37. Hereditary Colorectal Cancer

James Church

Introduction

- Colorectal cancer is both a genetic and epigenetic disease.
- The classes of genes primarily involved are largely those concerned with regulation of cell growth, tumor suppressor genes and proto-oncogenes, and the average sporadic colorectal cancer has accumulated 90 different mutations.
- Most mutations occur because of the environment and about one third of colorectal cancers have a hereditary component.
- Hereditary colorectal cancer is important because members of affected families can be identified as high risk and be advised to have early, intensive surveillance or even prophylactic surgery.
- Hereditary colorectal cancer can be broadly divided into non-syndromic and syndromic conditions (Fig. 37.1).
- Non-syndromic hereditary colorectal cancer refers to familial clustering that does not fit criteria for the definition of a syndrome and no germ line mutation is found.
- Syndromic hereditary colorectal cancer is more important, however, because of the extremely high level of risk associated with it and because it is relatively easier to identify.

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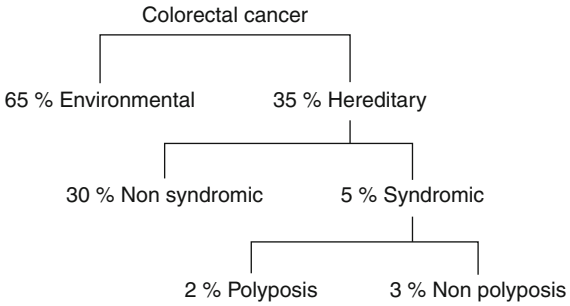

Fig. 37.1 Colorectal cancer viewed broadly

Syndromic Hereditary Colorectal Cancer

- A syndrome is a condition characterized by a constellation of symptoms, signs, and associations that go together so that the presence of one feature may alert the clinician to the presence of others.
- Hereditary colorectal cancer syndromes can be broadly separated into those that are associated with multiple polyps (the hereditary polyposis syndromes) and those that are not (hereditary nonpolyposis colorectal cancer (HNPCC)). These syndromes and their definitions are listed in Table 37.1.
- All of them confer an enhanced risk of colorectal and extracolonic cancers on affected patients and demand a sophisticated knowledge of genetics and medical and surgical treatment from caregivers.

The Polyposis Syndromes

The Adenomatous Polyposes

Familial Adenomatous Polyposis

- Familial adenomatous polyposis (FAP) is an autosomal, dominantly inherited condition due to a germ line mutation of *APC*, which occurs with a frequency of about 1:10,000 live births.
- About 22 % of germ line *APC* mutations occur "de novo," meaning that there is no family history of the syndrome.
- Inactivating mutations of this tumor suppressor gene result in a generalized disorder of growth regulation with a range of clinical manifestations, principally the formation of multiple gastrointestinal adenomas and carcinomas.
- FAP is thought to account for between 0.05 and 1 % of all colorectal cancers.
- Patients with a diagnosis of FAP and their family should be referred to a polyposis registry.

Table 37.1 Hereditary colorectal cancer syndromes

Polyposis syndromes	Phenotypic definition	Genotype
Familial adenomatous polyposis	Attenuated: <100 synchronous adenomas Mild: <1,000 synchronous adenomas Severe/profuse: >1,000 synchronous adenomas	Dominant inheritance of germ line mutation in *APC*
MYH-associated polyposis	Attenuated/mild polyposis	Recessive inheritance: biallelic mutations of *hMUTYH*
Hyperplastic polyposis	>20 hyperplastic polyps of any size or location >50 hyperplastic polyps proximal to sigmoid, 2 >10 mm Any number of hyperplastic polyps with a family history of hyperplastic polyposis	Unknown
Hamartomatous polyposes	Two of the following criteria:	
1. Peutz–Jeghers syndrome	Mucocutaneous pigmentation Gastrointestinal Peutz–Jeghers polyps Family history of Peutz–Jeghers polyposis	Dominant inheritance of germ line mutation in *STK11*
2. Juvenile polyposis coli	>4 juvenile polyps in the colorectum Any number of juvenile polyps and a family history of juvenile polyposis	Dominant inheritance of germ line mutation in *SMAD4* or *BMPR1*
3. PTEN tumor hamartoma syndromes		Dominant inheritance of a germ line mutation in *PTEN*
(a) Cowden's syndrome	International Cowden Consortium Criteria	
(b) Bannayan–Riley–Ruvalcaba syndrome		
(c) Proteus syndrome		
Nonpolyposis colorectal cancer		
Lynch syndrome	Dominant family history, microsatellite-unstable (high) colorectal cancer, young age of onset	Dominantly inherited germ line mutation of DNA mismatch repair gene: *hMLH1*, *hMSH2*, *hPMS2*, *hMSH6*
Familial Colorectal Cancer Type X	Dominant family history, microsatellite-stable tumor	Unknown

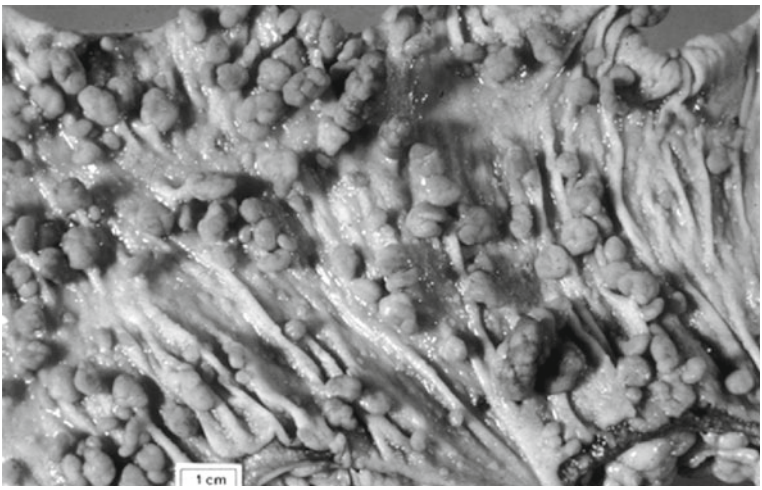

Fig. 37.2 The large bowel in classical familial adenomatous polyposis

Polyposis Registries

- The aim of polyposis registries is to provide counseling, support, and clinical services for families with FAP.
- This includes thorough pedigree analysis and identification of at-risk family members, who are offered genetic testing and clinical surveillance.
- Those shown to be affected can be offered prophylactic surgery.
- Some registries also coordinate postoperative surveillance and provide a focal point for education, audit, and research.
- Observational studies suggest that the introduction of registries, together with the use of prophylactic surgery, has led to increased life expectancy and a dramatic reduction in the incidence of colorectal cancer in FAP.

Features of FAP

- The Large Bowel. The cardinal manifestation of FAP is the development of over 100 colorectal adenomatous polyps, one or more of which inevitably progress to carcinoma if not removed (Fig. 37.2).
- Polyps usually appear in adolescence, with colorectal cancer diagnosed at an average age of about 40 years.
- The severity of the colorectal polyposis is an important determinant of treatment and is used to define the pattern of FAP.
- Patients with less than 100 adenomas are classified as having attenuated FAP, and this phenotype overlaps significantly that of *MYH*-associated polyposis (MAP).
- Patients with 100–1,000 adenomas have classical FAP, while those with >1,000 adenomas have profuse FAP.

- Polyposis severity is partly a reflection of the location of the *APC* mutation and partly due to unidentified modifying factors. The "hotspot" mutation at *APC* codon 1309 is reliably associated with profuse polyposis.

Genetics

- The *APC* Gene. *APC* is a large gene on chromosome 5q21 (q = the long arm).
- It is a key (gatekeeper) gene in colorectal carcinogenesis and is mutated in a majority of sporadic colorectal cancers.
- Over 820 different germ line *APC* mutations causing FAP have been identified, almost all resulting in truncation of the APC protein. Mutations have been found between codons 168 (exon 4) and 2839 (exon 15), but most are between codons 168 and 1640 (exon 15) in the 5′ half of the coding region, with a particular concentration at two "hotspots," codons 1061 and 1309.
- The *APC* Protein. *APC* is expressed in all organs, but the mRNA is found at particularly high levels in normal colonic mucosa.
- In many epithelia, APC is only found when cell replication has ceased and terminal differentiation is established.
- The 300 kDa APC protein is found in the cytoplasm and has sites of interaction with a range of other proteins, including β-catenin and the cytoskeleton. It plays a central role in the highly conserved Wnt signaling pathway, which is involved in the normal development of three-dimensional structures and is abnormally activated in some malignancies.
- *APC* binds and downregulates cytoplasmic β-catenin, preventing its translocation to the nucleus. Abnormal *APC* fails to do this so that β-catenin is free to enter the nucleus and form a complex, which results in specific transcription of cell cycle stimulating DNA sequences, and hence cell proliferation.

Genotype–Phenotype Correlation in FAP

- There is evidence of correlation between the position of the germ line *APC* mutation (genotype) and some aspects of phenotype (Fig. 37.3).
- Mutation at codon 1309 is associated with profuse polyposis and between codons 1250 and 1464 with earlier onset of, and death from, colorectal cancer.
- Mutations located 5′ of codon 160 and 3′ of codon 1597 are associated with mild or attenuated colonic polyposis, accounting for about 10 % of those affected.
- Some extracolonic manifestations have also been associated with mutations at certain sites, although not upper gastrointestinal polyposis.
- Congenital hypertrophy of the retinal pigmented epithelium (CHRPE) occurs only with mutations between codons 450 (exon 9) and 1444.

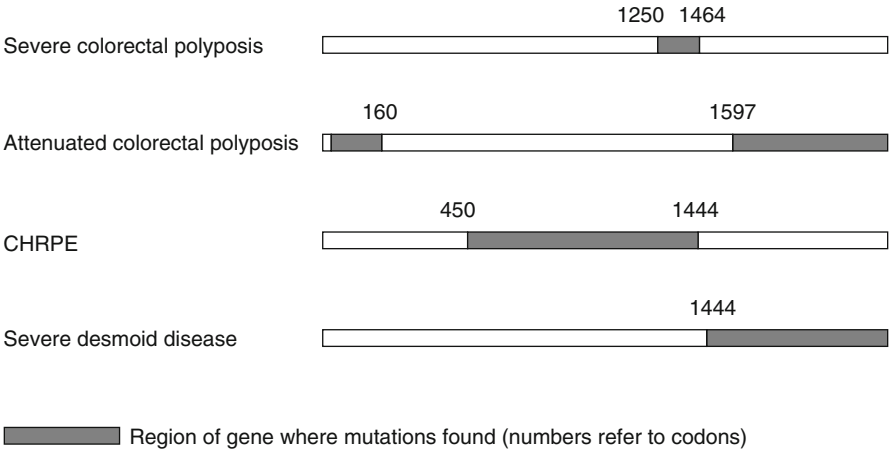

Fig. 37.3 Schematic representation of the APC gene showing genotype–phenotype correlations

Table 37.2 Extracolonic features of familial adenomatous polyposis

System	Feature	Frequency (%)
Upper gastrointestinal tract	Upper gastrointestinal adenom	95
	Upper gastrointestinal carcinoma	5
	Fundic gland polyps	40
Connective tissue	Osteomas (especially jaw)	80
	Desmoid tumor	15
Dental	Unerupted and supernumerary teeth	17
Cutaneous	Epidermoid cysts	50
Endocrine	Adrenocortical adenomas	5
	Papillary thyroid carcinoma	1
Hepatobiliary	Biliary tract carcinoma	<1
	Hepatoblastoma	<1
Central nervous system	Congenital hypertrophy of the retinal pigmented epithelium (CHRPE)	75
	Tumors (especially medulloblastoma)	<1

- The association of desmoid disease with germ line *APC* mutations 3′ of codon 1444 can be clinically important, although identical *APC* mutations may be associated with diverse phenotypes, suggesting that other genetic modifiers are involved.

Clinical Variations of FAP

Extracolonic Manifestations

- The extracolonic manifestations of FAP are shown in Table 37.2.
- Two of these, duodenal cancer and desmoid disease, are major sources of morbidity and mortality (Fig. 37.3).

- Other features may be a useful clue in diagnosis. CHRPE are hyper- or hypopigmented spots seen on retinal examination. They have no effect on vision but act as markers of FAP in the 66 % of families that have a total of at least four CHRPEs in both eyes.

Attenuated Familial Adenomatous Polyposis

- A group of patients have been described who develop fewer than 100 colorectal adenomas (oligopolyposis) at a greater age (34–44 years) than in "classical" FAP, but who are at high risk of colorectal cancer, may exhibit extracolonic manifestations, and carry a germ line *APC* mutation.
- The colorectal cancers have a later age of onset than with classical or profuse FAP (mean age 56 years).
- The polyps have a rather different distribution, being more frequently found proximal to the splenic flexure, and their number varies significantly between family members, some of whom may have hundreds of adenomas.
- The genotype of this group of patients may be one of the three: germ line *APC* mutation, biallelic *MYH* mutations, and germ line DNA mismatch repair (MMR) gene mutations.
- *APC* mutations associated with attenuated familial adenomatous polyposis (AFAP) are either at in exons 3 and 4; at the 5′ end of the gene; or at the 3′ end of exon 15.
- Fundic gland polyps (FGPs) and duodenal adenomas are frequent, but CHRPEs are not found in there patients.
- Desmoid disease is rare in those with a 5′ mutation, but families with 3′ mutations (beyond about codon 1444) have a high risk of desmoid disease together with attenuated polyposis.
- The missense *APC* mutation I1307K has been identified in Ashkenazi Jews with multiple adenomas, and E1317Q has also been found in association with AFAP.
- When *APC* is normal, up to 30 % of patients with oligopolyposis have biallelic *MYH* mutations.
- It is can be difficult to recognize AFAP clinically, leading to the clinical situation of an obstructing transverse colon cancer where right-sided polyposis is only found when the specimen is opened.
- Because the polyps in AFAP are predominantly right sided, screening and work-up must include a full colonoscopy.
- Genetic testing for germ line *APC* and *MYH* mutations has a relatively low yield, partially because of technical difficulties in detection of abnormalities that may be present and partly because gene expression may be lost for reasons other than a mutation.
- A careful search (including upper gastrointestinal endoscopy) for extracolonic features of FAP, dye-spray colonoscopy to confirm polyp number, and testing of tumor or polyp tissue for microsatellite instability (MSI)

and MMR immunohistochemistry (IHC) (to exclude Lynch syndrome) may be helpful.

- Genetic testing for a germ line *APC*/*MYH* mutation should be pursued in patients with a total of ten or more colorectal adenomas, especially if there is a positive family history for colorectal adenomas or cancers.
- A positive result has implication for family screening, but the patient is managed in the same way regardless of the result.
- If the polyps are controllable endoscopically, then yearly colonoscopy is reasonable. If the adenoma burden is uncontrollable or dangerous, colectomy with ileorectal anastomosis (IRA) should be performed.

Gardner's Syndrome

- Gardner described the association between FAP and epidermoid cysts, osteomas, and "fibromas" (later found to be desmoid tumors) in 1953.
- The term "Gardner's syndrome" was later used to describe colorectal adenomatous polyposis occurring with these extracolonic manifestations.
- Gardner's syndrome is genetically the same as FAP, and systematic examination has revealed that most patients with FAP have at least one extraintestinal feature.
- Though it is of historical interest, the term "Gardner's syndrome" is no longer considered genetic or clinically useful and should be regarded as obsolete.

Turcot's Syndrome

- This is the association between colorectal adenomatous polyposis and central nervous system tumors. Recent molecular genetic investigation has shown that about two thirds of families have mutations in *APC*, with cerebellar medulloblastoma as the predominant brain tumor. Most of the other third, including Turcot's original family, appear to be variants of hereditary nonpolyposis colorectal cancer (HNPCC) with glioblastoma as the predominant brain tumor and multiple (but fewer than 100) colorectal adenomas.

Presentation

- Patients with FAP present either with or without symptoms (on screening).
- There is a significant difference in cancer incidence between these two groups, with over 60 % of unscreened, symptomatic patients having colorectal cancer at presentation.

Screening

- Clinical FAP screening begins at puberty because the risk of colorectal cancer under the age of 12 years is very small.
- Genetic testing of at-risk family members in a family with a known mutation usually starts when endoscopic surveillance would start, at ages 12–14.

- When a relative is identified as a mutation carrier, full colonoscopy is performed. EGD screening usually begins at age 20 years. Thyroid screening with ultrasound should also start then.
- If genetic testing is uninformative or cannot be done in a family with classical FAP, endoscopic screening starts at age 12–14 with flexible sigmoidoscopy. Polyps are biopsied to prove they are adenomas.
- An alternative would be to do retinal examinations for CHRPE or look for other extracolonic examinations with a skull X-ray or panorex examination of the jaw.
- If a marker of FAP is found, full colonoscopy follows. The polyp burden is documented endoscopically and histologically and a decision made regarding the timing and type of surgery.

Symptoms

- About 22 % of FAP patients have no family history. Clinical symptoms are often related to colorectal cancers, and should be investigated immediately.

Diagnosis

Genetic Testing

- Genetic testing should be preceded by counseling, ideally by a genetic counselor. Counseling includes the provision of written information about the process and its consequences, after which informed consent is documented. The implications of genetic testing with respect to confidentiality, employment, insurance, and other financial issues vary from country to country but must be discussed prior to testing. In the USA, the Genetic Information Nondiscrimination Act (GINA) that became law in 2008 offers protection against genetic discrimination in Health and Life insurance. Posttest counseling deals with the implications of the genetic test results and may include psychological help to deal with emotional reactions, such as guilt (in an unaffected person), anxiety (in an affected person), and the effect of the results on family relationships.
- DNA from an individual with clinically obvious FAP is sequenced to identify a mutation in *APC*, a process which is successful in about 80 % of cases. Failure to detect an *APC* mutation does not exclude a diagnosis of FAP and may occur for a variety of reasons, including the presence of large deletions or missense mutations. Such results have been misinterpreted as ruling out the diagnosis of FAP, with potentially serious consequences.
- If a deleterious mutation is found in an affected family member, at-risk family members can be offered predictive testing with a high degree of accuracy. This is generally done between the ages of 12 and 15 years, when the individual is old enough to take part in genetic counseling.
- When an individual does not carry the family mutation, that person can be discharged from further surveillance and be reassured that they do not have FAP.

- A positive test result allows surveillance and prophylaxis to be targeted to those who need it, and knowledge of the site of mutation can aid decision making with regard to prophylactic surgery.
- If no mutation can be found in an affected patient, then the family must be managed without genetic testing.
- The negative result does not mean that the family does not have FAP; it means that the genetic cause of the FAP has not been found.

Management of the Large Bowel

- Aims of Treatment. While the prevention of cancer remains an important priority in the management of patients with hereditary colorectal cancer, maintaining the quality of life is also important. This is especially the case in young, asymptomatic patients who have been diagnosed by screening. Where options exist for the timing and type of surgery, those with the least impact on social, academic, and vocational activities should be chosen. After all, surgery will not cure FAP.
- Prophylactic Surgery. Patients with FAP, if untreated, are almost guaranteed to develop colorectal cancer.
- Prevention of cancer by endoscopic control of the polyposis is not usually possible, and so colectomy or proctocolectomy is necessary to prevent cancer.
- Timing. Patients with severe polyposis (over 1,000 colonic or over 20 rectal polyps), or those who are symptomatic, should have surgery as soon as possible.
- In asymptomatic patients with mild disease (100–1,000 adenomas, all <1 cm, none with severe dysplasia), surgery can usually be delayed until the patient reaches appropriate physical and intellectual maturity.
- An important reason for delay is the concern for the development of desmoid disease. Affected women with a family history of desmoid disease, extracolonic manifestations of Gardner's syndrome, and a 3′ *APC* mutation are at highest risk.
- As long as surgery is delayed, annual colonoscopy is recommended to monitor the polyps. Most patients with classical polyposis have surgery between the ages of 16 and 20, which is well before cancer usually develops.
- Choice of Operation. The colorectal surgical options for the management of FAP are proctocolectomy with end ileostomy (with or without Koch pouch), colectomy with IRA, and proctocolectomy with ileoanal pouch (IPAA). Few patients desire a permanent ileostomy, and so proctocolectomy with ileostomy is rarely done.
- IRA is more straightforward to perform than IPAA and requires only one procedure, with a shorter hospital stay and fewer complications. The risks of erectile and ejaculatory dysfunction caused by nerve damage during pelvic dissection are minimized, as is the significant reduction in

fecundity observed in women after IPAA. In addition, bowel frequency and soiling are less, and no temporary stoma is necessary.

- Polyp counts are a reliable way to identify a low-risk rectum, but patients still need yearly surveillance proctoscopy.
- Any polyps over 5 mm should be removed, and polyps with high-grade dysplasia are relative indications for completion proctectomy.
- Compared to an IRA, IPAA has the advantage of removing the entire colon and rectum. Although complication rates and functional results have improved with experience, they are still worse than those associated with IRA.
- There has been controversy over the need for mucosectomy to remove the anorectal transition zone, which theoretically prevents cuff neoplasia, but causes more complications and perhaps poorer function. Dysplasia in the transition zone occurs after both double-stapled and mucosectomy techniques and the latter is probably only indicated in individuals with severe low rectal polyposis. The indications and contraindications and advantages and disadvantages of each surgical option are summarized in Table 37.3.
- In summary, IRA is reasonable and safe in mildly affected patients, particularly if there are fewer than five rectal polyps.
- Most individuals presenting with severe polyposis or those known to carry a mutation in codon 1309 should be advised to undergo IPAA.
- But there are other issues. Pouch surgery in young men has an approximately 1 % risk of damage to erection, ejaculation, and bladder function; in women, fertility may be compromised.

Postoperative Surveillance

- After IRA the retained rectum should be examined using a flexible sigmoidoscope, with a basic interval of 12 months or shorter, depending on the severity of disease. Polyps over 5 mm should be removed cleanly with a snare. Repeated polyp fulguration can result in rectal scarring, making future surveillance difficult and unreliable. In patients with chronically scarred rectal mucosa, random biopsy is recommended to detect invisible dysplasia. If severe dysplasia or uncontrolled polyposis develops, completion proctectomy with or without ileoanal pouch formation is indicated.
- Surveillance of ileoanal pouches at several centers has shown adenomas in up to 53 % and even some cancers. Treatment of pouch adenomas depends on their number and size. Polyps over 5 mm should be removed by snare excision, while multiple small polyps respond to sulindac (150 mg by mouth twice daily).
- Anal transition zone (ATZ) adenomas occur commonly after both stapled and hand-sewn IPAA, although they are twice as common in the former as the latter.

Table 37.3 Surgical options for familial adenomatous polyposis

Surgical option	Indication	Advantages	Disadvantages
Colectomy and ileorectal anastomosis (leave 15 cm rectum)	<20 rectal adenomas <1000 colon adenomas	Low complication rate No stoma Close to normal bowel function	Risk of rectal cancer
Proctocolectomy and ileal pouch anal anastomosis (stapled)	>20 rectal adenomas >1000 colon adenomas	Minimizes risk of rectal cancer	Complex surgery
	Large rectal adenoma	Avoids permanent stoma	Often needs stoma
	Rectal adenoma with severe dysplasia	Bowel function better than with mucosectomy and hand-sewn anastomosis	Bowel function unpredictable but may be quite abnormal
	Sparing of low rectum		Risk of damage to pelvic nerves and decreased the ability of women to conceive Risk of pouch and anal transitional adenomas and cancer
Proctocolectomy and ileal pouch anal anastomosis (hand sewn)	As above but with adenomas to dentate line	Minimizes risk of rectal cancer Avoids permanent stoma	As above but bowel function is worse than with stapled anastomosis
Proctocolectomy with end ileostomy	Low rectal cancer Poor anal sphincters	Simple operation with lower complication rate and minimal chance of reoperation	Permanent stoma

- Several case reports of cancer in the ATZ underline the difficulty in following this critical area.
- Adenomas in the ATZ can be excised individually (under anesthesia), or the entire ATZ can be stripped. If stripping is chosen because of the extent of the polyposis, the procedure should be performed in two stages to avoid stenosis.

Adenoma Chemoprevention

- A range of chemopreventive agents have been studied in FAP, in part because of the problems of managing the retained rectum after IRA, but also because this disease provides a useful experimental model of colorectal carcinogenesis. In placebo-controlled trials, both the nonsteroidal anti-inflammatory drugs (NSAIDs) sulindac and the COX-2 inhibitor celecoxib have reduced the number and size of colorectal adenomas.

- Chemoprevention, however, is not an alternative to prophylactic surgery, as no benefit in terms of cancer reduction has been demonstrated, and there have been reports of rectal carcinoma occurring in patients on sulindac despite reduction in polyp number and size.

Upper Gastrointestinal Polyposis

- Fundic gland polyps (FGPs), made up of areas of cystic hyperplasia,[42] are found in the stomach of about 80–90 % of individuals with FAP. These are benign but a recent prospective survey showed that low-grade dysplasia was present in FGP in 41 % of patients.
- Three percent of patients had high-grade dysplasia in FGP. This is concerning as some patients have profuse FGP, impossible to survey.
- Current practice is to biopsy representative FGPs during regular surveillance, but not to try and treat all.
- Gastric adenomas can be found, usually in the antrum, in 10 % of patients in western series. It is likely that these give rise to the very rare gastric cancers in western patients.
- The incidence of gastric cancers in FAP patients in Japan is seven times that in the West, and for Korea, three times.
- An excess of gall bladder and bile duct adenomas and carcinoma has also been reported.
- Prospective studies have demonstrated that over 95 % of individuals with FAP have duodenal adenomas, which tend to occur about 15 years later than large bowel polyps.
- Duodenal cancers are the second most common cause of death in patients with FAP because although they are relatively rare (5 %), they are highly lethal. Average age at diagnosis is 50 years.
- The highest density of adenomas is on and around the ampulla of Vater, testimony to the tumorigenic effect of bile.
- Fifty percent of normal-appearing ampullae are dysplastic on biopsy.
- Adenomas can also be found throughout the small intestine, and early studies of capsule endoscopy show that incidence of jejunal and ileal adenomas is higher in patients with severe duodenal polyposis (Spigelman stages III and IV).
- Occasional cases of small bowel adenocarcinoma occur, but routine small bowel screening is not recommended.
- Surveillance of the Duodenum. Duodenal adenomas are flat, white mucosal patches, completely different in appearance to colorectal adenomas.
- The Spigelman staging system allows an objective assessment of the severity of duodenal polyposis in FAP (Table 37.4).
- A prospective 10-year follow-up of Spigelman's original cohort has identified a 36 % risk of developing invasive carcinoma in those with stage IV disease at the start of the study and a 2 % risk in those with stage II or III disease. Several carcinomas were missed on endoscopy, and all of those who developed cancer died as a result, despite surgery.

Table 37.4 Scoring of polyp features in Spigelman staging for duodenal adenomas

Points allocated	Number of polyps	Size of polyps (mm)	Histology	Dysplasia
1	1–4	1–4	Tubular	Mild
2	5–20	5–10	Tubulovillous	Moderate
3	>20	>10	Villous	Severe

Table 37.5 Derivation of Spigelman stage from scores

Total points	Spigelman stage	Suggested interval to next duodenoscopy (years)
0	0	5
1–4	I	3–5
5–6	II	3
7–8	III	1
9–12	IV	Consider duodenectomy. If not, rescope in 6 months

- Regular endoscopic surveillance of the stomach and duodenum is recommended so that individuals at high risk of developing carcinoma can be identified and offered intervention (although there is currently no evidence that this approach decreases the rate of invasive disease). Table 37.5 shows recommended surveillance intervals according to the severity of duodenal polyposis. Duodenal polyps are sampled for histology and even a normal-appearing ampulla is biopsied.
- Management. Management of severe duodenal polyposis is difficult, but once invasive carcinoma has developed, the outcome is poor.
- Duodenectomy and open polypectomy is associated with 100 % recurrence a year after surgery.
- Endoscopic mucosal resection seems a more attractive option but is made difficult by the frequently plaque-like morphology of the polyps and involvement of the ampulla.
- The use of chemoprevention to prevent progression of earlier-stage disease has attracted great interest. Sulindac can result in regression of small polyps but has little effect on larger ones.
- A randomized trial of the COX-2 inhibitor celecoxib showed significant improvement in the Spigelman stage for those with mild to moderate disease.
- Duodeotomy, whether by classical Whipple's procedure or using pylorus or pancreas-preserving techniques, has been considered a last resort because of its significant morbidity and mortality.
- However, given the very poor prognosis once neoplasia becomes frankly invasive, preemptive duodenectomy should be seriously considered for Spigelman IV disease. Pancreas-preserving duodenectomy provides satisfactory control with reasonably low morbidity.
- When cancer is suspected, a Whipple's procedure is the better choice but carries a high rate of complications.

Desmoid Disease

- Desmoids are locally invasive, non-metastasizing clonal proliferations of myofibroblasts that are rare in the general population but can be found in 30 % of patients with FAP.
- Their etiology, pathogenesis, and natural history are not clearly understood.
- Desmoid disease is the third most common cause of death in FAP patients overall, after colorectal cancer and duodenal cancer.
- Overall desmoid-related mortality ranges from 10 to 50 %, and desmoids can also contribute to death from other causes by making surgery for rectal or upper gastrointestinal malignancy difficult or even impossible.
- Desmoid disease is a spectrum from white, sheetlike plaques to large rapidly growing tumors.
- When found within the abdomen, desmoid disease can be seen to pucker and distort adjacent tissues, causing obstruction in tubular organs.
- Ten to fifteen percent of patients with FAP develop desmoid tumors, while another 15 % develop the plaques.
- The peak incidence is around 30 years of age, 2–3 years after surgery. While sporadic desmoids are considerably more common in females than males, this difference is less marked in the setting of FAP.
- Clinical Features. Desmoids occurring in association with FAP typically arise within the abdomen (50 %), especially in the small bowel mesentery, and in the abdominal wall (45 %), although many extra-abdominal sites have been described.
- Mesenteric desmoids (Fig. 37.4) encase or compress mesenteric blood vessels. Rarely, this can result in ischemia and perforation of the bowel, but it always makes resection hazardous.
- Trauma (particularly in the form of surgery) and estrogens have both been identified as causes of desmoids, although they can occur spontaneously.
- There is evidence for some degree of genotype–phenotype correlation in that desmoids have been reported to occur more frequently in patients with 3′ germ line *APC* mutations. However many patients with desmoid disease have mutations in the 5′ half of the gene so modifier genes may well also play a part.
- Recent publication of a “desmoid risk factor” score underlines the importance of female gender, the presence of extracolonic manifestations (especially Gardner’s syndrome), and most importantly a family history of desmoids, in alerting surgeons to the likelihood of desmoid disease in their patients.
- Abdominal surgery in patients at high risk of desmoid disease should be delayed as long as possible and, when performed, should preferably be a laparoscopic ileorectal anastomosis.

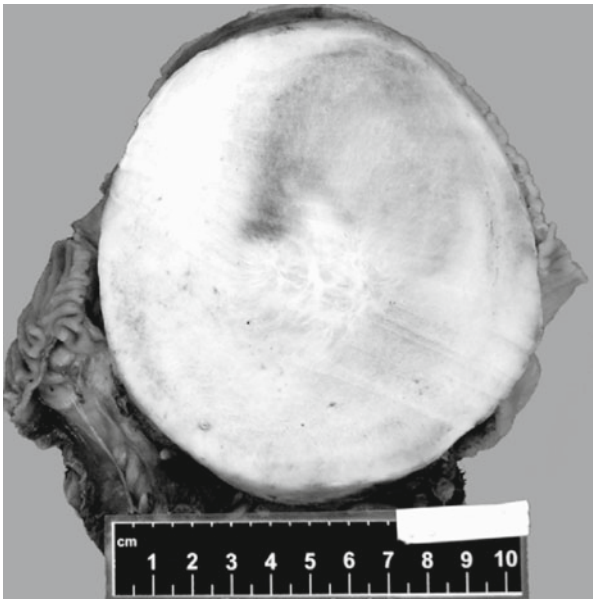

Fig. 37.4 Desmoid tumor arising in the small bowel mesentery

Presentation

- Asymptomatic desmoid disease can be found incidentally, on physical examination, on CT scan, or at laparotomy.
- Symptomatic desmoids cause pain and bowel or ureteric obstruction or are apparent as a mass.

Investigation

- CT or MRI scans are the mainstays of investigation and follow-up (Fig. 37.5). There is some evidence that MRI, T2-weighted signal intensity correlates with subsequent growth.

Management

- The treatment of desmoids is controversial, often empirical and difficult.
- The natural history of desmoid disease in FAP is variable, with about 10 % resolving spontaneously, 10 % growing rapidly and relentlessly, and the remainder either showing cycles of growth and resolution or remaining stable.
- A desmoid staging system has been proposed that allows separation of desmoid tumors by prognosis and sets the stage for a more rational approach to treatment.

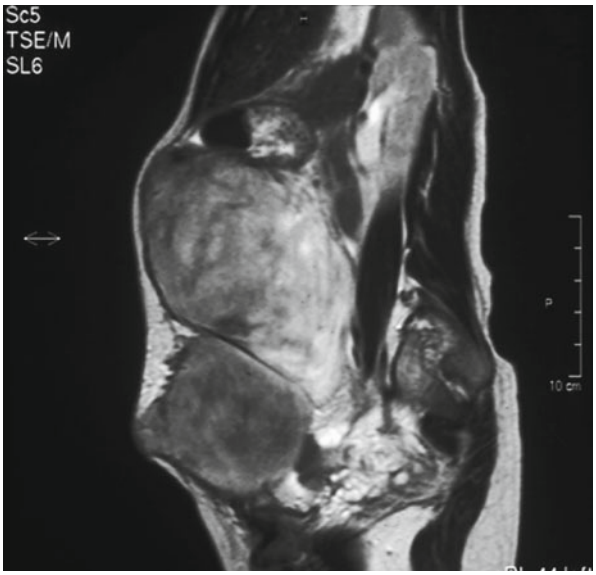

Fig. 37.5 MRI scan showing intra-abdominal desmoid tumor

- Surgery is widely accepted as the first-line treatment for troublesome extra-abdominal and abdominal wall desmoids. Recurrence is common (20–50 %), but complications are few.
- Within the abdomen the situation is very different, as the majority of desmoids develop in the small bowel mesentery. When the tumors are at the root of the mesentery, encasing the mesenteric vessels, surgery is a last resort and may mean small bowel transplant.
- Even after R0 resections, however, recurrence rates are in the order of 50 %.
- Attempts at resection of desmoids in the mesenteric root may lead to perioperative mortality (usually from hemorrhage) and substantial morbidity, particularly due to extensive loss of small bowel.
- Ureteric obstruction is best managed with stents, although even stents may be poorly tolerated due to pain or sepsis.
- Ureterolysis is rarely effective and may lead to nephrectomy. Renal autotransplant has proven effective, however, when medical treatments do not resolve the ureteric obstruction.
- Nonresective surgery may be needed to treat the complications of desmoid disease. Various medical treatments for desmoid disease have been reported, the most widely used being NSAIDs (particularly sulindac) and antiestrogens (raloxifene, tamoxifen, or toremifene). There have been no prospective controlled trials, and particularly in view of the unpredictable and variable behavior of desmoids, the small retrospective series are difficult to interpret. Cytotoxic chemotherapy has been used in

Table 37.6 Staging system for abdominal desmoid tumors

Stage	Definition
I	Size <10 cm, not growing, asymptomatic
II	Size <10 cm, mildly symptomatic, slow growing[a]
III	Size 10–20 cm, moderate symptoms (bowel obstruction, ureteric obstruction), slow growing
IV	Size >20 cm or rapid growth[b] or severe symptoms (abscess, fistula, hemorrhage)

[a]Slow growth = <50 % increase in maximum diameter in 6 months
[b]Rapid growth = >50 % increase in maximum diameter in 6 months

irresectable or aggressive desmoid disease, and objective remissions have been noted with a variety of different agents. There have been a number of encouraging reports of an antisarcoma regimen consisting of doxorubicin and dacarbazine in the treatment of life-threatening intra-abdominal desmoid disease, and more recently the better-tolerated liposomal doxorubicin has shown benefit. A less toxic combination of vinblastine and methotrexate has also produced some responses.

- A treatment regimen can be proposed that uses the staging system outlined in Table 37.6. Stage I tumors may receive either no treatment or sulindac, 150–200 mg twice daily. Stage II tumors are treated with sulindac and an estrogen-modifying agent (tamoxifen or raloxifene 120 mg per day). Stages III and IV require chemotherapy. Liposomal doxorubicin is a reasonable agent to use, with methotrexate/vinorelbine as an alternative. If a septic complication precludes chemotherapy or if the maximum safe dose of Adriamycin has been reached, agents such as Gleevec, bevacizumab, or Erbitux can be tried.

MYH-Associated Polyposis

- MAP is an autosomal recessive form of familial adenomatous polyposis, due to mutations in the human MutY homolog (*hMUTYH*) gene.
- Many of the individuals identified with biallelic *hMUTYH* mutations have fewer than 100 polyps; some have many hundreds and thus appear as if they are a genuine clinical case of FAP.
- Colonic microadenomas and duodenal adenomas, desmoids and fundic gland polyps, sessile serrated polyps, and a variety of extracolonic cancers have also been reported in this group.
- MAP can mimic many of the other hereditary forms of colorectal cancer, from sporadic cancer to FAP, from Lynch syndrome to serrated polyposis (SPS).
- MAP has major implications for genetic counseling as, for the first time, an autosomal recessive form of FAP has been identified.
- This diagnosis should be considered in patients where no *APC* mutation has been identified, the mode of inheritance is not clearly autosomal dominant, or polyp numbers are low.

- Genetics. Base excision repair corrects the sequelae of oxidative damage to the DNA. Oxidation changes the pattern of guanine coupling from G=C to G^{o}=T. In subsequent cell division, an uncorrected G^{o}=T becomes A=T, creating a "G=C to A=T transversion." This change, when uncorrected, produces mutations in several genes, including *APC* and *KRAS*. The effect on *APC* is enough to produce adenomatous polyposis, and serrated polyps harboring similar mutations in *KRAS* have been reported in patients with MAP.
- The locations of the pathogenic *hMUTYH* mutations vary according to ethnicity. The common mutations in the USA are Y179C and G396D, and these are screened for in Caucasian patients. There is some evidence that the Y179C mutation is associated with a more severe phenotype.
- Clinical. Patients usually present with oligopolyposis (<100 adenomas), although some cases with hundreds of polyps have been reported. Patients may present with young age onset colon cancer.
- Prior to awareness of these syndromes, patients with MAP were sometimes diagnosed as having attenuated FAP. Although some affected individuals have a very few adenomas, the presence of ten or more synchronous adenomas should trigger a referral for genetic counseling and testing, regardless of family history of colorectal neoplasia. The presence of serrated polyps with multiple adenomas should also stimulate a referral for genetic testing.
- Once the genotype of MAP is confirmed, full colonoscopy and EGD are performed. The syndrome has not been known for long enough to have an accurate list of all extracolonic manifestations.
- Treatment of the large bowel depends on whether the adenomas can be controlled endoscopically. If this can be done, surgery may be avoided. However, surgery is often necessary, usually colectomy with ileorectal anastomosis.
- Genetic Testing. MAP generally follows an autosomal recessive pattern of inheritance, although monoallelic mutations (carriers) have a mildly increased risk of colorectal cancer. There has been a report of MAP with a dominant pattern of inheritance.
- However, recessive inheritance means that both parents of a proband are likely to be unaffected carriers, with the risk to siblings being 25 %.
- Carriers should have enhanced colonoscopic surveillance, beginning 10 years before any cancer in the family and continuing at least 5 yearly. If the spouse is a carrier, then the inheritance pattern within that family becomes dominant, with each child at 50 % risk of having MAP. In addition, antecedents on both sides of the family must be alerted to the possibility that they are carriers or affected.
- In a study screening 9,268 colorectal cancer patients for the two commonly mutated alleles, Lubbe et al. found biallelic hMutYH mutations in 0.3 % of cases. This conferred a 28-fold increase in colorectal cancer risk and was associated with proximal tumors and synchronous adenomas. Monoallelic mutations were not associated with an increase in colorectal cancer risk.

The Hamartomatous Polyposes

Peutz–Jeghers Syndrome

- Peutz–Jeghers syndrome (PJS) is a dominantly inherited cancer syndrome defined by the presence of two of the following three characteristics: perioral, buccal, and occasionally genital melanin pigmentation; gastrointestinal hamartomatous (Peutz–Jeghers) polyposis; and a family history of PJS. The pigmentation can also be seen on the lips and sometimes on the eyelids, hands, and feet or be absent altogether. It usually appears in early childhood and tends to fade in the late 20s. The polyps occur predominantly in the small intestine (78 %) but are also found in the stomach (38 %), colon (42 %), and rectum (28 %). They are hamartomas with a characteristic branching morphology, containing smooth muscle in the submucosa. Adenomatous change with dysplasia and progression to invasive adenocarcinoma has been observed. PJS has an incidence of 1 in 200,000.

Inheritance

- Peutz–Jeghers polyposis is autosomal, dominantly inherited with high penetrance, and is caused by mutation of *LKB1* (also known as *STK11*) on chromosome 19 p13.3. The gene encodes a serine–threonine kinase. Mutation of *LKB1* is only found in about 60–70 % of cases and has been formally excluded in some, suggesting that either other genes are responsible or *LKB1* may be inactivated by epigenetic mechanisms. While a family history is common, de novo mutations are responsible for a significant number of cases.

Clinical Issues

- Polyp-Related Complications. The most common clinical problems in PJS are anemia due to chronic blood loss from large polyps and small bowel obstruction due to intussusception with a polyp at the apex. Repeated emergency bowel resections can lead to increasing operative difficulty and even short-bowel syndrome.
- Risk of Malignancy. Follow-up studies have shown that individuals with this syndrome are at increased risk of developing a range of malignancies at a particularly young age. Approximately half of all patients in one series had died of cancer by age 57, with 50 % being GI. The lifetime risk of any cancer in affected patients is over 90 %. It is estimated that there is a 50-fold excess of gastrointestinal cancer in Peutz–Jeghers syndrome, resulting in a lifetime risk of approximately 20 % of colorectal cancer and about 5 % of gastric cancer, as well as breast, pancreatic (30 % lifetime risk), and ovarian sex-cord tumors (10 % of females); feminizing Sertoli cell testicular tumors in prepubertal boys; and pulmonary and cervical malignancies.

Management

- Probands usually present at a young age with complications of their small bowel polyposis. This often involves laparotomy for intussusception or bleeding. A symptom-focused approach predisposes to frequent laparotomies as untreated polyps enlarge to cause a new set of symptoms. The technique of laparotomy with intraoperative enteroscopy was introduced to reduce the number of repeat emergency laparotomies and small bowel resections. During laparotomy a colonoscope is passed from below through the colon and, with the assistance of the surgeon, into the small bowel for as far as it will go. The most proximal site of insertion is marked with a suture or tape. Then, the colonoscope is withdrawn in a darkened operating room and the sites of polyps marked as it is withdrawn. The procedure is repeated with an enteroscope inserted through the stomach and encouraged to pass distally. The mucosa between the limits of endoscopy can usually be examined through an enterotomy. In most patients, the intussusception is obvious and even if it is reduced, a serosal dimple can be seen at the site of the polyp. The bowel is palpated, and at the site of palpable polyp, an enterotomy is made. The polyps are removed and the bowel intussuscepted through the incision up and down as far as possible. All visible lesions are either removed or cauterized. The enterotomies are closed. Polypectomy is best done by ligating the stalk and excising the polyp with cautery distal to the tie. Otherwise, the stalk may bleed copiously. The fourth part of the duodenum and proximal jejunum is typically a difficult part of the bowel to palpate and to operate.
- Using this "clean sweep" technique, the entire small bowel is cleared of all macroscopic lesions, minimizing the number of laparotomies in subsequent years. The recent availability of capsule endoscopy and double/single balloon enteroscopy offers the potential for endoscopic diagnosis and treatment of the polyps; however, the vascularity of the polyps makes endoscopic treatment in the mid small bowel worrisome. There is a role for capsule endoscopy, however, in surveillance of asymptomatic patients. Colonic polyps can usually be controlled colonoscopically.
- Gastrointestinal Surveillance. Surveillance intervals depend on polyp number, size, histology, and location. A near normal examination can be followed 2 or 3 years later by repeat EGD, capsule endoscopy, and colonoscopy. Hemoglobin should be checked annually. Small bowel polyps causing symptoms or anemia, or measuring over 1.5 cm, should be removed, either endoscopically or at laparotomy with intraoperative enteroscopy.
- Extraintestinal Surveillance. Mammography in premenopausal woman lacks sensitivity, but there is little evidence to support ultrasound or MRI as alternatives. Testicular tumors tend to occur in prepubertal boys, and it would seem sensible to encourage regular examination. Women should undergo standard cervical and breast screening according to nationally agreed protocols. While in some centers regular ultrasound scanning of the pancreas and ovaries are performed, there is no evidence that such measures have any impact on prognosis.

Juvenile Polyposis

- Juvenile polyps are hamartomas, which lack smooth muscle histologically, having poor anchorage to the bowel wall. Solitary juvenile polyps are the commonest colorectal lesion in children, being found in up to 2 %. They have little or no malignant potential. Juvenile polyposis (JPS) is defined as the presence of five or more juvenile polyps in the large bowel or any number of juvenile polyps in a patient with a family history of JPS. Although the colorectum is always affected, the stomach (and perhaps small intestine) is also affected in about 50 %. Most affected individuals develop 50–200 polyps, but some have very few.
- JPS is rare with a frequency of about 1 per 100,000. It presents with rectal bleeding, anemia, or polyp prolapse, at an average age of about 9 years. The polyps are hamartomas, with a characteristic hyperplastic stroma, abundant lamina propria, cystic glands, and inflammation. Adenomatous dysplasia occurs in up to half, which may then progress to adenocarcinoma.
- Other morphologic abnormalities, including macrocephaly, mental retardation, cleft lip or palate, congenital heart disease, genitourinary malformations, and malrotations, are found in 10–20 %. Some patients with JPS have a familial pattern of disease, while in others there is no family history. In those with familial disease, the chances of finding a causative mutation are relatively high (>60 %).

Genetics

- This syndrome is genetically heterogeneous, with three separate genes currently implicated. Mutations in *SMAD4* have been identified in affected individuals. *SMAD4* is a tumor suppressor gene on chromosome 18q21 and is implicated in sporadic colorectal carcinogenesis. It codes for a protein involved in the TGFp signaling pathway. Germ line mutations have been found in 35–60 % of juvenile polyposis patients in the USA, but rather fewer (3–28 %) in Europe.
- Germ line mutations in a second gene, *BMPR1A* on 10q22, have been found in a further 15 % of cases. *BMPR1A* encodes a protein involved in the same signaling pathway.
- *PTEN* mutations have also been reported in so-called juvenile polyposis, but it is as yet unclear whether these cases have Cowden's syndrome or whether they represent a variant of juvenile polyposis.
- Patients with JPS due to a *SMAD4* mutation have a high likelihood of also having hereditary hemorrhagic telangiectasia (HHT). Such patients need a vascular assessment to diagnose or exclude this potentially dangerous condition.

Cancer Risk and Management

- The cumulative risk of colorectal cancer in patients with JPS has been estimated at 30–50 % and that of upper gastrointestinal cancer at 10–20 %. First-degree relatives of affected individuals should be screened by

colonoscopy from around the age of 12 years if asymptomatic and, if normal, 5 yearly thereafter. In many cases, the polyps can be controlled by regular endoscopic polypectomy, with both upper gastrointestinal endoscopy and colonoscopy recommended at least every 2 years. In cases where polyps are either too numerous or too large to be managed in this way, or when patients are symptomatic with diarrhea, mucus, bleeding, and cramps, colectomy with IRA or restorative proctocolectomy is advised.

- It is not clear whether endoscopic surveillance and polypectomy is adequate to prevent malignancy, but there are insufficient data to justify purely prophylactic colectomy. Affected individuals should also undergo upper gastrointestinal surveillance from the age of 25 years.

PTEN Tumor Hamartoma Syndromes

- *PTEN* is an important tumor suppressor gene with key roles in the mTOR/AKT pathway.

Cowden's Syndrome

- This autosomal dominantly inherited syndrome is characterized by macrocephaly (30 %), trichilemmomas (which are considered pathognomonic), and both benign and malignant neoplasms of the thyroid, breast, uterus, and skin. Hamartomas occur in the mouth as well as other parts of the gastrointestinal tract, resulting in a nodular appearance of the buccal mucosa. The International Cowden's Syndrome Group has described a set of major and minor criteria by which to diagnose the syndrome.
- In CS patients, the colon is affected with a variety of polyps, the histology of which includes hamartomas, lipomas, fibromas, neurofibromas, ganglioneuromas, and adenomas.
- Although CS has not been considered a high risk for colorectal cancer, recent data seems to suggest otherwise.
- Certainly, it is safe to start colonoscopic screening when patients are in their 30s and to continue it at least every 3 years, or more often if findings indicate.
- Prophylactic colectomy is indicated when polyposis cannot be controlled endoscopically.

Bannayan–Riley–Ruvalcaba Syndrome

- Here, the colorectal hamartomas (50 %) are associated with characteristic pigmented penile macules, macrocephaly, mental retardation (50 %), lipomatosis, and hemangiomas. It seems likely that as Cowden's and Bannayan–Riley–Ruvalcaba syndromes are caused by mutations of the same gene, they are slightly different forms of the same disorder, and families have been identified in which both phenotypes are evident. There is no evidence to suggest an increased risk of colorectal cancer in this syndrome.

Serrated Polyposis

- Serrated polyps are lesions of the large bowel that were until recently thought to have no premalignant potential. A new nomenclature has arisen wherein serrated polyps with abnormal proliferation are termed sessile serrated polyps (or sessile serrated adenomas) and are now known to be premalignant precursors in a serrated polyp to cancer pathway.
- This pathway is linked genetically to *BRAF* mutations and DNA hypermethylation, particularly when it leads to loss of expression of *hMLH1*.
- The WHO definition for serrated polyposis is any one of the following: 20 or more serrated polyps of any size and location; more than 5 serrated polyps proximal to the sigmoid color, of which 2 are larger than 10 mm; and any number or size of serrated polyps with a family history of SPP.
- No germ line mutation has been identified as the cause of serrated polyposis, and the pattern of inheritance is still not clear. Occasionally patients with a genuine mutation in a DNA mismatch repair gene (i.e. Lynch syndrome) may present with multiple serrated polyps. Fulfiling the cetena for serrated polyps. The presence of multiple synchronous-serrated polyps has, however, been shown to confer a very high risk of colorectal cancer, approaching 50 %.

Treatment

- Treatment of patients with SPP is either endoscopic or surgical. Colonoscopy must be careful as serrated polyps can be difficult to recognize and are likely to be easier to miss than adenomas.
- Yearly, colonoscopy is necessary to prevent cancer.
- If the polyps are not controllable endoscopically, colectomy with IRA is indicated.
- First-degree relatives of patients with SPP are candidates for early screening colonoscopy (10 years prior to the earliest age at diagnosis of a neoplastic lesion in the family).

Hereditary Nonpolyposis Colorectal Cancer

Introduction

- HNPCC refers to a dominant pattern of inheritance of colorectal cancer predisposition without an association with unusual numbers of colorectal polyps.
- Multiple diagnostic criteria have been proposed for the identification of HNPCC families. The most widely used are the Amsterdam I and II criteria, originally proposed to facilitate research but almost immediately adapted for clinical use (see Table 37.7).

Table 37.7 Amsterdam criteria

Amsterdam criteria
At least 3 family members with colorectal cancer, one of whom is first-degree relative of the other 2
At least 2 generations with colorectal cancer
At least 1 individual <50 years at diagnosis of colorectal cancer
Amsterdam criteria II
At least 3 family members with HNPCC-related cancer, one of whom is first-degree relative of the other 2
At least 2 generations with HNPCC-related cancer
At least 1 individual <50 years at diagnosis of HNPCC-related cancer Modified Amsterdam criteria
Two first-degree relatives with CRC involving 2 generations
At least one case diagnosed before 55 years
Two first-degree relatives with CRC and a third-degree relative with endometrial cancer or another HNPCC-related cancer.

Modified from Chung DC, Rustgi AK. The hereditary nonpolyposis colorectal cancer syndrome: genetics and clinical implications. Ann Intern Med. 2003;138:560–70

- Subsequent research has shown that Amsterdam I patients can be divided into two broad subgroups: those whose tumors are microsatellite unstable evidence of defective mismatch repair and presumably (Lynch syndrome) and those whose tumors are microsatellite stable (Familial Colorectal Cancer Type X). Type families are likely to be a heterogeneous group of colorectal cancer predisposition states.
- Type families have a significantly lower risk of colorectal cancer than that found with Lynch syndrome, and they do not have the same array of extracolonic cancers.

Lynch Syndrome

Definition

- Lynch syndrome is hereditary DNA MMR deficiency associated with the early onset of colorectal and other cancers (mean age for colorectal cancer, 45 years).
- Multiple generations are affected with a pattern suggesting dominant inheritance.
- Colorectal cancers tend to be proximal to the splenic flexure, and there is an increased frequency of synchronous and metachronous cancers.
- There is also a high risk of extracolonic cancers, including endometrial, ovarian, gastric, small bowel, hepatobiliary, and transitional cell carcinomas.
- The lifetime risk of cancer is up to 80 %, with colon cancer being the most commonly diagnosed.

History

- By the mid-1980s, two patterns of disease became apparent; Lynch I (colorectal cancer only) and Lynch II (colorectal and other malignancies).
- Concurrent observations showed that the number of colorectal adenomas in these patients was no greater than that in the general population and that there was considerable overlap between Lynch I and II syndromes. Terminology has now come full circle with Lynch syndrome, now a genetic diagnosis, referring to families with a germ line mutation in a MMR gene.
- A set of diagnostic guidelines was agreed upon that would allow researchers to gather homogeneous populations to be studied (Amsterdam I criteria, see Table 37.7).
- Tumors from affected patients show multiple mismatched nucleotides in areas of genes called "microsatellites" described by the term "microsatellite instability."

Genetics

DNA Microsatellites

- When the number of repeats in a microsatellite sequence in a cancer cell is different from the surrounding normal tissue, this is termed "microsatellite instability (MSI)."
- It is assessed using a panel of microsatellite markers. Over 40 % instability in termed MSI-high and is a strong indication of defective DNA mismatch repair.

DNA Mismatch Repair

- DNA mismatches occur during cell division when one strand slips on the other as a new DNA molecule is reconstituted. This is especially likely to happen in DNA microsatellites that can be thought of as "slippery" parts of the DNA.
- Unrepaired mismatches are seen as MSI (Fig. 37.6). The mismatch repair genes are *hMLH1*, *hPMS1*, *hPMS2*, *hMSH2*, *hMSH3*, and *hMSH6*. Both *MSH3* and *MSH6* must be abnormal to have complete loss of hMSH2-dependent mismatch repair.
- MLH1 and PMS2 bind to form a second heteroduplex that interacts with the MutS duplex, stimulating excision and resynthesis. When an inactivating mutation silences expression of an MMR gene, the microsatellite mismatches go unrepaired and are propagated into lines of daughter cells as mutations. This so-called mutator phenotype of Lynch syndrome is characterized by an increased genome-wide mutation rate. When tumor suppressor genes contain a microsatellite, they are vulnerable to loss of expression in the mutator phenotype. Examples of such genes are *MSH3*, *MSH6*, *TCF4*, *BLM*, *caspase-5*, *TGFβRII*, *IGFRII*, *BAX*, *PTEN*, and *APC*, many of which are involved in control of colonocyte growth.
- The most commonly mutated genes in Lynch syndrome families are *MLH1* (33 % of families) and *MLH2* (31 %). Recently, a meta-analysis

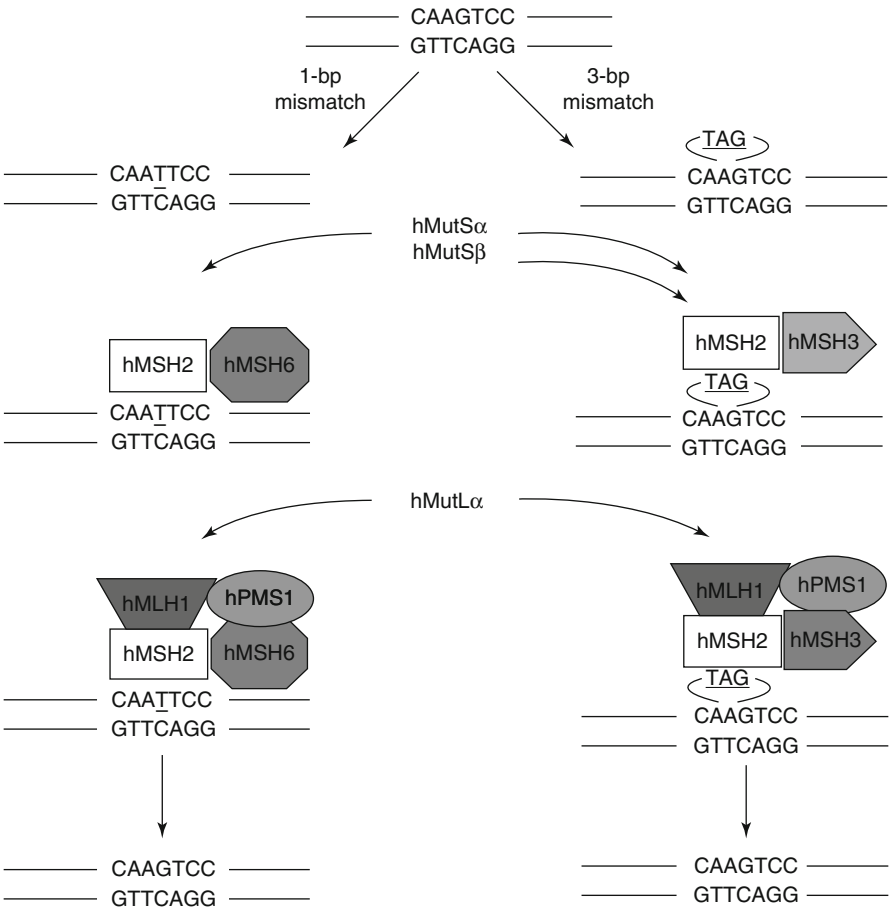

Fig. 37.6 The DNA mismatch repair system can correct either single base-pair mismatches or larger loops of mismatched DNA. hMSH2 serves as the "scout" that recognizes mismatched DNA. It forms a complex with either hMSH6 or hMSH3, depending on the number of mismatched nucleotides. A second heterodimeric complex (hMLH1/hPMSI) is then recruited to excise the mispaired nucleotides. hMUTSα = hMSH2/hMSH6; hMuTSβ = hMSH2/hMSH3; hMutLα = hMLH1/hPMS1. *bp* base pair (Reprinted with permission from Chung DC, Rustgi AK. The hereditary non-polyposis colorectal cancer syndrome: genetics and clinical implications. Ann Intern Med. 2003;138:560–70)

of index families fulfilling the Amsterdam criteria revealed that a mutation in *MLH1* is found in 25.5–29.6 % of families and *MSH2* is found in 14.8–21.6 % of the families.

Pathology

- Some pathologic features can be seen in tumors associated with the mutator phenotype and MSI. These include mucinous differentiation with signet ring cells, the presence of tumor-infiltrating lymphocytes

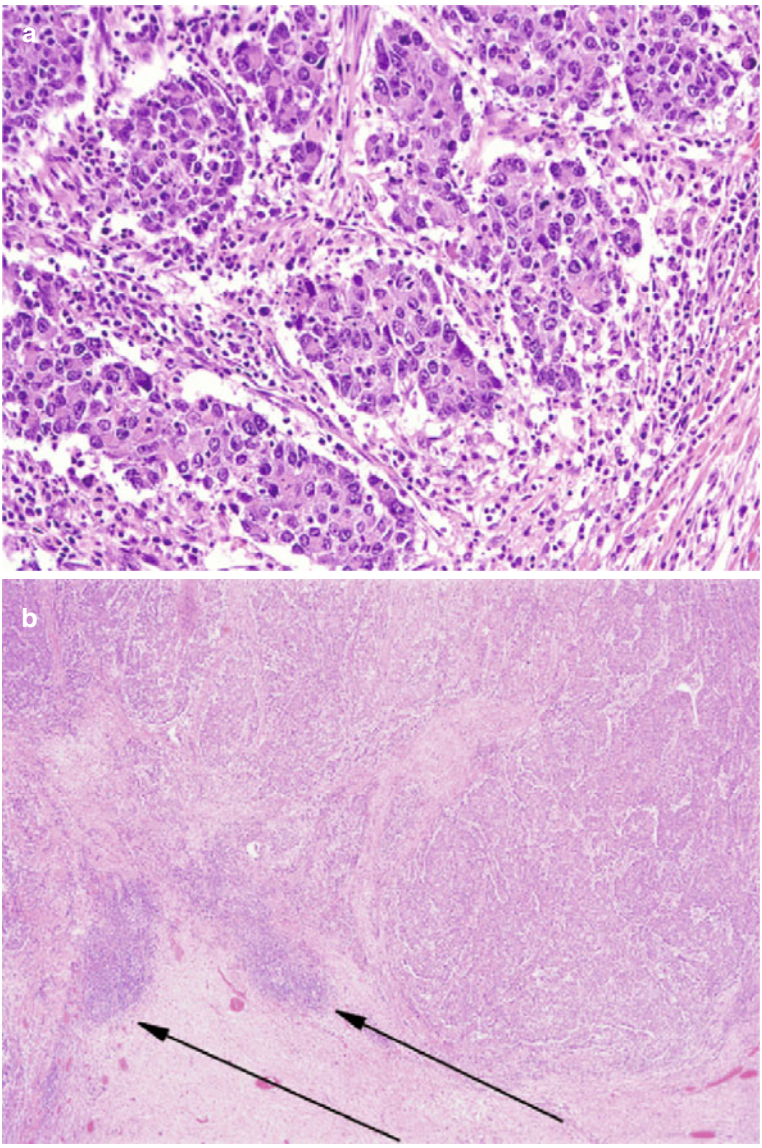

Fig. 37.7 (**a**) Medullary carcinoma-type pattern with peritumoral lymphocytic infiltrate. (**b**) MSI-H cancer with *marked* peritumoral lymphocytic infiltrate (*black arrows*) (Crohn's-like reaction), ×20 magnification (Courtesy of Robert E. Petras, MD, National Director Gastrointestinal Pathology Services, Ameripath Inc., Oakwood Village, OH and Associate Professor of Pathology, Northeastern Ohio University College of Medicine)

(Fig. 37.7a), a Crohn's-like reaction (Fig. 37.7b), and the absence of dirty necrosis. Despite what appears to be unfavorable histology, the incidence of metastatic tumor in lymph nodes is less than that found with sporadic colon cancer.

Table 37.8 Lifetime risks for cancer associated with the hereditary nonpolyposis colorectal cancer syndrome

Type of cancer	Persons with HNPCC	General population
Colorectal	80–82	5–6
Endometrial	50–60	2–3
Gastric	13	1
Ovarian	12	1–2
Small bowel	1–4	0.01
Bladder	4	1–3
Brain	4	0.6
Kidney, renal, pelvis	3	1
Biliary tract	2	0.6

Adapted from Chung DC, Rustgi AK. The hereditary nonpolyposis colorectal cancer syndrome: genetics and clinical implications. Ann Intern Med. 2003; 138:560–70

- Most Lynch syndrome tumors are diploid compared to sporadic chromosomal unstable tumors which are frequently aneuploid, where tumorigenesis is related to sporadic mutations and loss of heterozygosity (LOH).

Clinical Features

- Patients with Lynch syndrome have an increased lifetime risk of colon cancer and other extracolonic cancers (see Table 37.8).
- Colon cancer is the most frequently diagnosed cancer (80 %).
- Endometrial cancer is the most frequent extracolonic cancer (50–60 %).
- Colorectal cancers in Lynch syndrome are usually proximal to the splenic flexure (68 % vs. 49 % of sporadic cancers), more likely to have associated synchronous cancers (7 % vs. 1 % sporadic colon cancer), and have increased metachronous cancers at 10 years (29 % vs. 5 % sporadic cancers).
- Similarly, women with Lynch syndrome-related endometrial cancer have a 75 % risk of a second cancer during a 26-year follow-up.
- The median age of onset of colon cancer is 42 years, and for endometrial cancer, it is 49 years.
- In Lynch syndrome, an adenoma is the precursor lesion for cancer. Adenomas are located in the proximal colon and 70 % of the polyps have an absent MMR protein on immunohistochemistry. It is estimated that malignant transformation occurs in 1 to 3 years in Lynch syndrome as opposed to 10 years in sporadic colon cancer.
- Two other types of polyps – the flat adenoma and serrated adenoma – have been implicated as possible precursors of Lynch syndrome cancers. Flat adenomas are found proximally in up to 50 % of Lynch syndrome patients (Fig. 37.8a, b). About 20 % of flat adenomas show MSI-H and have a mutation in the *TGFβRII* gene. These polyps are difficult to detect during

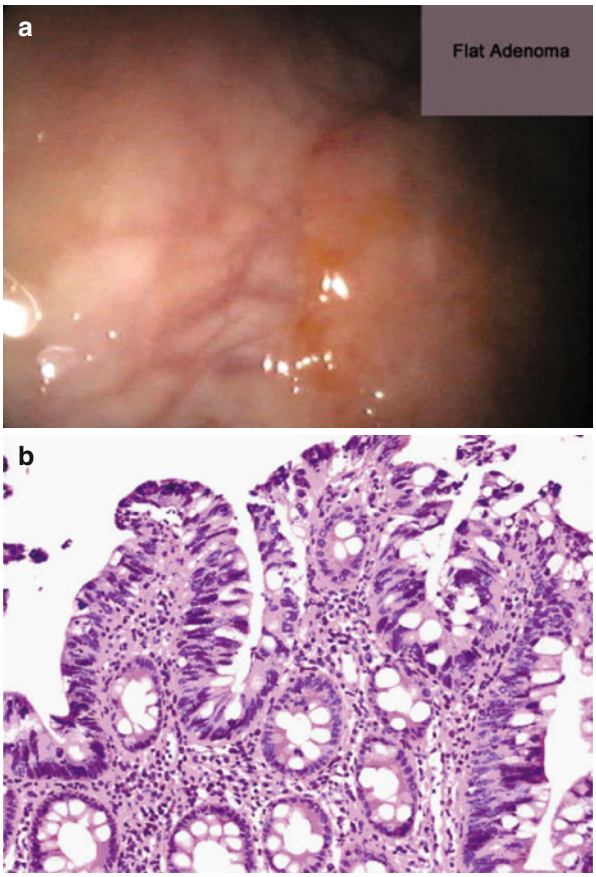

Fig. 37.8 (**a**) Colonoscopic view of a flat adenoma in the cecum that could easily be overlooked. Such polyps are more easily seen using dye-spraying techniques. (**b**) Microscopic view of same polyp following endoscopic removal, showing severe dysplasia, ×100 magnification (Courtesy of Dr. Robert E. Petras, MD, National Director Gastrointestinal Pathology Services, Ameripath Inc., Oakwood Village, OH and Associate Professor of Pathology, Northeastern Ohio University College of Medicine)

colonoscopy, and flat adenomas with advanced histology (high-grade dysplasia or cancer) are significantly smaller (10.7 mm) than comparable polypoid lesions (20 mm).

Genotype–Phenotype Relationships

- *MSH2* mutation appears to be associated with a later age of onset of rectal cancer and more extracolonic cancers than in the *MLH1* mutation-positive group.
- Germ line *MSH6* mutations are uncommon and associated with a particularly high risk of uterine cancer, which is more common than colon cancer in affected women.

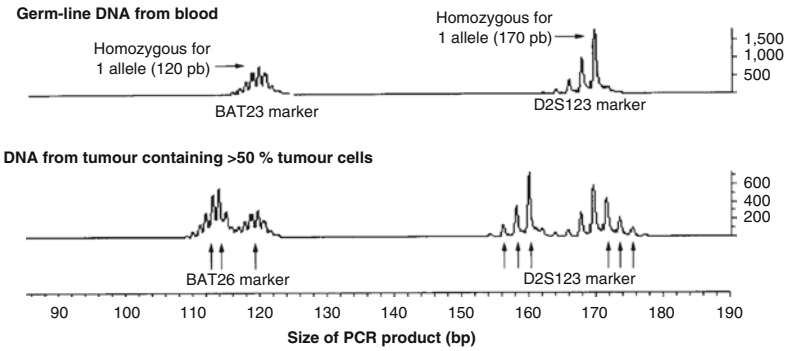

Fig. 37.9 Detection of microsatellite instability with the use of fluorescent labeling of polymerase chain reaction (*PCR*) products analyzed in an automatic sequencer. Two markers are analyzed in the same track: the mononucleotide repeat marker BAT26 is shown on the *left*, and the dinucleotide marker D2S123 is shown on the *right*. The *upper* tracking is from germ line DNA from blood. The *lower* tracing is from DNA extracted from a histologic section of a tumor containing more than 50 % tumor cells. For marker BAT26, germ line DNA shows a single peak, indicating that the patient is homozygous for this marker (*arrow*). Tumor DNA shows, in addition to the normal allele (*single arrow*), a new allele (*double arrows*) that has lost approximately five nucleotides. This constitutes microsatellite stability. For marker D2S123, germ line DNA is homozygous, whereas tumor DNA shows two new alleles (*triple arrows*), one with a loss of approximately 10 nucleotides (*left*) and one with a gain of two nucleotides (*right*). Thus, the tumor shows microsatellite instability with both markers. All peaks display "stutter" – that is, small amounts of material with a gain or a loss of one or a few nucleotides. This is a normal phenomenon (Reprinted with permission from Lynch HT, De la Chapelle A. Hereditary colorectal cancer. N Engl J Med. 2003;348:919–32. Copyright © 2003 Massachusetts Medicine Society. All rights reserved)

- Over 30 potentially pathogenic *MSH6* mutations exist, and 35 % involve only one amino acid.
- Colorectal cancers are more frequently left sided in *MSH6* carriers (Figs. 37.9, 37.10, and 37.11).

Muir–Torre Syndrome

- The Muir–Torre syndrome is the combination of Lynch syndrome and sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas.
- Colorectal cancers are most commonly found (51 %) and are often proximal to the splenic flexure (60 %).
- Although only 25 % of Muir–Torre patients develop a polyp, 90 % of patients who develop polyps develop colon cancer.
- The second most frequent tumors are genitourinary (24 %).
- Germ line mutations in *MLH1* and *MSH2* have been identified, and many of the tumors exhibit MSI.
- The median age of diagnosis is 55 years and only 60 % has a positive family history.

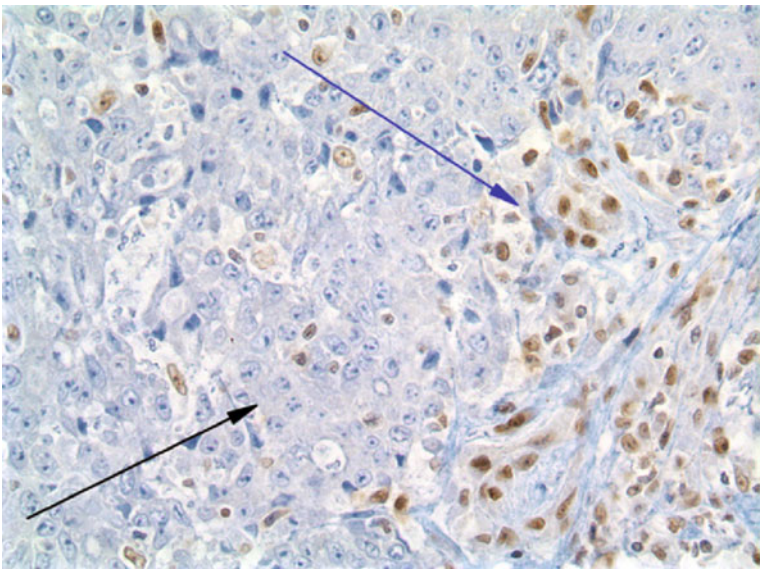

Fig. 37.10 hMLH1 immunohistochemistry. *Blue arrow* indicates positive nuclear staining for the presence of hMLH1 protein within an inflammatory cell. *Black arrow* demonstrates the absence of protein within cancer cells, ×400 magnification (Courtesy of Robert E. Petras, MD, National Director Gastrointestinal Pathology Services, Ameripath Inc., Oakwood Village, OH, and Associate Professor of Pathology, Northeastern Ohio University College of Medicine)

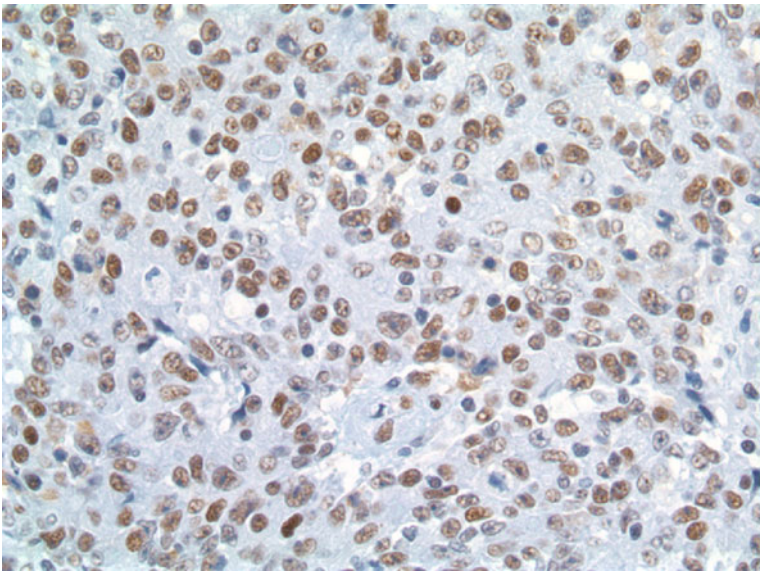

Fig. 37.11 hMSH2 immunohistochemistry. Positive nuclear staining demonstrates the normal presence of hMSH2 protein, ×400 magnification (Courtesy of Robert E. Petras, MD, National Director Gastrointestinal Pathology Services, Ameripath Inc., Oakwood Village, OH, and Associate Professor of Pathology, Northeastern Ohio University College of Medicine)

Table 37.9 Modified Bethesda guidelines

Patient with 2 HNPCC-related tumors
Patient with CRC with first-degree relative with HNPCC-related cancer; one of the cancers at <50 years or adenoma at <40 years
Patient with CRC or endometrial cancer at <50 years
Patient with right-sided, undifferentiated CRC at <50 years
Patient with signet ring CRC at <50 years
Patient with adenoma at <40 years

Modified from Rodriguez-Bigas MA, Boland CR, Hamilton SR, Henson DE, Jass JR, Khan PM, Lynch H, Perucho M, Smyrk T, Sobin L, Srivastava S. A National Cancer Institute Workshop on hereditary nonpolyposis colorectal cancer syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst. 1997;89:1758–62

Diagnosis

Amsterdam Criteria

- The key to the diagnosis of Lynch syndrome is a high index of suspicion and an awareness of some of the subtle phenotypic clues. The easiest clue to detect is a strong family history of colorectal and Lynch syndrome cancers. The first Amsterdam criteria (I) (Table 37.7) were created to identify patients with a high probability of having HNPCC. However, the Amsterdam I criteria were faulted for not including extracolonic cancers, and so Amsterdam II criteria were published to correct this (Table 37.7). A third set of Amsterdam criteria (Amsterdam-like) have been used, where an advanced adenoma is allowed to qualify one of the three affected individuals, accounting for the phenotype attenuation caused by increasingly widespread screening. However Hampel et al. have shown that when Lynch syndrome was diagnosed by MSI-directed mutational testing, 22 % of families did not meet Amsterdam criteria and 10/23 probands were older than 50 years. Therefore, although Amsterdam criteria are still useful, on their own they have a high false-negative rate. The "false-positive" rate of Amsterdam criteria for MMR gene mutation carriers (Lynch syndrome) represents Familial Colorectal Cancer Type X.

Bethesda Criteria

- In 1996, a National Cancer Institute workshop on MSI produced a set of criteria to identify patients whose cancers are likely to be microsatellite unstable. These Bethesda criteria and their revision (Table 37.9) include family history as well as tumor characteristics, such as histology and site. The Bethesda criteria are a useful screen for triaging colorectal cancers for MSI testing but were never intended as diagnostic criteria for Lynch syndrome.

Tumor Testing with MSI and Immunohistochemistry

- MSI testing is being used as a screening test to detect Lynch syndrome although 15 % of sporadic colorectal cancers are unstable due to promoter methylation of *hMLH1*. If *hMSH2* is not expressed, this is good evidence for Lynch syndrome. If *hMLH1* is not expressed, the clinical situation (i.e., family history, age, and site of the cancer) may give a clue as to the existence of Lynch syndrome. The tumor can also be tested for a *BRAF* mutation which, if present, suggests a sporadic, hypermethylated cancer rather than Lynch. After tumor triage by MSI and IHC testing, patients can be selected for genetic testing for a germ line mutation.

Histology

- Pathologists may recognize cancers that have arisen due to the mutator phenotype by the presence of tumor-infiltrating lymphocytes, a Crohn's-like reaction, mucinous differentiation, signet ring cells, and the absence of dirty necrosis.

Predictive Models

- Jenkins et al. using tumor-infiltrating lymphocytes, tumor location (proximal vs. distal), mucinous histology, poor differentiation, Crohn's-like reaction, and diagnosis before age 50 years had a sensitivity of 93 % and a specificity of 55 % for MSI-high.
- MMRpro was devised by Chen et al. to predict the probability that a patient carries a deleterious mutation of *MLH1*, *MSH2*, or *MSH6* and the chances of developing colorectal or endometrial cancer in the future. It includes family history, endometrial cancer status, and current age or age at last follow-up (in years) if unaffected. The formula had a concordance index of 0.83 and a ratio of observed to predicted cases of 0.94. It is available online at http://www4.utsouthwestern.edu/breasthealth/cagene/.
- Barnetson et al. produced a predictive formula to calculate the risk of carrying a germ line MMR gene mutation. It is as follows: $Pr/(1-Pr) = 1.39 \times 0.89$ age at diagnosis $\times 2.57$ gender (male = 1, female = 0.57) $\times 4.45$ (site of tumor, proximal = 1, distal = 0) $\times 9.53$ synchronous or metachronous tumor (yes = 1, no = 0) $\times 46.26$ family history of colorectal cancer (youngest < 50) $\times 7.04$ family history of colorectal cancer (youngest > 50 years of age) (yes = 1, no = 0) $\times 59.36$ family history of endometrial cancer <50 years of age (yes = 1, no = 0). This model provided a subset of patients in whom preoperative tumor biopsies could be subjected to IHC, and the combination has a positive predictive value of 80 % for mutation carriers.

Table 37.10 Direct mutation finding ($n=70$)

Category	Sensitivity (%)	Specificity (%)
Amsterdam [$n=28$]	61	67
Amsterdam II [$n=34$]	78	61
Bethesda [$n=56$]	94	25
Bethesda (1–3) [$n=44$]	94	49

Adapted and reproduced from Syngal S, Fox EA, Eng C, Kolodner RD, Garber JE. Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations in MSH2 and MLH1. J Med Genet. 2000;37:641–45

Genetic Testing for a Germ Line MMR Gene Mutation

Indications

- Patients whose families fulfill Amsterdam I, II, and like criteria; patients fulfilling revised Bethesda criteria; patients with MSI-high tumors with wild-type *BRAF* or loss of expression of an MMR protein are candidates for genetic testing (Table 37.10).

Procedure

- Genetic counseling is routine.
- Sequencing of *MSH2*, *MLH1*, *PMS2*, and *hMSH6* is now commercially available. The cost of this testing is usually covered by the patient's health insurance. Once the pathologic mutation in the family has been found, screening of at-risk relatives is considerably cheaper. A data bank of known mutations is kept by the International Society for Gastrointestinal Hereditary Tumors (InSiGHT).

Strategy of Genetic Testing

- Testing should begin with an affected individual (in whom a Lynch syndrome cancer has been diagnosed). When the proband has a negative or a noninformative test (including variant of unknown significance), genetic testing of at-risk family members is not helpful and all at-risk family members require intensive surveillance.
- When the proband has a pathologic mutation, at-risk family members can be offered genetic screening.

Surveillance

- Colorectal cancers in Lynch syndrome can occur in very young patients and develop within a year of a negative colonoscopy.
- Adenomas occur earlier and are more likely to be villous.

- The adenoma to carcinoma transition occurs early and small cancers can be missed.
- Most guidelines suggest beginning colonoscopy at age 21, or 10 years younger than the youngest affected relative's age at diagnosis (whichever is younger).
- Colonoscopies continue every 2 years until age 40 when they are every year. If an adenoma is found, colonoscopy is every year thereafter.
- The value of screening colonoscopy in Lynch syndrome was demonstrated by Jārvinen and colleagues who studied a group of 252 individuals belonging to 22 HNPCC families. Colorectal cancer developed in 8 % of the screened family members, compared to 16 % of those who refused screening. In those individuals who were known to have a DNA MMR gene mutation (Lynch syndrome), the rate of colorectal cancer in those who underwent screening was 18 % compared to 41 % in those who did not undergo screening.
- Due to the high risk of endometrial cancer in women, annual pelvic ultrasound to examine the endometrium is recommended beginning between ages 25 and 35 years as the increased risk for gynecological cancer in these patients begins at age 25.
- Prophylactic colectomy and hysterectomy is the most effective way to prevent cancer in Lynch syndrome patients. Although prophylactic colectomy is not commonly performed in unaffected mutation carriers, its benefits must be discussed.

Treatment

Surgery

- The surgical options for colon cancer in a Lynch syndrome patient are a standard right, left, or sigmoid colectomy or a colectomy and ileorectal anastomosis. Oncologically, IRA is the operation of choice for colon cancer. It minimizes cancer risk, preserves anal sphincter function, and retains the reservoir capacity of the rectum. The estimated risk of rectal cancer after colectomy and IRA is 12 % at 12 years. The risk for a metachronous colon cancer in HNPCC is 45 % with only segmental colectomy.
- In women undergoing colectomy, strong consideration should be given to performing a hysterectomy and bilateral salpingo-oophorectomy if their family is complete, due to the increased risk of both endometrial and ovarian carcinoma.

Prognosis

- The survival rate in Lynch syndrome patients with colorectal cancer is better than that of patients with sporadic colorectal cancer when matched for stage and age of onset. There is also evidence that patients with stage II or III microsatellite-unstable colorectal cancers do not benefit from 5-fluorouracil-based adjuvant therapy and may even do worse with it.

Chemoprevention

- Data exist to support the efficacy of NSAIDs in reducing the risk of colorectal cancer in the general population, and a recent study suggests the same benefits as high dose aspirin in patients with Lynch syndrome.
- This recent CAPP II trial was a controlled, randomized trial of colorectal polyp and cancer prevention using aspirin and resistant starch in carriers of a germ line MMR gene mutation. Its first report described no impact of this chemoprevention on the development of adenomas but a reduction in the rate of cancers of all types.
- Calcium and vitamin D intake have been associated with a decreased risk of sporadic colorectal cancer.

Familial Colorectal Cancer Type X

- This collection of families, where the history of colorectal cancer is strong enough to comply with Amsterdam criteria but where tumors are microsatellite stable, is poorly defined.
- A local registry can be found by accessing the Collaborative Group of the Americas on Inherited Colorectal Cancer at http://www.cgaicc.com.