recommended, as a British study has shown recurrence in all patients treated by this technique within a short time. To date, chemoprevention (nonsteroidal anti-inflammatory drugs) has not be shown to be effective in the treatment of duodenal polyposis.[59] In conclusion, the only curative treatment seems to be a proximal pancreaticoduodenostomy. Such an operation has considerable potential morbidity and mortality; this makes the indication and timing of surgery extremely difficult. Criteria of size,

rapid growth, polyp induration, or consistently severe dysplasia or villous change suggest that intervention is necessary. Surgery may be considered in patients who have consistently Spigelman stage IV duodenal adenomatosis.

Abdominal desmoids. The treatment of desmoids is based largely on anecdotal reports and on studies of small series of patients.[60] The extremely variable natural history hampers the evaluation of a specific treatment. There is general agreement that surgery should be avoided for mesenteric desmoids because of the risk of accelerated growth and the high risk of recurrence. Most investigators recommend sulindac as the initial treatment. If growth continues, tamoxifen or toremifene may be added. If the desmoid is still growing, then chemotherapy might be considered.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by hamartomatous polyps in the small bowel and melanin pigmentation of the skin and mucous membranes.[61] In approximately 40% of the families, the disease is due to a new mutation. The syndrome occurs in approximately one in 8,300 to 29,000 live births. Recently, two groups simultaneously identified the gene responsible for PJS. The gene codes for a new serine threonine kinase and is named *STK11*.[62,63]

Clinical Features

The key clinical feature is the hamartomatous polyposis of the gastrointestinal tract. PJS polyps occur throughout the whole digestive tract but have a predisposition for the small bowel. The melanin pigmentation of the skin and mucous membrane is the external hallmark of the syndrome. The pigmentation starts to appear in infancy and reaches a maximum in puberty. Over time, the pigmentation on the skin and lips tends to fade away, but the spots on the buccal mucosa are usually permanent.

Clinical symptoms are most prominent in adolescence and young adulthood. Intestinal obstruction caused by intussusception of the polyps is the most common symptom in PJS (in 86% of cases), followed by gastrointestinal blood loss (in 81%). A typical presentation in children is anal extrusion of polyps with rectal prolapse.

PJS is associated with an increased risk of developing cancer. The risk of developing cancer has been estimated to be nine to 18 times greater than that expected in the general population. The most frequently occurring cancers are cancer of the colon and breast (Table 5). The age at diagnosis of these cancers is relatively young, which is consistent with an inherited predisposition. Uncommon neoplasms may also be observed in PJS, including sex-cord tumors with annular tubules, Sertoli cell tumors, and adenoma malignum of the cervix. Studies on the natural history of the disease have shown that the survival of affected family members was reduced equally by intestinal obstruction and by the development of malignant disease.[64]

Table 5. Most Frequent Tumors and Mean Ages at Diagnosis Observed in 240 Patients With Peutz-Jeghers syndrome[64-70]

			Age at Diagnosis (years)	
Gastrointestinal	No. of Patients	%	Mean	Range
Colon	18	7.5	44.5	26-80
Stomach	9	3.7	44.7	30-60
Pancreas	5	2	48	34-60
Small bowel	5	2	36.2	26-57
Extraintestinal				
Breast	13	5	44.1	27-74
Lung	8	3.3	48.5	33-70
Ovary	6	2.5	35.8	19-60
Cervix	4	1.6	40.5	
Uterus	3	1.2	?	
Other	16		?	

Surveillance and Management

The follow-up of affected patients is recommended for two reasons. Several studies have reported that a large proportion of affected patients need numerous repeat laparotomies for symptomatic polyps. The usual indications are bleeding, intussusception, and obstruction. A combined endoscopic and surgical approach has been advocated for the prophylactic removal of any polyps demonstrated in the small bowel radiologically. During intraoperative endoscopy, the whole small bowel can be inspected and any polyps removed. Such an approach may reduce the number of laparotomies necessitated by symptomatic polyps. The surveillance protocol usually recommended includes gastroduodenoscopy and small bowel follow-through every 2 to 5 years from age 15 to 20 years. From a more advanced age (eg, 20 years), colonoscopy might be added to this protocol.

The second reason for follow-up is the increased risk of developing cancer. Unfortunately, a wide spectrum of cancers has been observed in PJS, which makes decisions on a surveillance program difficult. The most frequent cancers are colorectal, breast, and gynecologic cancer (Table 5). Therefore, regular mammography and gynecologic examination might be considered (Table 4). On the basis of the early onset of these cancers, the program should start from age 30 to 35 years. The incidence of the other cancers is probably too low to justify additional screening measures.

JUVENILE POLYPOSIS

Juvenile polyposis (JP) is an uncommon autosomal dominant inherited condition characterized by the development

of multiple (usually 50 to 200) juvenile polyps in the colorectum and, in some patients, also in the stomach and small bowel.[71] Juvenile polyps have a smooth spherical surface and are composed of cystic and irregularly branched crypts embedded within abundant lamina propria that is lacking smooth muscle.[72] The disease should be differentiated from JP that occurs in infancy and presents with diarrhea, hemorrhages, intussusception, and protein-losing enteropathy. The frequency of the disease is yet unknown. Recently, two genes have been shown to be involved in JP, ie, *SMAD4*[73] and *PTEN*.[74]

Clinical Features and Surveillance

The majority of patients will present in their first or second decade with rectal bleeding, anemia, or rectal prolapse. The following diagnostic criteria have been suggested for JP: (1) more than 5 to 10 colonic juvenile polyps, (2) JP throughout the gastrointestinal tract, and (3) any number of JP in an individual with a family history of JP.[72] Epithelial dysplasia occurs relatively frequently in JP. Several studies have shown that affected patients have an increased risk of developing colorectal cancer.[72,75-77] Among 87 patients known at the St Mark's Polyposis Registry were 18 male patients with colorectal cancer, diagnosed at an average age of 34 years (range, 15 to 59 years). Using survival analysis, it was estimated that the risk of developing colorectal cancer was 68% by age 60 years. This underlies the recommendation for endoscopic surveillance of the colorectum, starting, for example, from age 25 years (Table 4). The interval between the examinations depends on the number of polyps and the pathologic findings. Juvenile polyps may also be found in various genetic syndromes such as Cowden's syndrome, Gorlin's syndrome, Cronkhite-Canada syndrome, and the basal cell nevus syndrome.

OTHER POLYPOSIS SYNDROMES

In the majority of patients with polyposis, a clear-cut pathologic distinction can be made between FAP, JP, or PJS. There are some very rare cases, however, for which such distinctions cannot be made. Bizarre mixtures of different sorts of polyps (eg, hyperplastic, adenomatous, juvenile, and Peutz-Jeghers type) have been reported in the same patient. Whitelaw et al[78] recently reported a family with apparently dominant inherited mixed polyposis syndrome. The histology of 104 polyps in this family comprised adenomatous, juvenile, Peutz-Jeghers, and hyperplastic polyps. The characteristic lesion is the juvenile polyp with mixed features, including both adenomatous and hyperplastic. The pedigree also included 13 cases of colorectal cancer diagnosed at a mean age of 47 years. Although a few years ago linkage of the disease in this family was reported to a putative gene on the long arm of chromosome 6, the gene defect has not yet been identified.

Cases with large numbers of hyperplastic polyps have also been observed; this condition was termed hyperplastic polyposis. Williams et al[79] reported seven isolated cases that grossly seemed to represent FAP, but histologic examination showed hyperplastic rather than adenomatous polyposis. Torlakovic and Snover[80] described six patients—all of whom had originally been diagnosed as having hyperplastic polyposis—with multiple serrated adenomatous polyps; four of the patients also had colon cancer. Features that are helpful to distinguish serrated adenomas from classical hyperplastic polyposis are a larger polyp size (usually > 1 cm) and the presence of features of dysplasia in the serrated adenomas.

In conclusion, colorectal cancer is a heterogeneous disease that is reflected by different clinical, histopathologic, and molecular genetic features. All of these features should be considered carefully when assessing families with clustering of colorectal cancer. The classical features of FAP and HNPCC are relatively easy to diagnose. However, the atypical forms of FAP, which are characterized by fewer adenomas and a delayed age of onset of colorectal cancer, may be misdiagnosed as HNPCC. In addition, an increasing number of atypical HNPCC families (often *MSH6*-associated) are being identified that differ from the classical HNPCC families by incomplete penetrance and a late onset of colorectal cancer. Such families may be confused with families with clustering of late-onset colorectal cancer. To provide the best optimal care for these families, a multidisciplinary approach is required. To interpret appropriately the results of MSI, immunohistochemistry, and genetic analysis, and to discuss the clinical implications of these results in terms of the surveillance program, specialists such as molecular geneticists, clinical geneticists, psychologists, pathologists, gastroenterologists, and surgeons are all needed. To create an appropriate environment for molecular genetic testing, multidisciplinary collaboration is also important.

To promote maximal compliance with the recommended surveillance protocol strategies, careful education and counseling about all details of the disease are essential. Experience has shown that long-term surveillance of high-risk families cannot be adequately guaranteed by individual specialists, as this can lead to considerable morbidity and mortality. In several countries, these problems have inspired specialists to establish national and regional registries that monitor the continuity of the surveillance program by periodic assessment of the screening results. The registries also ensure that the same screening protocol is offered to the

various branches of large families that are followed-up by different specialists. The success of family-based registry-assisted surveillance is best illustrated by the decrease in the incidence of colorectal cancer in screening-detected cases of FAP compared with that in symptomatic cases.[81] Hereditary cancer registries also have a role in the assessment of the results of long-term surveillance. This is important, as the value of most suggested protocols is as yet unknown.

REFERENCES

1. Bussey HJ: Familial Polyposis Coli. Baltimore, MD, The Johns Hopkins University Press, 1975
2. Lynch HT, Smyrk TC, Watson P, et al: Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: An updated review. Gastroenterology 104:1535-1549, 1993
3. Aaltonen LA, Salovaara R, Kristo P, et al: Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 338:1481-1487, 1998
4. Slattery ML, Kerber RA: Family history of cancer and colon cancer risk: The Utah Population Database [published erratum appears in J Natl Cancer Inst 86:1802, 1994]. J Natl Cancer Inst 86:1618-1626, 1994
5. St John J, McDermott FT, Hopper JL, et al: Cancer risk in relatives of patients with common colorectal cancer. Ann Intern Med 118:785-790, 1993
6. Vasen HF, Wijnen JT, Menko FH, et al: Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis [published erratum appears in Gastroenterology 111:1402, 1996]. Gastroenterology 110:1020-1027, 1996
7. Aarnio M, Sankila R, Pukkala E, et al: Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 81:214-218, 1999
8. Cohen PR, Kohn SR, Kurzrock R: Association of sebaceous gland tumors and internal malignancy: The Muir-Torre syndrome. Am J Med 90:606-613, 1991
9. Peltomaki P, Vasen HF: Mutations predisposing to hereditary nonpolyposis colorectal cancer: Database and results of a collaborative study—The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer. Gastroenterology 113:1146-1158, 1997
10. Miyaki M, Konishi M, Tanaka K, et al: Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. Nat Genet 17:271-272, 1997
11. Lynch HT, de la Chapelle A: Genetic susceptibility to non-polyposis colorectal cancer. J Med Genet 36:801-818, 1999
12. Shashidharan M, Smyrk T, Lin KM, et al: Histologic comparison of hereditary nonpolyposis colorectal cancer associated with MSH2 and MLH1 and colorectal cancer from the general population. Dis Colon Rectum 42:722-726, 1999
13. Vasen HF, Mecklin JP, Khan PM, et al: The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 34:424-425, 1991
14. Vasen HF, Watson P, Mecklin JP, et al: New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 116:1453-1456, 1999
15. Wijnen JT, Vasen HF, Khan PM, et al: Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. N Engl J Med 339:511-518, 1998
16. Farrington SM, Lin-Goerke J, Ling J, et al: Systematic analysis of hMSH2 and hMLH1 in young colon cancer patients and controls. Am J Hum Genet 63:749-759, 1998
17. Liu B, Farrington SM, Petersen GM, et al: Genetic instability occurs in the majority of young patients with colorectal cancer. Nat Med 1:348-352, 1995
18. Wu Y, Berends MJ, Mensink RG, et al: Association of hereditary nonpolyposis colorectal cancer-related tumors displaying low microsatellite instability with MSH6 germline mutations. Am J Hum Genet 65:1291-1298, 1999
19. Wijnen J, de Leeuw W, Vasen H, et al: Familial endometrial cancer in female carriers of MSH6 germline mutations. Nat Genet 23:142-144, 1999
20. Thibodeau SN, French AJ, Roche PC, et al: Altered expression of hMSH2 and hMLH1 in tumors with microsatellite instability and genetic alterations in mismatch repair genes. Cancer Res 56:4836-4840, 1996
21. Dietmaier W, Wallinger S, Bocker T, et al: Diagnostic microsatellite instability: definition and correlation with mismatch repair protein expression. Cancer Res 57:4749-4756, 1997
22. de Leeuw W, Diersen JW, Vasen HF, et al: Prediction of a mismatch repair defect by microsatellite instability and immunohistochemical analysis in endometrial tumours from HNPCC patients. J Pathol (in press)
23. Lerman C, Hughes C, Trock BJ, et al: Genetic testing in families with hereditary nonpolyposis colon cancer. JAMA 281:1618-1622, 1999
24. Aktan-Collan K, Mecklin JP, Jarvinen H, et al: Predictive genetic testing for hereditary nonpolyposis colorectal cancer: Uptake and long-term satisfaction. Int J Cancer 89:44-50, 2000
25. Jager AC, Bisgaard ML, Myrhoj T, et al: Reduced frequency of extracolonic cancers in hereditary nonpolyposis colorectal cancer families with monoallelic hMLH1 expression. Am J Hum Genet 61:129-138, 1997
26. Dunlop MG, Farrington SM, Carothers AD, et al: Cancer risk associated with germline DNA mismatch repair gene mutations. Hum Mol Genet 6:105-110, 1997
27. Vasen HF, den Hartog J, Menko FH, et al: Screening for hereditary non-polyposis colorectal cancer: A study of 22 kindreds in the Netherlands. Am J Med 86:278-281, 1989
28. Jarvinen HJ, Mecklin JP, Sistonen P: Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 108:1405-1411, 1995
29. Jarvinen HJ, Aarnio M, Mustonen H, et al: Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 118:829-834, 2000
30. Vasen HF, Nagengast FM, Khan PM: Interval cancers in hereditary non-polyposis colorectal cancer (Lynch syndrome). Lancet 345:1183-1184, 1995
31. Vasen HF, van Ballegooijen M, Buskens E, et al: A cost-effectiveness analysis of colorectal screening of hereditary nonpolyposis colorectal carcinoma gene carriers. Cancer 82:1632-1637, 1998
32. Syngal S, Weeks JC, Schrag D, et al: Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. Ann Intern Med 129:787-796, 1998
33. Fink D, Aebi S, Howell SB: The role of DNA mismatch repair in drug resistance. Clin Cancer Res 4:1-6, 1998

34. Carethers JM, Chauhan DP, Fink D, et al: Mismatch repair proficiency and in vitro response to 5-fluorouracil. Gastroenterology 117:123-131, 1999

35. Burt RW, Bishop DT, Cannon LA, et al: Dominant inheritance of adenomatous colonic polyps and colorectal cancer. N Engl J Med 312:1540-1544, 1985

36. Cannon-Albright LA, Skolnick MH, Bishop DT, et al: Common inheritance of susceptibility to colonic adenomatous polyps and associated colorectal cancers. N Engl J Med 319:533-537, 1988

37. Vasen HF, Taal BG, Griffioen G, et al: Clinical heterogeneity of familial colorectal cancer and its influence on screening protocols. Gut 35:1262-1266, 1994

38. Jass JR, Pokos V, Arnold JL, et al: Colorectal neoplasms detected colonoscopically in at-risk members of colorectal cancer families stratified by the demonstration of DNA microsatellite instability. J Mol Med 74:547-551, 1996

39. Laken SJ, Petersen GM, Gruber SB, et al: Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. Nat Genet 17:79-83, 1997

40. Lu SL, Kawabata M, Imamura T, et al: HNPCC associated with germline mutation in the TGF-beta type II receptor gene. Nat Genet 19:17-18, 1998

41. Bisgaard ML, Fenger K, Bulow S, et al: Familial adenomatous polyposis (FAP): Frequency, penetrance, and mutation rate. Hum Mutat 3:121-125, 1994

42. Bulow S, Alm T, Fausa O, et al: Duodenal adenomatosis in familial adenomatous polyposis: DAF Project Group. Int J Colorectal Dis 10:43-46, 1995

43. Vasen HF, Bulow S, Myrhoj T, et al: Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis. Gut 40:716-719, 1997

44. Soravia C, Berk T, Madlensky L, et al: Genotype-phenotype correlations in attenuated adenomatous polyposis coli. Am J Hum Genet 62:1290-1301, 1998

45. Nagase H, Miyoshi Y, Horii A, et al: Correlation between the location of germ-line mutations in the APC gene and the number of colorectal polyps in familial adenomatous polyposis patients. Cancer Res 52:4055-4057, 1992

46. Olschwang S, Tiret A, Laurent-Puig P, et al: Restriction of ocular fundus lesions to a specific subgroup of APC mutations in adenomatous polyposis coli patients. Cell 75:959-968, 1993

47. Caspari R, Olschwang S, Friedl W, et al: Familial adenomatous polyposis: Desmoid tumours and lack of ophthalmic lesions (CHRPE) associated with APC mutations beyond codon 1444. Hum Mol Genet 4:337-340, 1995

48. Giardiello FM, Brensinger JD, Luce MC, et al: Phenotypic expression of disease in families that have mutations in the 5′ region of the adenomatous polyposis coli gene. Ann Intern Med 126:514-519, 1997

49. Gebert JF, Dupon C, Kadmon M, et al: Combined molecular and clinical approaches for the identification of families with familial adenomatous polyposis coli. Ann Surg 229:350-361, 1999

50. Vasen HF, van der Luijt RB, Slors JF, et al: Molecular genetic tests as a guide to surgical management of familial adenomatous polyposis. Lancet 348:433-435, 1996

51. Wu JS, Paul P, McGannon EA, et al: APC genotype, polyp number, and surgical options in familial adenomatous polyposis. Ann Surg 227:57-62, 1998

52. Vasen HF: When should endoscopic screening in familial adenomatous polyposis be started? Gastroenterology 118:808-809, 2000

53. Vasen HF, Bulow S: Guidelines for the surveillance and management of familial adenomatous polyposis (FAP): A world wide survey among 41 registries—The Leeds Castle Polyposis Group. Colorectal Dis 1:214-221, 1999

54. Spigelman AD, Williams CB, Talbot IC, et al: Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 2:783-785, 1989

55. De Cosse JJ, Bulow S, Neale K, et al: Rectal cancer risk in patients treated for familial adenomatous polyposis: The Leeds Castle Polyposis Group. Br J Surg 79:1372-1375, 1992

56. van Duijvendijk P, Slors JF, Taat CW, et al: Functional outcome after colectomy and ileorectal anastomosis compared with proctocolectomy and ileal pouch-anal anastomosis in familial adenomatous polyposis. Ann Surg 230:648-654, 1999

57. van Duijvendijk P, Slors JF, Taat CW, et al: Quality of life after total colectomy with ileorectal or proctocolectomy and ileoanal anastomosis for familial adenomatous polyposis. Br J Surg 87:590-596, 2000

58. Giardiello FM, Hamilton SR, Krush AJ, et al: Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 328:1313-1316, 1993

59. Nugent KP, Farmer KC, Spigelman AD, et al: Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. Br J Surg 80:1618-1619, 1993

60. Clark SK, Phillips RK: Desmoids in familial adenomatous polyposis. Br J Surg 83:1494-1504, 1996

61. Westerman AM, Wilson JH: Peutz-Jeghers syndrome: Risks of a hereditary condition. Scand J Gastroenterol Suppl 230:64-70, 1999

62. Jenne DE, Reimann H, Nezu J, et al: Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat Genet 18:38-43, 1998

63. Hemminki A, Markie D, Tomlinson I, et al: A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature 391:184-187, 1998

64. Westerman AM, Entius MM, de Baar E, et al: Peutz-Jeghers syndrome: 78-year follow-up of the original family. Lancet 353:1211-1215, 1999

65. Giardiello FM, Welsh SB, Hamilton SR, et al: Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med 316:1511-1514, 1987

66. Boardman LA, Thibodeau SN, Schaid DJ, et al: Increased risk for cancer in patients with the Peutz-Jeghers syndrome. Ann Intern Med 128:896-899, 1998

67. Tomlinson IP, Houlston RS: Peutz-Jeghers syndrome. J Med Genet 34:1007-1011, 1997

68. Spigelman AD, Murday V, Phillips RK: Cancer and the Peutz-Jeghers syndrome. Gut 30:1588-1590, 1989

69. Foley TR, McGarrity TJ, Abt AB: Peutz-Jeghers syndrome: A clinicopathologic survey of the "Harrisburg family" with a 49-year follow-up. Gastroenterology 95:1535-1540, 1988

70. Linos DA, Dozois RR, Dahlin DC, et al: Does Peutz-Jeghers syndrome predispose to gastrointestinal malignancy? A later look. Arch Surg 116:1182-1184, 1981

71. Desai DC, Murday V, Phillips RK, et al: A survey of phenotypic features in juvenile polyposis. J Med Genet 35:476-481, 1998

72. Jass JR, Williams CB, Bussey HJ, et al: Juvenile polyposis: A precancerous condition. Histopathology 13:619-630, 1988

73. Howe JR, Roth S, Ringold JC, et al: Mutations in the SMAD4/DPC4 gene in juvenile polyposis. Science 280:1086-1088, 1998

74. Olschwang S, Serova-Sinilnikova OM, Lenoir GM, et al: PTEN germ-line mutations in juvenile polyposis coli. Nat Genet 18:12-14, 1998

75. Howe JR, Mitros FA, Summers RW: The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol 5:751-756, 1998

76. Giardiello FM, Hamilton SR, Kern SE, et al: Colorectal neoplasia in juvenile polyposis or juvenile polyps. Arch Dis Child 66:971-975, 1991

77. Jarvinen H, Franssila KO: Familial juvenile polyposis coli: Increased risk of colorectal cancer. Gut 25:792-800, 1984

78. Whitelaw SC, Murday VA, Tomlinson IP, et al: Clinical and molecular features of the hereditary mixed polyposis syndrome. Gastroenterology 112:327-334, 1997

79. Williams GT, Arthur JF, Bussey HJ, et al: Metaplastic polyps and polyposis of the colorectum. Histopathology 4:155-170, 1980

80. Torlakovic E, Snover DC: Serrated adenomatous polyposis in humans. Gastroenterology 110:748-755, 1996

81. Vasen HF, Griffioen G, Offerhaus GJ, et al: The value of screening and central registration of families with familial adenomatous polyposis: A study of 82 families in the Netherlands. Dis Colon Rectum 33:227-230, 1990