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Lower Gastrointestinal Tract Cancer Predisposition Syndromes

N. B. Shah, M.B., Ch.B. and

Department of Medical Genetics, Mayo Clinic, Rochester, MN. Tel - (507) 266 2967, Fax - (507) 284 1067

N.M. Lindor, M.D.

Department of Medical Genetics, Mayo Clinic, Rochester, MN. Tel - (507) 266 2967, Fax - (507) 284 1067

N. B. Shah: shah.neel2@mayo.edu; N.M. Lindor: nlindor@mayo.edu

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Introduction

Though inherited predisposition to colorectal cancer (CRC) has been suspected for over 100 years, definitive proof of Mendelian syndromes had to await maturation of molecular genetic technologies. Since the 1980s, the genetics of several clinically distinct entities has been revealed. Five disorders that share a hereditary predisposition to CRC are reviewed in this chapter. They are summarized in Table 1.

Peutz-Jeghers Syndrome (PJS)

Clinical Overview

PJS is a rare, highly penetrant, autosomal dominant disorder characterized by hamartomatous polyposis and mucocutaneous pigmentation. Polyps may occur anywhere along the gastrointestinal tract but occur most consistently in the jejunum. Extraintestinal sites of PJS polyps include kidney, ureter, gallbladder, bronchus and nasal passages. Around one third of patients will develop polyp-related symptoms by age 10 years and close to two thirds by age 20 years [1].

The incidence of PJS is estimated as 1 in 8,300 to 1 in 200,000 live births [2]; 25% of cases appear to be non-familial. PJS has been reported worldwide [3, 4] and occurs in males and females equally. There is variability in both the severity of disease as well as age of onset of symptoms.

The hyperpigmented macules of PJS develop in 95% of affected individuals and arise most commonly in the perioral region, around the eyes and nostrils, on the buccal mucosa, the

Correspondence to: N. B. Shah, shah.neel2@mayo.edu.

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perianal area and on the digits of hands and feet. They usually appear by the end of the first year of life and are almost always present by age 5 years [5]. The macules may be dark blue to dark brown, vary in size from 1-5mm and may fade in puberty and adulthood, and are not precancerous.

Classical PJS intestinal polyps are hamartomata and experienced pathologists are capable of distinguishing PJS polyps from juvenile polyps. PJS polyps manifest characteristic hypertrophy or hyperplasia of the smooth-muscle layer branching in tree-like fashion (arborizes) into the superficial epithelial layer. Multiple adenomas may also occur, especially in the colon.

Cancer Risk

PJS carries an increased risk for multiple benign and malignant tumors (Table 1). The cumulative risk of any cancer is 67-85% by age 70 and the cumulative risk for CRC is 3% (40 years), 5% (50 years), 15% (60 years), 39% (70 years) [6, 7]. The risk to age 70 for cancers of the pancreas, uterus/ovary/cervix, breast, and lung were 11%, 18%, 45%, and 17%, in the same series, respectively. An increased risk of primitive biliary cancer was reported in PJS [8]. No correlation has been found between risk of cancer and severity of polyposis or presence of pigmentation [9].

Molecular Basis of Disease

Germline mutations in *STK11* (also known as *LKB1*) encoding a tyrosine kinase on chromosome 19p13.3, have been identified in most PJS families [10, 11] and 94% of PJS patients overall [12]. Families without an identified mutation do not differ clinically or ethnically from those with a mutation. Only one transcript is known, a 433 amino acid protein that is ubiquitously expressed and present primarily in the cytoplasm and to a lesser extent in the nucleus [13, 14]. *STK11* is a highly conserved gene with approximately 88 and 84% homology, respectively, with mouse (*LKB1*) and *Xenopus* homologs. *STK11* is the only tyrosine kinase known to function as a tumor suppressor by physically associating with *TP53* to regulate *TP53*-dependent apoptosis pathways [15, 16]. *STK11* also interacts with *PTEN*, which is responsible for other hereditary hamartoma syndromes and also plays a role in the VEGF pathway and cellular polarity.

Inactivation of *STK11* is a critical early event in the development of hamartomas and adenocarcinomas [17]. Adenocarcinomas in Peutz-Jeghers syndrome demonstrate altered *TP53* expression and loss of heterozygosity (LOH) in 17p and 18q. Microsatellite instability, LOH near the *APC* gene, or *KRAS* mutations have been identified in some tumors [17] with indications that tumorigenic potential of *STK11* mutations is mediated through alternative mechanisms in different tissues, especially those in which hamartoma development is not a feature.

Hamartomatous polyps have generally been considered to have a very low malignant potential and it was uncertain that PJS-associated hamartomas were the premalignant lesions in PJS. However, molecular and histological studies have confirmed that hamartomatous polyps can undergo malignant transformation in PJS [18]. It is not known whether

inactivation of both *STK11* alleles is necessary for carcinogenesis or if a 50% decrease in protein expression is sufficient (haploinsufficiency). Data from studies in *LKB1* $-/+$ and *LKB1* $-/-$ mice support both possibilities [19, 20].

Clinical Risk Management

The cancer risk with PJS supports efforts at directed surveillance strategies for early detection of tumors. Multiple guidelines based solely on expert opinion exist; none have been validated in controlled trials. Table 2 shows one set of screening recommendations for PJS [21]. A guiding principle in management is prevention of bowel intussusception or obstructions. In one series, laparotomy for bowel obstruction was performed in 30% of individuals by age ten years and in 68% by age 18 years [22]. Substantial morbidity arises from short-gut syndrome, as a consequence of multiple small-bowel resections for intussusception; therefore prophylactic removal of small bowel polyps is advised. For small bowel polyps not accessible endoscopically, surgery has been recommended if symptomatic or when larger than 1.5cm. Intraoperative small bowel endoscopy can allow removal of all identifiable polyps and may decrease the overall frequency of laparotomy [23, 24].

Clinical genetic testing for PJS is available and has greater than 90% sensitivity for mutation discovery. If a disease-causing mutation has been identified it is appropriate to offer genetic testing to at-risk relatives and, if positive, surveillance is indicated. If no disease-causing mutation is found in an individual with PJS, then first degree relatives must be advised that they may still be at risk for PJS and that PJS cancer surveillance is advisable.

Juvenile Polyposis (JP)

Clinical Overview

JP is an autosomal dominant disorder characterized by multiple (5-200) hamartomatous polyps of the gastrointestinal tract [25]. It is the most common of the hamartomatous polyp syndromes. Population incidence is estimated to be between 1 in 16,000 and 1 in 100,000 [26]. Twenty to fifty percent of cases are inherited.

Solitary juvenile polyps may be seen in approximately 2% of normal children but these are seldom dysplastic and are not associated with increased malignancy or extracolonic manifestations [12, 27]. In JP, “juvenile” refers to the type of polyp (resembling sporadic inflammatory hamartomatous polyps of childhood) rather than the age of onset, though most affected individuals have some polyps by age 20 years. The hamartomas of JP have a frond-like growth pattern, less stroma and dilated glands with more proliferative smaller glands compared to solitary, sporadic juvenile polyps [28].

Clinical criteria for defining JP have been proposed (Table 3):

While 5 polyps have been proposed as the minimum number for diagnosis, some individuals will have greater than 100 polyps. In a review of 272 individuals with JP of undefined genetic subtype, 98% had involvement of the colorectum, 14% of the stomach, 7% of the jejunum and ileum, and 2% of the duodenum [29]. Polyps usually range from 5 – 50 mm in size, can be single or multilobulated, spherical in shape and commonly show surface

erosion. Clinical symptoms of JP may include bleeding, diarrhea, abdominal pain, intussusception and rectal prolapse and even protein-losing enteropathy. Digital clubbing has been noted, perhaps due to the overlap with hereditary hemorrhagic telangiectasia and arteriovenous shunting in those patients [30].

JP may be misdiagnosed as it shares clinical features with several other colonic hamartomatous polyp syndromes (Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers, Basal Cell Nevus/Gorlin) so is therefore a diagnosis of exclusion. Physical examination, family history, and molecular testing may help differentiate between these possibilities [31, 32].

Cancer Risk

Most juvenile polyps are benign but malignant transformation may occur resulting in increased lifetime risk for cancers of the colon (10-40%), stomach (21%), and, less commonly involving the small bowel, and pancreas. The lifetime risk of cancers has been hard to define and may vary with underlying genetic cause and may be likely being reduced by screening polypectomies.

Malignant transformation is suspected to follow a juvenile polyp-> adenomatous change-> dysplasia-> carcinoma sequence [33, 34]. However, additional work is required to determine if individuals with JP are also predisposed to malignancy separately from the predisposition to polyps.

Molecular Basis of Disease

JP is clinically and genetically heterogeneous. Three genes *SMAD4*, *BMPRIA* and *ENG* have been implicated so far. Each encodes proteins of either TGF- β or BMP-signaling pathways. The low combined mutation detection rate has prompted a search for other candidate genes/proteins within these pathways.

About 20% of individuals with JP have a mutation of *SMAD* (also known as *MADH4* or *DPC*) [32, 35, 36]. *SMAD4* is part of the TGF- β signal transduction pathway. The *SMAD* gene family is on chromosome 18q21.1, adjacent to DCC (deleted in colon cancer). *SMAD4* complexes combine with other members of the *SMAD* family of proteins to transmit the TGF- β growth suppressing signal from the cell surface receptor to nuclear downstream targets, mediating apoptosis and growth inhibition. It has been postulated that the abundant stroma in JP may create an abnormal microenvironment, disrupting TGF- β signaling [37, 38]. This theory is supported by the fact that as hamartomatous polyps enlarge and mesenchymal component expands, they take on a serrated or villous-type configuration associated with epithelial dysplasia.

Mutations in *BMPRIA* (*ALK3*) at 10q22.3, are found in around 20-25% of individuals with JP [32, 35, 36]. *BMPRIA* is a serine-threonine kinase type I receptor of the TGF- β superfamily which when activated leads to phosphorylation of *SMAD4*. A reduced number of gastric polyps have been observed in *BMPRIA* mutation-positive compared to *SMAD4* mutation-positive patients [35, 39, 40].

Mutations in *ENG* on chromosome 9q34.1 have been reported in very early-onset JP [41]. *ENG* encodes endoglin an accessory receptor protein that binds to specific TGF- β proteins [42]. Mutations in *ENG* are more often found in individuals with Hereditary Hemorrhagic Telangiectasia. The combined syndrome of JPS and hereditary hemorrhagic telangiectasia (HHT) (termed JPS/HHT) may be present in 15%-22% of individuals with a *SMAD4* mutation and has also been associated with *ENG* (Table 4). The prevalence of *ENG* mutations in JP patients without HHT has yet to be adequately described [43].

Clinical Risk Management

No evidence-based guidelines exist to determine optimal screening modalities or intervals in JP. Because of the perceived high risk for malignancies, guidelines based on expert opinion have advised that those affected with or at-risk for JP receive a complete blood count, upper gastrointestinal endoscopy and colonoscopy beginning from the onset of symptoms or the age of 15. If no polyps are found, screening should be repeated every 1-3 years. Any polyps found should be removed and screening should be annual or based on polyp burden until no polyps are found [44]. For those with extremely numerous polyps, colectomy and/or gastrectomy may be indicated. Colorectal adenocarcinoma should be treated with definitive surgery, and consideration of total colectomy with or without ileorectal anastomosis based on clinical findings.

Familial Adenomatous Polyposis (FAP)

Clinical Overview

FAP is a highly penetrant, autosomal dominant syndrome caused by germline mutations of the adenomatous polyposis coli (*APC*) gene [45] at 5q21. FAP has a frequency of 1 in 5,000-10,000 live births and affects males and females equally [46]. It accounts for 1% of all CRC [47]. 10-30% of cases arise from *de novo* mutations [48]. It was the first CRC syndrome to be recognized clinically [49] and the first for which a gene was identified. It offers a model for the adenoma→carcinoma paradigm that is shared by sporadic as well as several familial colorectal cancers and through this, offers a basis for the concept of all CRC being 'genetic'.

FAP is the result of an inactivating mutation in *APC* and clinical presentation may be associated with the site of mutation, although it may also be clinically heterogeneous even within the same family. This suggests a role for modifier genes and/or environmental factors in modulating disease expression [50]. Colorectal polyposis, numbering from hundreds to thousands, is nearly pathognomic of FAP. Polyps are generally less than 1cm and occur throughout the colorectum with a predilection for sigmoid colon and rectum [51]. They may be sessile or pedunculated with histology varying from tubular to villous adenoma.

FAP has multiple extracolonic manifestations involving all three embryological layers. The term Gardner syndrome refers to FAP and these extracolonic features. Endodermal lesions include gastric and small bowel polyps and carcinomas. Mesodermal abnormalities include desmoid tumors, osteomas and dental abnormalities. Ectodermal lesions may affect the eye, brain and skin. The combination of CRC and brain tumors was referred to as Turcot syndrome. However, molecular studies have shown that while colonic polyposis and

medulloblastoma was associated with *APC* mutations, CRC and glioblastoma was associated with mismatch repair genes [52].

Desmoid tumors are histologically benign clonal neoplasms comprised of fibrous tissue. They arise as mostly intra-abdominal soft-tissue tumors [53] and occur in approximately 10-25% of FAP patients [54]. Trauma has been suggested to be a factor as 84% of FAP-associated desmoids developed within 5 years of abdominal surgery in one series [55]. They do not usually metastasize but they are very locally invasive and can cause significant mass effect, obstruction and pain. They may also occur sporadically or in a hereditary manner without colon findings [56, 57] but in cases of families with desmoid tumors or individuals with 2 or more, attempts should be made to exclude *APC* mutation.

Osteomas may occur in any bone but often localize to the face. Dental abnormalities affect 70% of FAP patients and include supernumerary teeth, congenitally absent teeth, fused roots and osteomas of the jaw [51]. Depending on the location they can lead to symptoms and indeed identification of FAP. Congenital hypertrophy of retinal pigment epithelium (CHRPE) is an asymptomatic hamartoma of the retinal epithelium occurring in 66-92% of FAP patients [58].

‘Attenuated FAP’ (AFAP), defined as fewer than 100 synchronous colorectal adenomas, shows a right-sided colonic predilection with rectal sparing and a later presentation [59]. Extracolonic manifestations may occur similar to classic FAP. It has been linked to mutations in exons 1-4, 3’ regions of *APC* distal to codon 1580 and the alternatively spliced site of exon 9 [45, 60-62]. However, some patients with this phenotype and no identified *APC* mutation have been shown to have compound heterozygous mutations in base excision repair gene *MYH* [63] leaving open the possibility that cases of AFAP may be hitherto unidentified *MYH*-associated polyposis (MAP). If germline *APC* mutation testing is negative in suspected AFAP, testing for *MYH* mutations may be indicated.

Cancer Risk

The age at onset of colorectal adenomas is variable, being present in only 15% of FAP gene carriers at age 10 years, 75% by age 20 and 90% by 30 years [64, 65] if untreated. In a review of over 180 families and 922 affected individuals, the mean age at presentation was 27 and mean age at colectomy was 29 [66].

Extracolonic tumors (Table 5) cause significant morbidity in FAP with desmoid tumors and duodenal cancers being the second and third commonest causes of death after CRC [67]. In one series, 88% of FAP patients developed duodenal polyps, often near the ampulla and papilla [68], with a lifetime risk of duodenal carcinoma of 4-12% [69]. Duodenal polyps may be associated with different germline *APC* mutations than those with severe colonic polyposis [70]. Gastric cystic fundic gland polyps may develop in up to 33% of FAP patients. Gastric carcinoma is rare in FAP (Marcello et al. 1996) but may be higher in Asian populations [71, 72].

Hepatoblastoma occurs in an estimated 0.6% of children prior to 6 years but is rare thereafter [73]. Thyroid carcinoma may affect 12 % of FAP patients [74] but carries a good

prognosis. They are predominantly well-differentiated papillary cancers affecting young women.

Molecular Basis of Disease

APC is a tumor suppressor gene consisting of 15 exons and encodes a protein of 2843 amino acids [75] that is involved in cell adhesion, signal transduction, transcription regulation, cell cycle control, apoptosis and maintenance of the fidelity of chromosomal segregation. As part of a scaffolding protein complex it negatively regulates Wnt signaling [75, 76].

APC inactivation is the hallmark of the chromosomal instability pathway (CIN) phenotype that occurs in the majority of CRC. Increasing size, number and worsening histology of polyps reflect the linear process of carcinogenesis along the CIN pathway.

Over 800 *APC* germline mutations have been reported [62] with the vast majority associated with FAP being frameshift or nonsense mutations [45]. *APC* mutations are not distributed evenly, with 'hotspots' at codons 1061 and 1309 accounting for approximately 11 and 17%, respectively, of germline mutations. The majority lie in the 'mutation cluster region' (MCR) between codons 1250 and 1464 in the 5' region of exon 15 [62].

Clinical Risk Management

Mutation analysis can identify sequence changes in up to 95% of classic FAP cases. However, the early development of adenomas raises special considerations relating to genetic testing of children. Genetic consultation is recommended for newly diagnosed FAP families as this can determine whether genetic testing would be informative for at-risk relatives. A negative test within a family with a known *APC* mutation allows colorectal screening to revert to that recommended to the population with background cancer risk i.e. colonoscopy or equivalent test starting age 50.

Management may be affected by genotype as severity of disease and extracolonic tumors may correlate with the location of *APC* mutations. Mutations between codons 1250 and 1464, especially codon 1309, often lead to profuse polyposis with earlier presentations [77-80].

For those with an FAP phenotype/confirmed mutation or from an affected family but where they have not yet been tested the following surveillance is advised:

- Annual palpation of the thyroid gland.

Birth to 6 years:

- Annual hepatoblastoma screening by abdominal ultrasound and alpha-fetoprotein serum concentration.

10 years and up:

- Sigmoidoscopy or colonoscopy every 1-2 years. Once polyps are detected by either procedure, full colonoscopy should be repeated annually. AFAP family members may begin in the late teens and repeat every 2-3 years.

- Esophagogastroduodenoscopy (EGD) with side-viewing endoscope should be performed after the development of colonic polyposis or age 25, whichever is sooner. EGD should be repeated every 1-3 years depending on number, size and degree of dysplasia of duodenal adenomas. Removal of duodenal adenomas is indicated if polyps (1) exhibit villous or severe dysplastic histology, (2) exceed 1cm in size, or (3) cause symptoms.

Small bowel contrast studies or computerized tomography (CT) of abdomen and pelvis with oral contrast may also assist in monitoring duodenal and colorectal adenomas. Biopsy of an enlarged but otherwise normal ampullary papilla and endoscopic retrograde cholangiopancreatography (ERCP) to identify duodenal and common bile duct adenomas may also be indicated. Gastric cancer risk may be higher in Asian populations and specific screening may be indicated for these groups [81].

Prophylactic colectomy before malignant transformation is recommended for classic FAP once polyps have appeared but timing will depend on adenoma size, number and degree of dysplasia. Colectomy for AFAP is often deferred until polyps become too difficult to control. For desmoid tumors, as surgery may accelerate growth, a conservative approach may be reasonable [82, 83].

Lynch Syndrome or Defective DNA Mismatch Repair Type HNPCC (Hereditary Non-Polyposis Colon Cancer)

Clinical Overview

Lynch syndrome is an autosomal dominant condition caused by mutation in one of several DNA mismatch repair genes [84, 85] that maintain DNA fidelity. These genes encode proteins that form a multimeric DNA mismatch repair (MMR) complex that corrects the small insertions or deletions that frequently occur during somatic replication [86-88]. Defective MMR leads to the so-called “mutator” or “replication error” phenotype where a markedly increased rate of mutation, inevitably involving cell-cycle regulation, increases the potential for malignancy [89].

Lynch syndrome accounts for approximately 3-5% of all CRC [90, 91] and 2% of endometrial cancer [92]. This makes it the commonest inherited colon cancer syndrome. Patients may have synchronous and metachronous CRC with a predilection for right-sided cancer, proximal to the splenic flexure. Other cancers associated with Lynch syndrome include stomach, small intestine, liver, pancreas and biliary tract, brain, ovarian and transitional cell carcinoma of the ureter and renal pelvis [93-96] (Table 6). Small bowel cancer is sufficiently rare in the general population that its diagnosis should instigate a careful history, including pedigree, and physical examination for signs of a cancer syndrome.

Muir-Torre syndrome is a variant of Lynch that combines colorectal tumors with multiple cutaneous adnexal neoplasms (sebaceous adenomas and carcinomas and keratoacanthomas) and tumors in endometrium, kidney, ovaries, stomach and small intestine. Mutations in *MSH2* account for the majority of Muir-Torre [97-99]. Glioblastoma in Lynch syndrome

may be referred to as ‘Turcot syndrome’ but should not be confused with medulloblastoma in familial adenomatous polyposis (FAP), also called Turcot syndrome.

Diagnosis

The research criteria for identifying Lynch syndrome families were established by the International Collaborative Group (ICG) meeting in Amsterdam in 1990 and are hence known as the ‘Amsterdam criteria’ [100]. However, 39% MMR gene mutation positive Lynch syndrome families do not meet these criteria [101] so they were revised in 1999 to Amsterdam II [102-104] to take suspicious extracolonic malignancies into account. An even less stringent third set of criteria have been devised expressly to identify individuals for whom tumor MSI testing is recommended [105] (Revised Bethesda guidelines); broadening the criteria enhances sensitivity but greatly reduces the specificity for Lynch syndrome.

Amsterdam Criteria (1990):

1. One member diagnosed with CRC before age 50.
2. Two affected generations.
3. Three affected relatives, one of them a first-degree relative of the other two.
4. FAP excluded.
5. Tumors verified by pathological examination.

Amsterdam II Criteria (1999): Identical to the above except in broadening the third criterion: It still requires at least 3 affected relatives, but now with any recognized Lynch syndrome-related cancer i.e. colorectal, endometrial, small bowel, ureter or renal pelvis.

Revised Bethesda Criteria (2004): Any one criterion would support MSI testing.

1. One member diagnosed with CRC before age 50.
2. Presence of synchronous, metachronous CRC or other Lynch syndrome-associated tumor* in an individual regardless of age.
3. CRC with MSI-H pathologic features diagnosed in an individual less than 60 years (presence of tumor infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern).
4. CRC or Lynch syndrome-associated tumor* in at least one first-degree relative younger than 50.
5. CRC or Lynch syndrome-associated tumor* diagnosed in two first degree or second-degree relatives at any age.

*endometrial, stomach, ovarian, pancreas, small bowel, biliary tract, ureter or renal pelvis, brain, sebaceous gland adenoma or keratoacanthoma.

Distinguishing Lynch syndrome from HNPCC

There are families who fulfill the classical Amsterdam I criteria but do not have evidence of defects in MMR pathways and who do not appear to have the same risk of syndrome-

associated cancers as those with defective MMR. Families meeting Amsterdam I criteria with intact MMR have been classified as 'Familial Colorectal Cancer Type X' [106-111] and it is probable that there are as yet unidentified genes that are associated with this phenotype. There is a move, therefore, to only refer to Lynch as the syndrome of HNPCC with genomic instability; the term HNPCC remains as an umbrella term including broadly all those who fulfill Amsterdam criteria regardless of MSI status.

Cancer Risk

The average age of CRC diagnosis in Lynch syndrome is 44 years, versus 64 years in sporadic cancer, though individuals with mutations in *MSH6* have a mean age at CRC diagnosis of 55-57 years [112]. The lifetime risk for developing CRC is 80% though evidence of differing patterns of penetrance are emerging for each gene [113-115] with CRC occurring earlier in male *MLH1*-carriers than female.

The commonest extracolonic cancer is endometrial adenocarcinoma which affects at least one female in about half of all Lynch syndrome families with mean age at diagnosis also in the fifth decade [116]. The lifetime risk for endometrial cancer in women may be 21-71% at age 70 [112]; risk varies with the underlying gene involved. *MSH2* has higher endometrial cancer risk than does *MLH1* for example. Lifetime risks for ovarian cancer are 3-13%; gastric cancer 2-13%; urinary tract cancer 1-12%; small bowel cancer 4-7%; and pancreas cancer 4% [116]. Associated endometrial cancer subtypes include endometrioid, clear cell carcinoma, uterine papillary serous carcinoma and malignant mixed Müllerian tumors [117].

Molecular Basis of Disease

Microsatellites are short, repeating units of 1-3 nucleotides located throughout the genome, primarily in introns [118]. They are particularly susceptible to errors from MMR gene defects. Tumor DNA showing alterations in microsatellite regions is an indicator of defective MMR which can arise from somatic or germline mutations [119]. These mutations are termed microsatellite instability (MSI). For the designation of MSI in an adenocarcinoma, a minimum percentage of unstable loci are required as many CRCs show frameshift mutations in a small percentage of microsatellite repeats. If a tumor shows more than 30% of markers unstable it is MSI-high (MSI-H), if less than 30%, MSI-low (MSI-L). If no loci are unstable it is designated microsatellite stable (MSS).

Recognized genes include *MLH1* (*human mutL homolog 1*) at 3p21.3, *MSH2* (*human mutS homolog 2*) at 2p21-p22, *MSH6* at 2p16 and *PMS2* (*postmeiotic segregation 2*) at 7p22. The exact roles of *PMS1* at 2q31-q33 and *MSH3* at 5q11-q12 remain unclear. Approximately 90% of CRC in Lynch syndrome is MSI-H [120, 121] except those with mutations in *MSH6* who do not necessarily manifest this phenotype.

Testing for loss of *MSH2*, *MLH1*, *MSH6* and *PMS2* expression by immunohistochemistry (IHC) in colorectal cancer using monoclonal antibodies and can help identify the mutated gene [122-124]. Absent expression has a high predictive value to detect germline mutations though it is not seen in all MSI-H tumors [125, 126] as MSI-H itself is not specific for a

germline MMR defect. Age-related methylation of *MLH1* accounts for the sporadic majority of MSI-H tumors [102].

Germline mutation analysis for *MSH2*, *MLH1*, *MSH6* and *PMS2* may be performed for suspected Lynch syndrome after screening tumors for microsatellite instability and/or absence of protein expression [127, 128]. Using both screening tests together increases the yield for finding Lynch syndrome mutations [90, 113, 115, 129]. The Revised Bethesda Guidelines [105 1997] describe the clinical indications for MSI and tumor analysis. Up to 90% of Lynch syndrome families have mutations in *MSH2* and *MLH1* [130, 131]. The majority of mutations are detected by sequencing, but deletion and duplication analysis is required to be complete. Using both sequence and deletion testing together may increase sensitivity to 95% [132-134].

Clinical Risk Management

For those at-risk and others with strong family histories but no diagnostic confirmation by genetic or prior tumor testing, colonoscopy every 1-2 years, starting around age 20 or at least 10 years before the earliest CRC in the family, is recommended [116, 135, 136]. If there is a history of cancer below the age of 25 in the family, this may require genetic testing of children with similar considerations to FAP. Once a mutation is identified in a family, testing can be offered to at-risk relatives and those without the mutation exempted from intensive surveillance. If no mutation can be identified, an inherited cancer pre-disposition is not excluded but testing of relatives would be uninformative. Members of such families should continue intensive screening.

The progression from normal mucosa to adenoma to cancer may be accelerated in Lynch and because of the only modest or no increase in number of polyps, it seems a larger proportion undergo malignant transformation [137, 138]. This would suggest a requirement for frequent screening and optimal quality examinations to ensure no lesions are missed.

The choice of CRC surveillance techniques has widened in recent years. However, since neoplasms in Lynch syndrome may be subtle, flat lesions, there is evidence that CT colonography (or virtual colonoscopy) would have inferior sensitivity compared to standard optical colonoscopy [139]. Chromo-endoscopy using indigo carmine may be used to augment standard screening as data suggest it aids detection of small but histologically advanced adenomas [140, 141]. Unlike for FAP, sigmoidoscopy is not a recommended option due to the preponderance of right-sided cancers. Stool DNA testing for somatic gene mutations cannot replace germline mutation testing and has not been adequately studied in CRC predisposition syndromes.

Polypectomy reduces the incidence of CRC in Lynch syndrome [138]. Nevertheless, given the shortcomings of screening, some Lynch-syndrome family members will opt for prophylactic colectomy. Moreover, there remains a risk of CRC in the rectal remnant after subtotal colectomy [142] and individuals who have undergone partial resection should continue endoscopic surveillance. Once CRC is found, subtotal or total colectomy with ileorectal anastomosis has been recommended over a partial resection by some experts.

Endometrial cancer screening may be considered by age 25 [135] and options include pelvic exam +/- Papanicolaou smear, endometrial biopsy, CA-125 testing and/or transvaginal ultrasound (TVUS). Studies of the latter so far have been disappointing [143-146] though TVUS can also help evaluate the ovaries. Endometrial sampling may have better sensitivity [147] and is suggested by a National Institutes of Health task force to begin from age 30-35 [136]. Oral contraceptives reduce the incidence of sporadic endometrial and ovarian cancer but have not been demonstrated to have a benefit in Lynch syndrome. Women may consider prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) for similar reasons. This decision must be taken in light of childbearing plans and potential side-effects of long-term hormone replacement therapy. Though a retrospective study suggested hysterectomy and BSO were effective at preventing endometrial and ovarian cancer [148], all Lynch syndrome candidates for prophylactic surgery should be counseled on the limitations, especially regarding ovarian cancer prevention.

There is no defined role to screen for gastric and small intestinal neoplasms with upper gastrointestinal endoscopy at present. There is also no evidence for annual urinalysis with cytology for urinary tract cancer but it is non-invasive and inexpensive and hence generally advised. Careful skin exam on an annual basis would appear justified on the same basis, though no screening for cancer of the pancreas, biliary tract or brain is yet recommended. Rare patients with biallelic germline MMR mutations have been described with very early-onset Lynch tumors, café-au-lait macules and early onset hematologic or brain malignancies [149, 150]. Management of such individuals would have to be on a case by case basis.

MYH-Associated Polyposis (MAP)

Clinical Overview

Mutations in the *MYH* (or *MUTYH*) gene on 1p32.1-p34.3 cause an autosomal recessive CRC predisposition syndrome associated with multiple colonic polyps. It may be indistinguishable from classical or attenuated FAP [151] and it has been suggested that MAP is the real attenuated FAP [63]. Duodenal adenomas, gastric fundic gland polyps, CHRPE, osteomas and dental anomalies, and desmoids tumors, previously hallmarks of FAP have now been reported in MAP. The colorectal polyps range in number from a few to over 500 and tend to be mainly small tubular or tubulovillous adenomas with mild dysplasia with occasional hyperplastic polyps. Cancer can arise anywhere in the colorectum but the adenomas may show a right colonic predilection.

Cancer Risk

MAP tends to present later than classical FAP. In two major series, the mean ages at presentation were 46 and 51 with a range of 13 to 70 and the presenting feature in 50% of cases was CRC [152, 153]. Jenkins et al. [154], reported cumulative risk to age 70 of 80% representing a 50-fold risk of CRC. There was also a threefold increase in risk in monoallelic carriers (8% cumulative risk to age 70) but other data shows no appreciable increase risk in monoallelic *MYH* carriers [155-159]. Duodenal adenomas with or without duodenal adenocarcinoma have been reported in approximately 5% [160, 161].

Molecular Basis of Disease

MYH is a base-excision repair (BER) gene that repairs mutations caused by reactive oxygen species [162]. It codes for a DNA glycosylase that identifies and removes adenine residues that have been incorrectly paired with 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG) [163]. Failure to correct this causes an increase in G:C --> T:A transversions, particularly at GAA sequences, which leads to a stop codon, TAA. The *APC* gene is a major downstream target of *MYH* mutations [151]. MAP tumors are generally microsatellite stable (MSS).

Over 80 germline variants have been reported. The majority is missense, but also reported are 6 truncating mutations, splice-site mutations and several small insertion/deletions [164]. The commonest mutations in Caucasians are Y179C and G396D (formerly called Y165C and G382D, respectively) accounting for 53% and 32% of all mutations respectively. The Y179C mutation is more deleterious than the G396D mutation [155, 160].

Approximately 1% of the general population is heterozygous for an *MYH* mutation. *MYH* carriers could acquire a somatic mutation (a 'second hit') in the wild-type allele and develop CRC, however somatic *MYH* mutations are infrequent in CRC [165]. Moreover, the role of somatic mutations in *MYH* in the development of non-familial CRC is yet to be understood. It is notable that *MYH* mutations have not yet been implicated in non-gastrointestinal cancers in which reactive oxygen species are thought to play a role in carcinogenesis, including lung, breast, kidney, liver and prostate [132, 166-169].

Clinical Risk Management

Establishing the correct genetic diagnosis will direct cancer surveillance for family members. Classical and attenuated FAP are dominantly inherited with risk for successive generations whereas only a single generation is at risk for recessively inherited MAP. The National Comprehensive Cancer Network guidelines (http://www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf) from 2009 recommend colonoscopy starting at 25-30 years with repeat every 3-5 years if negative and upper endoscopy with side-viewing duodenoscope from age 30-35. If adenomas are found, then management should proceed as for FAP.

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Table 1

Lower Gastrointestinal Tract Cancer Predisposition Syndromes.

LOWER GASTROINTESTINAL TRACT CANCER PREDISPOSITION SYNDROMES						
Syndrome	Gene	Inheritance	Gastrointestinal Polyp Histology	Extra-Colonic Cancers	Other Associations	Estimated Cumulative Colorectal Cancer Risk
Peutz-Jeghers Syndrome	<i>STK11</i>	AD	Hamartoma + + + + , Adenoma +	Cervical, uterus, ovarian, breast, serotoli cell tumors, entire GI tract, pancreato-biliary	Hyperestrogenism, Mucosal pigmentation + + + + , Facial pigmentation + , Polyps in gallbladder, ureter, nasal and bronchial passages	39% by 70 years
Juvenile Polyposis	<i>BMPRIA</i> <i>SMAD4</i> <i>ENG</i>	AD	Hamartoma + + + + , Adenoma +	Gastric, small intestine, pancreas	HHT	17-68% by 60 years
Familial Adenomatous Polyposis	<i>APC</i>	AD	Adenoma + + + + , Cystic fundic gland polyp	Duodenal, hepatoblastoma medulloblastoma, papillary thyroid	Desmoid tumors, osteomas, CHRPE, dental anomalies, gastric polyps	90% by 45 years 69% by 80 years attenuated FAP)
Lynch Syndrome	<i>MLH1</i> <i>MSH2</i> <i>PMS2</i> <i>MSH6</i>	AD	Adenoma +	Endometrial, ovarian, gastric, small intestine, pancreato-biliary, renal pelvis and ureter, sebaceous carcinoma, keratoacanthoma, glioblastoma	Sebaceous adenoma	80% by 75 years
MYH- Associated Polyposis	<i>MYH</i>	AR	Adenoma + + + + , Hyperplastic + , Gastric fundic gland polyp	Duodenal	Duodenal adenoma, gastric polyps, CHRPE, osteomas, dental anomalies, desmoid tumors	80% by 70 years

LEGEND

AD = Autosomal Dominant

AR = Autosomal Recessive

+ = seen in this condition

+ + + = very common in this condition

CHRPE = Congenital hypertrophy of retinal pigment epithelium

HHT = Hereditary Hemorrhagic Telangiectasia

Table 2

Cancer Screening and Surveillance Screening Guidelines based on expert opinion for Peutz-Jeghers Syndrome
No evidenced based data exists to support these guidelines [21].

Site	Procedure	Starting age (years)	Interval (years)
Stomach, small and large bowel	Upper and lower endoscopy	8	2
	Small bowel follow-through / capsule enteroscopy	8	2*
Breast (Female only)	Clinical breast examination	20	1
	Mammography	20	2-3
Testicle	Testicular examination	10	1
Ovary, cervix, uterus	Pelvic examination with cervical cytology	20	1
	Pelvic ultrasound	20	1
Pancreas	Endoscopic ultrasound or transabdominal ultrasound	30	1-2

* Consider laparotomy and intraoperative endoscopy to remove polyps >1.5 cm.

Table 3

Diagnostic criteria for JP [170]
One or more of the following:-
- >5 juvenile polyps in the colon/rectum.*
- Juvenile polyps throughout the gastrointestinal tract
- Any number of juvenile polyps with a family history of JP.

* Modified by Giardiello et al. (1991) to 3 more polyps.

Table 4

Juvenile polyposis and hereditary hemorrhagic telangiectasia.

Gene (OMIM number)	Juvenile polyposis	HHT*
<i>BMPRIA/ALK3</i> (601299)	Approx. 20%–25%	Not yet reported
<i>SMAD4/MADH4</i> (600993)	Approx. 20%	<20% some features
<i>ENG</i> (131195)	Reported	30%–40%
<i>ACVRI/ALK1</i> (601284)	Not reported	30%–40%
Unknown	>50%	>20%

OMIM = online Mendelian inheritance in man.

* HHT = hereditary hemorrhagic telangiectasia (also known as Osler–Weber–Rendu syndrome [OMIM # 187300, 175050, 600376]).

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Table 5

Extracolonic Tumor Risks in Familial Adenomatous Polyposis [45, 56, 171-174].

Malignancy	Relative Risk	Absolute Lifetime Risk (%)
Desmoid	852.0	15.0
Duodenum	330.8	3.0–5.0
Thyroid	7.6	2.0
Brain	7.0	2.0
Ampullary	123.7	1.7
Pancreas	4.5	1.7
Hepatoblastoma	847.0	1.6
Gastric	—	0.6 ^a

^aThe Leeds Castle Polyposis Group.

From Genetics of Colorectal Cancer (NCI). Downloaded Nov 30 2009 from <http://www.cancer.gov/cancertopics/pdq/genetics/colorectal/HealthProfessional/Table4>

Table 6

Cancer Risks in Individuals with Lynch syndrome up to Age 70 Years [95, 120, 175-180].

Cancer	General Population Risk	Lynch Syndrome	
		Risks	Mean Age of Onset
Colon	5.5%	80%	44 years
Endometrium	2.7%	20%-60%	46 years
Stomach	<1%	11%-19%	56 years
Ovary	1.6%	9%-12%	42.5 years
Hepatobiliary tract	<1%	2%-7%	Not reported
Urinary tract	<1%	4%-5%	~55 years
Small bowel	<1%	1%-4%	49 years
Brain	<1%	1%-3%	~50 years
Pancreas	1%	4%	~53