

Practical genetics of colorectal cancer

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Abstract: Hereditary colorectal cancer (CRC) is highly heterogeneous, both genotypically and phenotypically. The most frequently occurring hereditary colorectal cancer syndrome is Lynch syndrome, accounting for approximately 3% of the total colorectal cancer burden. Polyposis syndromes, such as familial adenomatous polyposis, account for a lesser percentage. Familial colorectal cancer, defined by family history, occurs in an estimated 20% of all colorectal cancer cases. With a worldwide annual colorectal cancer incidence of over one million, and annual mortality of over 600,000, hereditary and familial forms of colorectal cancer are a major public health problem.

Lynch syndrome is attributable to DNA mismatch repair germline mutations, with the *MSH2*, *MLH1*, *MSH6*, and *PMS2* genes being implicated. The characteristics of Lynch syndrome-associated colorectal tumors, including early age of onset and predilection to the proximal colon, mandate surveillance by colonoscopy beginning by age 20 to 25 and repeated every other year through age 40 and annually thereafter. Besides colorectal cancer, Lynch syndrome also predisposes to a litany of extracolonic cancers, foremost of which is endometrial cancer, followed by cancer of the ovary, stomach, renal pelvis and ureter, small bowel, hepatobiliary tract, pancreas, glioblastoma multiforme in the Turcot's variant, and sebaceous skin tumors in the Muir-Torre variant and, more recently identified, cancers of the breast and prostate.

The most common polyposis syndrome is familial adenomatous polyposis, caused by mutations in the *APC* gene. Affected individuals have multiple colonic adenomas and, without treatment invariably develop colorectal cancer. Colonic surveillance with polypectomy may be pursued until the appearance of multiple colonic adenomas, at which time prophylactic colectomy should be considered. Extra-intestinal manifestations include desmoid tumor, hepatoblastoma, thyroid carcinoma, and medulloblastoma. Other polyposis syndromes include the hamartomatous polyp syndromes, including juvenile polyposis syndrome, Peutz-Jeghers syndrome, Cowden syndrome, and Bannayan-Ruvalcaba-Riley syndrome.

Key Words: Colorectal cancer (CRC); genetics; Lynch syndrome; familial adenomatous polyposis (FAP); Polyposis syndromes; MYH (MUTYH) mutations; gene



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Overview

The estimated incidence of colorectal cancer (CRC) in the United States during 2013 is 142,820, with an estimated mortality of 50,830 (1). Worldwide estimates for 2008 are an incidence of 1,234,000 and mortality of approximately 608,000 (2). Approximately 3% (1 of every 35 cases) of CRC is attributable to Lynch syndrome (LS), the most common hereditary syndrome predisposing to CRC (3). Polyposis

syndromes such as familial adenomatous polyposis (FAP) contribute a lesser percentage of the total CRC burden. *Figure 1* demonstrates the heterogeneity of identified hereditary CRC syndromes.

Familial CRC, meaning one or more (and, by some definitions, two or more) first-degree and/or second-degree relatives of the index case manifesting CRC, indicates that the index case has an approximate 2-fold increased CRC

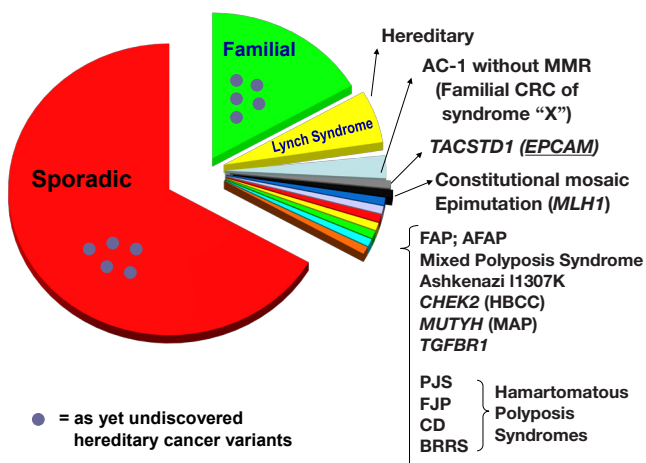


Figure 1 Circle graph depicting the marked genotypic and phenotypic heterogeneity in hereditary colorectal cancer syndromes. (Revised with permission from Lynch *et al.* *Cancer* 2004;100:53-64.) Abbreviations: AC-1, Amsterdam Criteria 1; MMR, mismatch repair; FAP, familial adenomatous polyposis; AFAP, attenuated familial adenomatous polyposis; HBCC, hereditary breast and colorectal cancer; PJS, Peutz-Jeghers syndrome; FJP, familial juvenile polyposis; CD, Cowden's disease; BRRS, Bannayan-Ruvalcaba-Riley syndrome

risk. Familial CRC by this definition constitutes about 20% of the total CRC incident burden.

Lynch syndrome

Mismatch repair mutations

LS is inherited in an autosomal dominant pattern. Mutations in mismatch repair (MMR) genes have been identified in LS patients (4): *MLH1* (5), located on chromosome 3p21.3; *MSH2* (6,7) and *MSH6* (8), both located on 2p21; and *PMS2* (9), located on 7p22. Approximately 90% of the identified LS mutations involve *MLH1* or *MSH2*, while mutations in the *MSH6* gene account for approximately 10%.

Individuals carrying germline mutations of *MLH1* or *MSH2* have a lifetime risk for CRC on the order of 80% (10). Seventy percent of the CRCs arise proximal to the splenic flexure. The average age at diagnosis is 45 years, compared with 63 years in the general population. Multiple synchronous and metachronous CRCs are seen in the syndrome, with 30% of patients developing a second cancer within 10 years if a limited operation (right hemicolectomy

or segmental resection) is done for the initial cancer as opposed to a subtotal colectomy should metastasis be absent. Even when total abdominal colectomy is performed, the rectum is still at risk; Rodriguez-Bigas *et al.* (11) reported that 12% of LS patients had rectal cancer within 12 years after colectomy.

Pathology of CRCs is more often poorly differentiated in LS, with an excess of mucoid and signet-cell features, a Crohn's-like reaction, and a significant excess of tumor-infiltrating lymphocytes. Increased survival from CRC also occurs in the syndrome (12-14).

Extracolonic cancers

Extracolonic cancers are common in LS (15). Endometrial carcinoma is the most notable, women with LS having a 20% to 60% lifetime risk for endometrial cancer (10,16). There is also an increased risk for carcinoma of the stomach, ovary, renal pelvis and ureter, small bowel, hepatobiliary tract, and pancreas. Glioblastoma multiforme is seen in the Turcot's syndrome variant (17). Benign and malignant sebaceous skin tumors occur in combination with CRC and other internal malignancies in the Muir-Torre syndrome variant (18). Quite recently, molecular genetic evidence has demonstrated that breast and prostate cancer in LS mutation carriers may not be spontaneously developing cancers, but rather are part of the LS tumor spectrum (19).

Genotype-phenotype heterogeneity

LS, not unlike other autosomal dominantly inherited disorders, is noteworthy for genotypic and phenotypic heterogeneity (20-22). *MSH2* mutations may predispose to an excess of extracolonic cancer compared with its *MSH1* counterpart. In a study that included 138 families with LS wherein mutations were identified in 79 of these families (34 with *MLH1*, 40 with *MSH2*, 5 with *MSH6*), Vasen *et al.* (23) found that the lifetime risk for developing cancer at any anatomic site was significantly higher for *MSH2* mutation carriers when compared with *MLH1* mutation carriers ($P < 0.01$). With respect to specific anatomic sites, *MSH2* mutation carriers in this study were found to have a significantly higher risk of developing cancer of the urinary tract ($P < 0.05$).

Carriers of *MSH6* germline mutations have been found to harbor a lower risk for CRC than carriers of *MSH2* and *MLH1* mutations. However, women with an *MSH6* mutation are at a higher risk for endometrial cancer than

those carrying one of the other mutations. In a study involving mutation analysis of 20 families with an *MSH6* germline mutation, Hendriks *et al.* (24) compared the cancer risks between *MSH6* and *MLH1/MSH2* mutation carriers. They identified a total of 146 *MSH6* mutation carriers, among whom the cumulative risk for CRC was 69% for men and only 30% for women. Endometrial carcinoma was present in 71% of the women by age 70. When all LS-related tumors were considered, the risk was significantly lower in *MSH6* mutation carriers compared with *MLH1* or *MSH2* mutation carriers ($P=0.002$). Among females with *MSH6* mutations, the risk of CRC was significantly lower ($P=0.0049$) but the risk for endometrial cancer significantly higher ($P=0.02$) than in *MLH1* and *MSH2* mutation carriers.

Childhood cancers and other unusual tumors

Although childhood and hematological cancers are not generally considered to be part of the LS tumor spectrum, Bandipalliam (25), de Vos and colleagues (26), and Scott and colleagues (27) have described a syndrome characterized by a biallelic inactivation of the MMR genes, leading to a recessive MMR-deficiency syndrome predisposing to "...childhood malignancies such as lymphoma, leukemia, brain and gastrointestinal tumors and features of neurofibromatosis type 1" (28). Menko and colleagues (29) have also noted that there has been recent evidence of homozygous mutations in the MMR genes *MLH1*, *MSH2*, and *PMS2* in children with hematological malignancies, solid tumors, and clinical signs (multiple *café-au-lait spots*) of neurofibromatosis type 1 (30-37), and have described a child with multiple *café-au-lait spots* in association with an oligodendroglioma at age 10, followed by rectal carcinoma at age 12, which lesions were ascribed to a homozygous *MSH6* mutation with predicted pathogenic effects.

Molecular pathogenesis of tumors outside the usual LS cancer spectrum remains controversial. Broaddus and colleagues (38) described two young *MSH2* mutation carriers, one age 34 who developed an adrenal cortical carcinoma, and the second a 39-year-old woman who had a diagnosis of anaplastic carcinoma of the thyroid, tumors not usually associated with LS. Berends and colleagues (39) reported a female with an *MSH2* germline mutation, ovarian cancer, and three metachronous CRCs who was also found to have an adrenal cortical carcinoma. It is of further interest that the original proband in Lynch's Family N, reported in 1966 (40), manifested adrenal cortical

carcinoma. Other reports of rare tumors in Lynch syndrome include a malignant fibrous histiocytoma arising in a patient with a germline *MSH2* mutation and a positive LS family history (41), and a male with a germline *MLH1* mutation and a positive LS family history who developed infiltrating ductal carcinoma of the breast 30 years after early-onset CRC (42). The dilemma remains as to whether these tumors are related to defects in DNA MMR, or whether they have arisen independently of this MMR defect.

EPCAM and LS

The underlying molecular defect responsible for a portion of families manifesting a LS phenotype without an identified MMR mutation, is a mutation in the epithelial cell adhesion molecule (*EPCAM*) gene, located immediately 5' of *MSH2* (43-45). A germline deletion removing the 3' end of *EPCAM* results in tissue-specific methylation and silencing of the otherwise intact *MSH2* gene.

Ligtenberg *et al.* (45) were the first to describe such families. Tumors from individuals with *EPCAM* mutations had high microsatellite instability (MSI) and immunohistochemistry (IHC) showed a loss of *MSH2* protein even though there was no identifiable mutation of the *MSH2* gene (43,45). In approximately 19% of LS-consonant families that lacked *MLH1/MSH2* mutations the *EPCAM* mutations co-segregated with the LS phenotype (43). In a study by Kuiper *et al.* (46), *EPCAM* deletions were found to account for about 2.3% of explained *MSH2*-deficient families.

Expression of the *EPCAM* gene is restricted primarily to epithelial tissues. This appears to influence the phenotypic expression associated with this type of mutation, which may differ from that of carriers of *MSH2* mutations. Notably, cancer expression appears to be almost exclusively limited to the colorectum, with a paucity of the endometrial cancers that would be expected with an *MSH2* mutation. It must be noted, however, that when the *EPCAM* deletion extends into, or is in close proximity to, the *MSH2* gene, the risk for endometrial cancer becomes equivalent to those with *MSH2* mutations. Determination of the precise boundaries of deletions involving *EPCAM* is likely to be important for clinical management of these families. CRC occurs in *EPCAM* deletion carriers with a frequency comparable to that of carriers of an *MSH2* mutation.

We have studied a family containing more than 700 individuals (47). An *EPCAM* deletion was identified in this highly-extended family, which has been studied by

us for more than 35 years; 50 members of this family have manifested CRC, providing strong evidence of the potential impact of a single mutation event (47).

Familial colorectal cancer type X

As mentioned earlier, a MMR germline mutation is able to be identified in approximately 60% of families fulfilling clinical criteria for LS. Lindor *et al.* (48) studied 161 pedigrees from such families divided into those with (group A) *vs.* those without (group B) MMR deficiency through tumor testing. This involved 3,422 relatives for the analysis. Findings disclosed that group A families showed an increased incidence of LS-related cancers, while group B families showed an increased incidence of only CRC [SIR, 2.3; 95% confidence interval (CI), 1.7-3.0], and to a lesser extent than group A (SIR, 6.1; 95% CI, 5.2-7.2) ($P < 0.001$). These authors indicated that such families should not be described or counseled as LS and suggested a designation of “familial colorectal cancer type X” (48).

Somewhat similar studies (49,50) assessed features of the clinically-defined LS families that lacked MSI. Individuals were found to be older at CRC diagnosis than those with MSI and therein their tumors were less commonly proximal, less often clearly differentiated and mucinous, and more often showed DNA aneuploidy. They did not present as often with multiple cancers and there was a lower incidence of CRC and endometrial cancer.

IHC and MSI

Thanks to molecular genetic advances, the diagnosis of LS can be aided significantly by demonstrating the presence of MSI within the tumor and/or IHC that identifies a loss of MMR proteins. Diagnosis of LS can be verified by the identification of a germline mutation in one of the MMR genes, the *sine qua non* for LS's confirmation. Ideally, this molecular testing is performed on high-risk individuals from families that show the clinical-pathology features of LS.

All cells of individuals affected with LS carry a nonfunctioning allele of a DNA MMR gene; if the wild-type allele is lost or inactivated, the cell can no longer repair DNA mismatches that inevitably arise during DNA replication, leading to the phenomenon of MSI, in which cells have varying lengths of a given microsatellite (an area with multiple repeats of one nucleotide or one pair of nucleotides). Therefore, testing for MSI has been used

in screening for CRC associated with MMR deficiency. However, it must be noted that 10-15% of sporadic CRCs demonstrate MSI, the vast majority of which are caused by acquired hypermethylation of the *MLH1* promoter (51). The presence of a *BRAF* mutation is a good surrogate for methylation testing to identify non-LS silencing of *MLH1*.

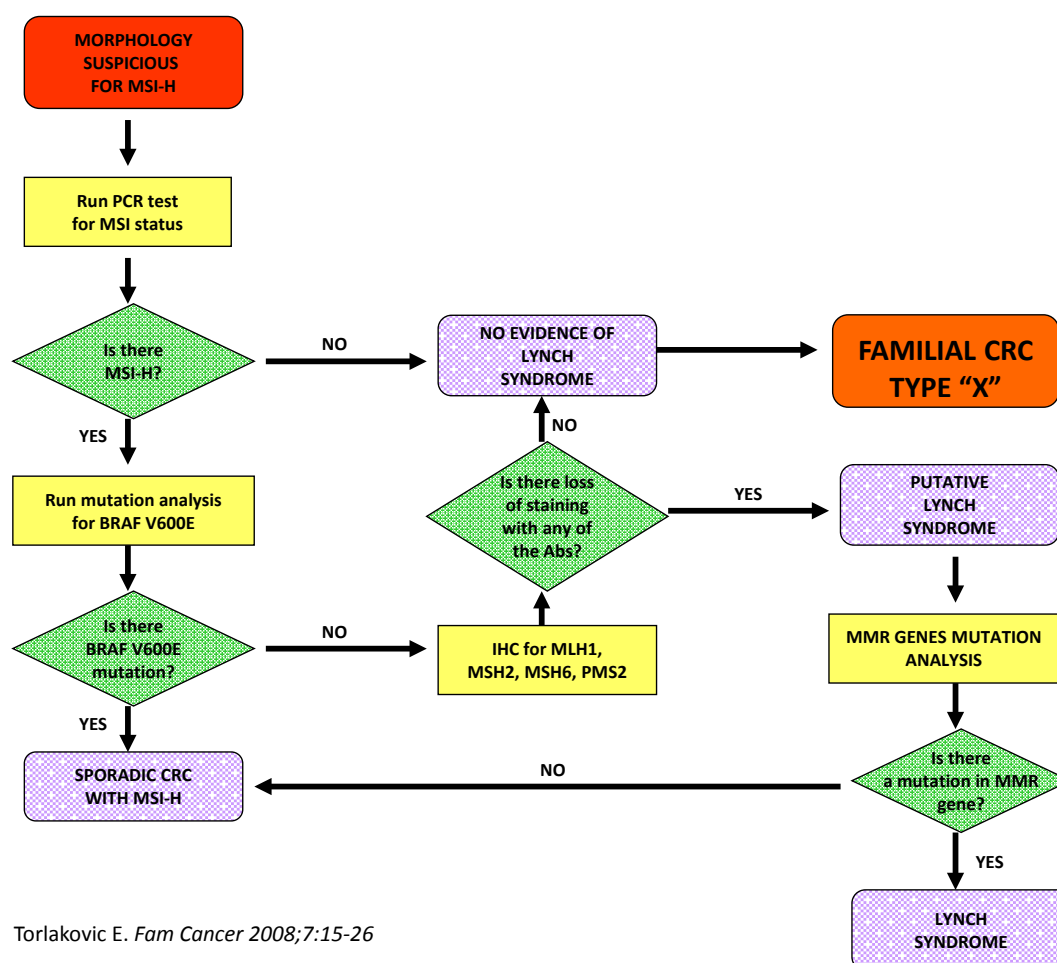
When one suspects that a tumor has high MSI (MSI-H), IHC stains for the protein product of the DNA MMR genes *MLH1* and *MSH2* can be used for confirmation. For example, Marcus *et al.* (52) found that 37 of 38 neoplasms known to be MSI-H showed an absence of *MLH1* or *MSH2* expression, and 34 of 34 microsatellite stable (MSS) tumors had intact staining.

Molecular genetic screening of all CRC patients

With the ability to identify patients at risk for LS cancers, and given the relative frequency of the syndrome, the question has been raised of whether all cases of CRC should be tested. Hampel *et al.* (3) investigated 500 consecutive CRC patients and found that 18 (3.6%) had met clinical criteria for LS. All of these patients had CRCs with MSI. LS was correctly diagnosed in 17 (94%) of these 18 cases by IHC. Of interest was the finding that only 8 cases (44%) were diagnosed at less than 50 years and only 13 cases (72%) met the revised Bethesda Guidelines for MSI testing; these authors point out that this means that if only patients fulfilling the Bethesda Guidelines were tested, 28% of LS mutation carriers would not be identified.

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (53) supported the Hampel *et al.* findings (3) and concluded that using genetic testing strategies to reduce morbidity and mortality in CRC probands and their relatives at high risk for and/or affected by LS is a sound and prudent cost-effective measure. Using IHC as the preliminary diagnostic test was shown to be the most efficient screening method, since it reduces the need for sequencing all four of the genes normally tested for LS, to sequencing of only the gene(s) indicated by lack of MMR protein.

Ladabaum *et al.* (54) investigated cost-effectiveness of a Markov model to identify LS with attention to sex, age at screening, and differential effects for probands and relatives. The target population comprised all of those with newly-diagnosed CRC and their relatives. The time horizon was lifetime, and the perspective was third-party payor. The outcome measures were life-years, cancer cases and deaths, costs coupled with incremental cost-effectiveness ratios.



Torlakovic E. *Fam Cancer* 2008;7:15-26

Figure 2 An algorithm for identification of Lynch syndrome. Reprinted with permission from Gatalica & Torlakovic. *Fam Cancer* 2008;7:15-26

The results considered current rates of germline testing, screening, and prophylactic surgery, which "...reduced deaths from colorectal cancer by 7% to 42% and deaths from endometrial and ovarian cancer by 1% to 6%. Among tumor-testing strategies, immunohistochemistry followed by *BRAF* mutation testing for all persons with CRC was preferred, with an incremental cost-effectiveness ratio of \$36,200 per life-year gained."

The authors concluded that widespread CRC testing led to LS diagnosis yielding substantial benefits at acceptable cost. This was particularly noteworthy for women with an LS mutation, enabling them to begin regular screening and consider the option of risk-reducing gynecologic surgery with the result of cost-effectiveness of this testing, which was dependent on the participation among relatives at risk for LS. In an accompanying editorial (55), Burt noted that the cost-effectiveness of these approaches "...was very

sensitive to the number of relatives who would undergo mutation-specific testing after a disease-causing mutation was found in an index case. It is interesting that success of tumor testing first has already led some institutions and health policy organizations to recommend MSI or IHC testing in all patients with colon cancer and perhaps in all women with endometrial cancer to find those who should then have genetic testing for Lynch syndrome (56-58)."

Such an approach to cancer prevention and control may not appear to be practical in most clinical practice settings at the community level. Nevertheless, the rapid development of centers with molecular genetic expertise and the increased availability of genetic counselors, heightened by the ongoing advances in molecular genetics, can potentially provide even more personalized genetic screening services to high-risk families. *Figure 2* depicts a possible algorithm

for identifying LS and similar disorders.

CRC prevention: colonoscopy screening

There are highly significant clinical implications for diagnosis of LS. Surveillance for CRC in those harboring a mutation is highly effective and considerably less costly than a lack of CRC surveillance (59,60).

Because of the early age of CRC onset in LS and its penchant for the proximal colon, full colonoscopy should be initiated by age 20 to 25 in germline mutation carriers and those at increased cancer risk based on their position in the pedigree. Colonoscopy should be performed at least every one to two years, given the problem of accelerated carcinogenesis of CRC in LS (20,61). We prefer every other year in high-risk patients who have not had DNA testing and annually in patients with LS germline mutations or who are obligate gene mutation carriers.

Järvinen and colleagues (59) showed the benefit of colonoscopic screening in LS through a controlled clinical trial extending over 15 years (59). The incidence of CRC was compared in two cohorts of at-risk members of 22 LS families. CRC developed in eight screened subjects (6%), compared with 19 controls (16%; $P=0.014$), providing a reduction of 62% in the CRC rate. All CRCs in the screened group were local and caused no deaths, compared with nine deaths caused by CRC in the controls. It was concluded that CRC screening at three-year intervals more than cuts in half the risk of CRC, prevents CRC deaths, and decreases overall mortality by about 65% in LS families. The relatively high incidence of CRC even in the screened subjects (albeit without deaths) argues for shorter screening intervals, a consideration also supported by Vasen *et al.* (62) who discovered five interval cancers in LS patients within 3-1/2 years following a normal colonoscopy.

In reviewing this subject, Church (63) has suggested that interval CRCs developed from normal epithelium within three years or from adenomas that were missed. It is important to realize that colonoscopy “miss” rates are as high as 29% for polyps <5 mm in diameter (64). Patients should be advised that colonoscopy is not a perfect screening procedure, and the option of prophylactic colectomy should be discussed (65,66).

Surgical measures

Subtotal colectomy as a prophylactic measure among LS patients remains controversial, but patients who carry

germline mutations should be offered this option as an alternative to lifetime colonoscopic surveillance. Genetic counseling must be provided so that patients can be in a better position to evaluate the various management strategies. Church (66) and Lynch (65) both suggest that prophylactic surgery should be an option for patients likely to show reduced compliance for colonoscopy.

Syngal and colleagues (67) examined the life expectancy and quality-adjusted life expectancy benefits resulting from endoscopic surveillance and prophylactic colectomy among carriers of germline mutations for LS. Compared with no intervention, both risk-reduction programs showed large gains in life expectancy for mutation carriers, with benefits of 13.5 years for surveillance and 15.6 years for prophylactic proctocolectomy at 25 years of age. The benefits of prophylactic colectomy decreased with increasing age.

Gynecologic screening and surgical management

Women who carry a germline mutation for LS should have annual screening for endometrial cancer beginning at age 30 to 35 years. Endometrial aspiration and transvaginal ultrasound are advised for screening; however, we lack evidence-based data showing survival benefit from such screening. Prophylactic hysterectomy and bilateral salpingo-oophorectomy can be considered when childbearing is completed. Schmeler *et al.* (68) showed a significant reduction in endometrial and ovarian cancer among those LS patients who underwent prophylactic surgery when compared with those who did not.

LS patients with a family history of kidney cancer and/or hematuria should have annual ultrasound and urinalysis with cytologic examination, beginning at age 30 or at first evidence of hematuria. Evidence-based data showing survival advantage for urologic, gastric, and small bowel screening are not available. Periodic upper endoscopy should be performed in families with gastric or small bowel cancer. Those of Asian origin show a higher frequency of gastric cancer.

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is inherited in an autosomal dominant pattern. The incidence is 1 in 6,000 to 1 in 13,000; Powell and colleagues estimated that more than 50,000 families in the United States could benefit from genetic counseling for this disorder (69). Affected individuals carry germline mutations of the *APC* gene on

chromosome 5q21-q22 (70-74). About one-third of FAP patients have no family history and probably represent new mutations. Many mutations of *APC* have been described; 80% of them are truncating. There is some correlation between the position of the truncating mutation and phenotype (discussed below).

Affected individuals have multiple colonic adenomas and, if untreated, will inevitably develop CRC. Adenomas generally arise in the mid to late teens; 95% of mutation carriers have adenomas by age 35. More than 90% of FAP patients develop duodenal adenomas, but only about 5% of these adenomas develop carcinogenesis. Gastric polyposis is seen in at least 50% of affected patients; most of the polyps are fundic gland polyps, but gastric adenomas do occur. Gastric carcinoma risk, however, is not appreciably elevated in Western FAP patients. In contrast, Japanese and Korean families with FAP have a three- to four-fold excess risk for gastric carcinoma (75).

Extra-intestinal manifestations of FAP include desmoid tumor, hepatoblastoma, thyroid carcinoma, medulloblastoma, and a litany of benign lesions: sebaceous or epidermoid cysts, lipomas, osteomas, supernumerary teeth, congenital hypertrophy of retinal pigment epithelium, and juvenile nasopharyngeal angiofibromas. Brain tumors, particularly medulloblastomas, are a feature of the Turcot's variant of FAP (17).

The attenuated variant of FAP (AFAP) presents a particularly difficult diagnostic challenge (76-78). Adenomas can be sparse (one or two in some patients, dozens in others) and are often right-sided, both features having the potential of confusion with LS. The adenomas appear at a later age (35-40 years) than in classic FAP, as do colon carcinomas (55 years). Upper gastrointestinal manifestations (fundic gland polyps and duodenal adenomas) are seen with the same, or possibly a greater, frequency as in classic FAP. AFAP families have been described that have mutations near the proximal end of the *APC* gene as well some that have mutations at the extreme distal end.

Genetic testing is available for FAP. If a mutation is found in an affected family member, other at-risk family members can easily be tested for the mutation. Genetic testing is not recommended for children younger than 10 years of age. If no mutation is found in an affected family member, the test is considered uninformative; a negative result in that setting does not rule out FAP.

Randomized, controlled trials demonstrating the efficacy of screening and management regimens have not been performed. Nevertheless, the following recommendations

are generally agreed upon: affected or at-risk individuals should have annual flexible sigmoidoscopy beginning by age 10 to 12. If the family history suggests AFAP, then colonoscopy is required because the adenomas are more likely to be proximal, but the screening can begin later (age 20). Prophylactic colectomy should be considered once multiple adenomas have appeared. However, it may be that prophylactic colectomy can be temporarily postponed in AFAP when management by polypectomy is possible. Endoscopic surveillance of the rectum and anus should be continued after prophylactic colectomy. A baseline upper endoscopy is advisable by age 20, with follow-up examinations every two to three years unless symptoms occur. Annual thyroid palpation is suggested, and children at risk for FAP should have serum α -fetoprotein testing every 6 months until 6 years of age in the interest of early detection of hepatoblastoma.

When duodenal adenomas are discovered, they should be removed endoscopically if feasible. Often, however, the adenomas are too numerous to remove; in that case, annual surveillance with biopsy of grossly suspicious lesions is a prudent course. It is hoped that chemoprevention will help control duodenal adenomas, but results thus far have not been encouraging [reviewed by Hawk and colleagues (79)].

Desmoid tumors can be a difficult management problem. These locally aggressive soft-tissue tumors typically arise in the abdominal wall or bowel mesentery. Relentless recurrences are the rule (80,81). The difficulty of surgical cure, complete with the fact that surgery may initiate the pathogenesis of desmoids, has led to the recommendation that only symptomatic desmoid tumors should be surgically resected (82). Desmoid tumors may occur in excess in certain FAP families (81,83,84).

MUTYH (MUTYH) mutations and CRC

MUTYH is a DNA-base-excision-repair gene located on chromosome 1p. Mutations in this gene predispose to an autosomal recessively inherited colonic polyposis that shows an average of 55 adenomas in an affected individual (85) and carries a risk for CRC of approximately 60% (86). The disorder, termed *MUTYH*-associated polyposis (MAP) is rare, occurring in approximately 1 out of 10,000 in the general population and accounting for about 5% of persons with a FAP-type phenotype (85). It is estimated that 1.5% of individuals in the general population are heterozygous carriers of a *MUTYH* mutation (86).

Nielsen *et al.* (86) combined data from the literature

as well as 40 Dutch MAP patients in order to construct a Markov model for developing a societal cost-utility analysis of genetic screening of MAP families, which involved testing the spouse when heterozygous and testing the progeny of that spouse. They recommended that counselees be offered the option of genetic testing of spouses and/or children. Biallelic *MUTYH* mutations are found in 10-25% of patients with "...between 10 and a few hundred adenomas and in 1% of patients with a colorectal carcinoma. Patients with more than 10 adenomas are currently being offered *MUTYH* mutation analysis. Siblings of a MAP patient have a 25% risk of having inherited biallelic mutations and are eligible for genetic testing. (86)" MAP patients have between 10 to about 100 adenomas at a mean age of 50 years; they are advised to have colonoscopic screening beginning at age 25 years.

Juvenile polyposis syndrome

Sporadic juvenile polyps are relatively common, with one autopsy study of patients under 21 years reporting a prevalence of 1% (87) and other studies estimating an occurrence in 2% of the pediatric population (88). Usually solitary, the polyps do not denote an increased risk for CRC (88,89).

Juvenile polyposis syndrome (JPS) is a rare autosomal dominantly inherited disorder characterized by multiple juvenile polyps in the gastrointestinal tract and an increased risk for gastrointestinal cancer. Mutations in *SMADH4* and *BMPRI1A* together account for approximately 50-60% of JPS cases. Various candidate genes have been investigated to account for the remainder of the disorder (88).

The clinical diagnosis of JPS requires histologic confirmation of a juvenile polyp, plus the presence of any of the following: more than five juvenile polyps in the colorectum, juvenile polyps elsewhere in the gastrointestinal tract, or a family history of juvenile polyposis. Even when there are multiple juvenile polyps and a family history of polyposis, the diagnosis of JPS must be made with care, because Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome have similar polyps but a very different spectrum of associated lesions (90).

Three variants of JPS have been described: a rare, usually fatal juvenile polyposis of infancy with diarrhea, protein-losing enteropathy, and alopecia; juvenile polyps of the colorectum; and generalized juvenile polyposis. However, the latter two are likely manifestations of the same disorder. Extraintestinal anomalies, while not common, have been

reported, including hydrocephalus, thyroglossal duct cyst, tetralogy of Fallot, coarctation of the aorta, idiopathic hypertrophic subaortic stenosis, and malrotation of the gut.

Juvenile polyps may be found in the colorectum (98%), stomach (14%), duodenum (2%), and small bowel (7%) (91,92). Although the polyps are considered benign, JPS patients are at increased risk for CRC. The cumulative lifetime risk was estimated by Järvinen to be 50% (93), an estimate supported by a report from the University of Iowa describing a large JPS kindred in which 16 of 29 (55%) affected individuals developed gastrointestinal cancer (94). Eleven members of the Iowa kindred had colon cancer and six had gastric cancer.

Affected individuals need regular endoscopic surveillance. Scott-Conner and colleagues (92) recommend upper and lower gastrointestinal endoscopy beginning at age 15 and continuing every three years as long as no lesions are detected. If a family carries a *SMADH4* or *BMPRI1A* mutation, at-risk individuals can be tested to determine whether surveillance is needed. Small numbers of polyps can be managed by polypectomy, in which case endoscopy should be repeated yearly until the patient is free of polyps. If there are multiple polyps in the colon, subtotal colectomy is recommended if the rectum can be cleared endoscopically; otherwise, total colectomy is a consideration. For young children with large numbers of polyps, regular colonoscopy with removal of the largest polyps is an option as a temporary measure until puberty is reached (94). Multiple gastric polyps, particularly if dysplasia is present, should prompt consideration of gastrectomy.

Peutz-Jeghers syndrome

PJS is inherited in an autosomal dominant pattern and has been mapped to a locus on chromosome 19p13.3 (95,96). The gene responsible for the syndrome encodes a serine threonine kinase, STK11 (also known as LKB1) (95). Abnormal (i.e., inactive) forms of this kinase may lead to defective control of cellular growth and differentiation. Not all PJS families can be linked to 19p13.3, leading to speculation that there are other loci for the syndrome (97,98). The incidence of PJS is approximately 1 in 200,000 (99).

The diagnosis of PJS requires histologic confirmation of a hamartomatous, Peutz-Jeghers-type polyp. Because such polyps can be seen in individuals who do not have PJS, clinical diagnosis also requires at least two of the following: small bowel polyposis, family history of PJS; or pigmented macules of buccal mucosa, lips, fingers, and toes (100).

Peutz-Jeghers polyps have been found in the entire gastrointestinal tract. The small bowel is the site affected most often, but stomach and colon are involved as well; esophageal polyps are rare. The polyps are almost always multiple but tend to number in the dozens rather than the hundreds. Peutz-Jeghers polyps have also been described in respiratory mucosa and the urinary tract. One member of the Dutch family originally studied by Peutz suffered from severe nasal polyposis and eventually developed a nasal carcinoma (101).

PJS carries an increased risk for malignancy. Giardiello and colleagues (100) found a relative risk for cancer 18 times that of the general population in 31 PJS patients. Malignancies involved pancreas [4], breast [2], stomach [2], colon [2], lung [2], and endometrium [1]. Spigelman and colleagues (102) reported that 72 retrospectively studied PJS patients were 13 times more likely than the general population to develop a malignancy. The tumors involved colon, stomach, small intestine, ovary, fallopian tube, thyroid, and lung. Investigators from the Mayo Clinic (103) found a relative risk for cancer of 9.9 in 34 PJS patients, with cancers of the colon [7], breast [6], lung [3], and cervix [2] predominating. The Mayo Clinic group found a particularly high incidence of breast and gynecologic cancers, contributing to a relative cancer risk of 18.5 in women, compared to 6.2 in men.

The Dutch family originally described by Peutz has been updated, and the findings further demonstrate that PJS is a cancer-prone condition (101). Of 22 affected individuals, seven developed carcinoma (3 colon, 1 stomach, 1 gastrointestinal not otherwise specified, 1 breast, and 1 nasal cavity). All patients with malignancy were dead of their disease before the age of 50 years.

Nearly every female PJS patient will have ovarian involvement by sex cord tumor with annular tubules (SCTAT). The tumors are bilateral in at least two-thirds of cases (in contrast to SCTAT in the sporadic setting, which is almost always unilateral). An unusual form of cervical cancer, minimal deviation adenocarcinoma (adenoma malignum), is also characteristic of PJS. This rare tumor accounts for 1% to 3% of all cervical adenocarcinoma but, in one series, affected 4 of 27 women with PJS (104).

The surveillance protocol advocated by the St. Mark's Polyposis Registry (105) includes yearly hemoglobin and yearly ultrasound of the pelvis in females and of the pancreas in all patients. Testicular ultrasound should also be done in males with feminizing features. Biannual upper and lower endoscopy with small-bowel X-ray are recommended.

Regular mammography and cervical smear are critical surveillance measures. Tomlinson and Houlston (106) suggest that upper endoscopy, colonoscopy, and small-bowel X-ray begin in the second decade and that mammography begin at age 25.

The gastrointestinal polyps may be associated with bleeding, obstruction, or intussusception. Conservative removal (snare polypectomy) is favored over segmental resection of bowel to avoid development of a short bowel syndrome.

Differentiating among JPS, Cowden syndrome, Bannayan-Ruvalcaba-Riley syndrome, and PJS can be difficult (90).

Importance of family studies

A patient found to have CRC may eventually be diagnosed as having an underlying hereditary cancer syndrome. The individual may be found to have a germline mutation in one of the several MMR genes and thus to have LS, in the *APC* gene thus causing FAP, or in one of the genes associated with a more uncommon syndrome. The diagnosis may be strongly suspected on the basis of a known family history of colorectal and extracolonic cancers or, in the case of LS, may be made through the performance of MSI or IHC testing. Perhaps more important than the diagnosis of a hereditary CRC syndrome in an individual patient is that such a diagnosis makes it possible to provide predictive mutational testing for at-risk relatives. Relatives found to be negative for the familial mutation can be spared the anxiety, cost, and risk associated with unnecessary clinical surveillance. Those found to be positive for the mutation can receive the benefit of intensive surveillance and, perhaps, surgical prophylaxis intended to reduce risk of cancer-associated morbidity and mortality.

In reality, however, relatively few at-risk relatives of CRC patients have benefitted from predisposition testing. This issue extends to families with other hereditary cancer-prone syndromes such as the hereditary breast-ovarian cancer (HBOC) syndrome caused by *BRCA* germline mutations.

Attention is sometimes given to the proband's first-degree relatives (siblings, parents, and progeny), and there is a modestly encouraging uptake of genetic testing seen among these family members. Rarely, however, is attention extended to more distant relatives who could benefit from genetic testing and counseling; it is not surprising that uptake of such procedures is more disappointing among these relatives. Such a difference is understandable, as

Patient's Modified Nuclear Pedigree

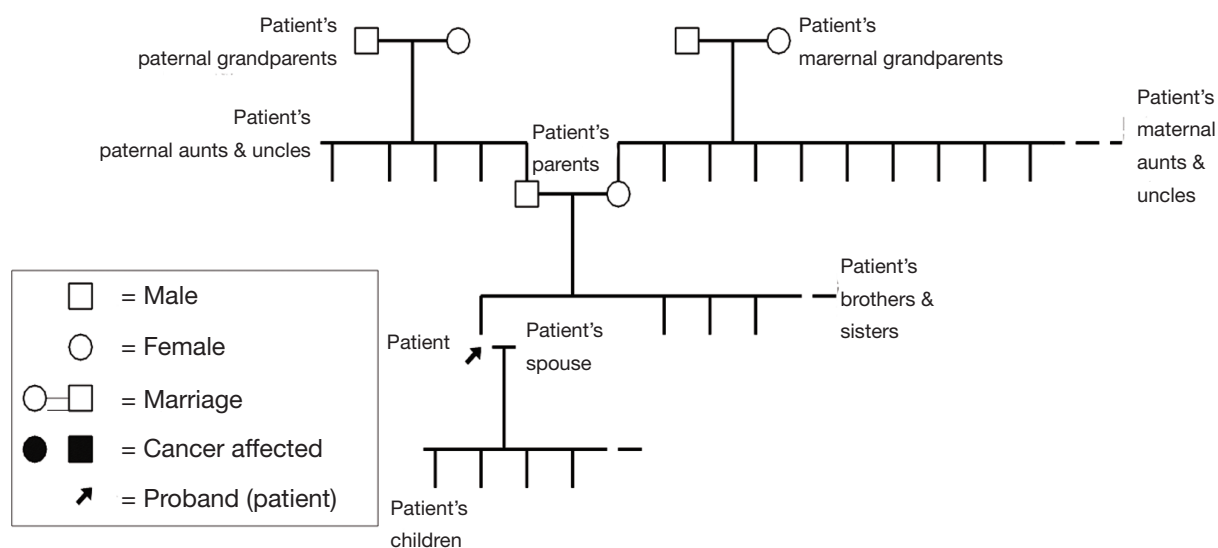


Figure 3 Diagram representing a simple, modified nuclear pedigree for clinical use. From Lynch HT, *et al. Surv Dig Dis* 1984;2:244-60. Reproduced by permission

most people are in more frequent contact with first-degree relatives and are highly motivated to seek their welfare. Communication with more distant relatives is less frequent and their health may not have the same perceived importance.

Watson *et al.* (107) studied Creighton's LS and HBOC families to show how the results of genetic testing can clarify the cancer risk status of even family members who are not tested. Testing of 1,408 family members effected a change in known carrier risk status of 2,906 individuals. Sixty percent of those who had a change in status were not tested themselves; their risk status changed because of the test result of another relative. Carrier risk status changes from uncertainty to certainty (that is, from high risk to known carrier or noncarrier status) accounted for 89% of the changes, affecting cancer prevention recommendations.

This current lack of detailed attention to study of the family, especially of relatives more distant than first-degree, may be depriving family members of cancer prevention, appropriate genetic counseling and, where indicated, DNA testing. It is clear that developing the family history (see *Figure 3*) and thereby implementing appropriate

screening and DNA testing to determine mutation status of family members, followed by appropriate management implications, could provide highly-targeted cancer preventive management.

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