The genetic understanding of colorectal cancer (CRC) continues to evolve rapidly. Currently, up to 10% of all CRCs are thought to be due to one of over 10 different hereditary syndromes. The colorectal cancer syndromes have been traditionally classified as polyposis and non-polyposis syndromes and the polyposis syndromes have been further separated histologically into adenomatous, hamartomatous and serrated polyposis syndromes. The genetic basis for most of these syndromes is well defined and clinical classifications are being supplemented and increasingly supplanted by genetic classification of the syndromes. Traditionally, genetic testing was performed for syndrome-specific genes in families that met the accepted clinical criteria for a known syndrome but, as more genetic testing is done, it is becoming increasingly clear that the cancer spectrum of many of the hereditary cancer syndromes is much broader than originally thought and that there is substantial overlap in their phenotypes. The observed overlap in phenotype, along with the rapidly decreasing costs of next-generation gene sequencing, has led to increasing use of cancer gene panels for diagnosis of the hereditary cancer syndromes. In this review, the clinical features and approach to management of the hereditary CRC syndromes is described along with an approach to selection of families that should be referred for genetic counseling and possible genetic testing.

INTRODUCTION

Up to 30% of all colorectal cancers (CRCs) have some familial component and about 5% of all CRC are thought to be due to known hereditary syndromes. Genetic identification of hereditary syndromes allows comprehensive prevention and management strategies tailored for specific mutation carriers and their family members. This review will focus on the approach to recognition of hereditary syndromes with emphasis on identification of patients/families that should be referred for genetic counseling and possible testing. Genomic analysis of CRCs and individualized treatment base on CRC genetics will be covered in other chapters of this issue.

IDENTIFICATION OF HEREDITARY CRC SYNDROMES CLASSIFICATION OF SYNDROMES

Hereditary CRC syndromes have been traditionally divided into polyposis or non-polyposis syndromes (continued on page 42)
Lynch Syndrome (LS)

LS, previously referred to as hereditary non-polyposis CRC (HNPPC), is the most common hereditary cause of CRC, accounting for 2-5% of all CRC cases and an estimated prevalence of one in 370 in the US. It is an autosomal dominant syndrome caused by a germline mutation in one of the mismatch repair (MMR) genes (MLH1, MSH2, MSH6 and PMS2) or deletions in the EPCAM gene which causes hypermethylation and subsequent silencing of the MSH2 gene. Somatic events lead to inactivation of the remaining wild-type allele, resulting in genomic instability due to an inability to correct single-base mismatches or insertion-deletion loops that occur commonly during normal DNA replication. This genomic instability is the basis of the increased colorectal, endometrial, ovarian and other cancer risks in LS (Table 1).

Cancer Risk in LS

CRC and endometrial cancer are the most common cancers in LS (30-60% lifetime risk), but LS mutation carriers also have an increased risk of other cancers, including ovarian, gastric, small bowel, ureter/renal pelvis and sebaceous skin cancers, among others (Table 1). Cancer risks in LS are dependent on the genotype with MSH6 and PMS2 generally having lower cancer risks than the other genotypes. Table 1 summarizes LS cancer risks by genotype.

Genetics of LS

MLH1 and MSH2 account for about 80% of LS cases but MLH6 and PMS2 families are likely underrepresented in high-risk registries due to their attenuated phenotype. Germline deletions of EPCAM cause the clinical picture of LS with MSH2 deficient, microsatellite unstable tumors but without detectable MSH2 mutation. These deletions involved the 3’ end of EPCAM leading to transcriptional read-through into, and subsequent epigenetic silencing of the neighboring MSH2 gene by promoter hypermethylation. CRC risk in EPCAM deletion carriers is similar to those with an MSH2 mutation but endometrial cancer risk is lower (Table 1).

Diagnosis

It has been estimated that only 1-2% of the 830,000 LS mutation carriers in the US are aware of their diagnosis. This is likely due to a combination of sub-optimal knowledge of multi-generation family history, under-recognition of those who have a family history that place them at risk for LS and poor clinical screening criteria for the detection of Lynch. The approaches to diagnosis of LS are discussed below.

Family History Criteria

The Amsterdam criteria for LS (Table 2) were developed before genetic testing was available; they are highly specific but have a low (~50%) sensitivity and positive predictive value for LS. The US Multi-Society Task Force (US-MSTF) recently recommended the use of a three question screening tool (Figure 1) to identify families who should be referred for additional family history assessment or genetic evaluation. When studied...
in a direct referral endoscopy center, this tool had a higher sensitivity for detecting high-risk CRC families (77%), and it identified 95% of patients in a validation cohort of Lynch mutation carriers. Individuals who answer yes to any of the three questions should be evaluated with a more detailed family history and/or referred to a genetics clinic.

Quantitative predictive models have also been developed to help identify potential LS patients. Three of these are accessible on the online; MMRPredict (http://hnpccpredict.hgu.mrc.ac.uk/); PREMM (http://premm.dfci.harvard.edu) and MMRPro (http://66.118.159.147/HRAExpressEntry/(S(o04sbxj2urqwghk21sv0o4e))/default.aspx). MMRPredict is designed to predict risk of gene mutation only in CRC-affected patients, whereas PREMM 1,2,6 and MMRPro predict risk in unaffected individuals as well. These models depend on collection of an accurate multi-generation family history. They performed similarly in predicting MMR mutation and all are superior to Amsterdam and Bethesda criteria. Individuals estimated by these models to have ≥5% risk of LS should be referred for genetic counseling/testing.

**Tumor Testing for LS**
The Bethesda criteria (Table 3) were developed to identify individuals with CRC who should have their cancers tested for evidence of MMR deficiency (loss of MMR protein expression or microsatellite instability [MSI] by polymerase chain reaction [PCR]). Individuals with MMR deficient CRCs should have further evaluation for LS. The Bethesda criteria are about 80% sensitive and specific for LS. Essentially all LS-associated CRCs are MMR deficient but about 15% of sporadic CRCs are also MMR deficient due to hypermethylation and transcriptional silencing of MLH1. If IHC shows loss of MLH1, testing for BRAF mutation or MLH-1 promoter hypermethylation can separate the sporadic MSI CRCs that arise through the CIMP/Serrated pathway from those that should be referred for genetic counseling/testing for LS.

**Universal MSI or IHC Testing**
Universal testing of all CRCs for evidence of MMR deficiency has been recommended as a means to increase the detection rate of patients with LS; it has higher sensitivity (100% vs 86%) for LS than the Bethesda criteria with similar specificity (96% vs 98%), and modeling studies suggest that universal testing can identify LS at an acceptable cost.

**Management**

**Screening & Surveillance**
Retrospective data strongly supports colonoscopic screening in LS. Jarvinen et al. demonstrated that LS patients who had regular screening had a markedly decreased incidence and mortality from CRC. Multiple professional societies support initiating colonoscopic screening between the age of 20 and 25 and screening every 1-2 years. Screening recommendations for extra-colonic malignancies are based largely on expert consensus and are summarized in Table 1.

**Chemoprevention**
A controlled trial of aspirin (600 mg/day) in 861 Lynch mutation carriers showed no benefit at the end of 24 months of treatment, but after 56 months of follow up, there was a lower CRC incidence (OR 0.56, 95% CI 0.32-0.99, p=0.05) in the aspirin-treated group. Aspirin chemoprevention is a reasonable option in LS mutation carriers, especially if they have an elevated cardiovascular risk and a low risk of bleeding complications. The optimal dose is not established; a dose-finding trial is currently under way.

**Surgical Management**
Although a total or subtotal colectomy is generally recommended in LS mutation carriers who require colonic resection, there is little controlled data comparing surgical approaches. Retrospective analyses have reported lower rates of metachronous CRCs after total or subtotal colectomy (0-6%) than after a segmental colectomy (22-26%).

**Familial Colorectal Cancer Type X (FCCTX)**
Families that meet Amsterdam I criteria but with microsatellite stable CRCs are classified as having FCCTX. No genetic basis has yet been found for these families. FCCTX families have an increased risk of CRC but not of endometrial or other Lynch-associated cancers. Regular colonoscopic screening is recommended for members of FCCTX families (Table 1).

**FAMILIAL ADENOMATOUS POLYPOSIS (FAP)**
FAP is a rare syndrome that accounts for less than 1% of all CRC cases with an estimated prevalence of 1/10,000 to 1/30,000. FAP is an autosomal dominant syndrome due to a germline mutation in the adenomatous polyposis coli (APC) gene. The classic phenotype of FAP is characterized by hundreds to thousands of colonic adenomas beginning in adolescence. Untreated,
## Traditional Classification of Hereditary CRC Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Polyp Histology</th>
<th>Inheritance Pattern</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NON-POLYPOSIS SYNDROMES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Adenomas</td>
<td>Autosomal Dominant</td>
<td>Multiplicity of cancers, young age of onset, microsatellite instability</td>
</tr>
<tr>
<td>Familial Colorectal Cancer Type X</td>
<td>Unknown</td>
<td>Adenomas</td>
<td>Autosomal Dominant</td>
<td>Amsterdam criteria +, Microsatellite stable</td>
</tr>
<tr>
<td><strong>POLYPOSIS SYNDROMES</strong></td>
<td></td>
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</tr>
<tr>
<td>Classic Familial Adenomatous Polyposis</td>
<td>APC</td>
<td>Adenomas</td>
<td>Autosomal Dominant</td>
<td>Colon: 100-1000s adenomas, Extra-colonic: duodenal adenomas, gastric fundic gland polyps, desmoid tumors, epidermoid cysts, extranumery teeth, osteomas</td>
</tr>
<tr>
<td>Attenuated Familial Adenomatous Polyposis</td>
<td>APC</td>
<td>Adenomas</td>
<td>Autosomal Dominant</td>
<td>Colon: &lt;100 adenomas, Extra-colonic: duodenal adenomas, gastric fundic gland polyps, desmoid tumors, epidermoid cysts, extranumery teeth, osteomas</td>
</tr>
<tr>
<td>MUTYH Associated Polyposis</td>
<td>MUTYH</td>
<td>Adenomas, serrated polyps (SSPs and HPs)</td>
<td>Autosomal Recessive</td>
<td>Colon: 0-100s adenomas, Extra-colonic: fundic gland polyps, duodenal adenomas, sebaceous gland adenomas, epitheliomas</td>
</tr>
<tr>
<td>Peutz-Jegher Syndrome</td>
<td>STK11</td>
<td>Hamartomas</td>
<td>Autosomal Dominant</td>
<td>GI tract hamartomas, Orucutaneous melanin pigmentation</td>
</tr>
<tr>
<td>Juvenile Polyposis Syndrome</td>
<td>BMPR1A, SMAD4</td>
<td>Hamartomas</td>
<td>Autosomal Dominant</td>
<td>GI Tract Juvenile Polyps, Gastric Polyps, Telangiectasias (HHT)</td>
</tr>
<tr>
<td>PTEN Hamartoma Tumor Syndrome</td>
<td>PTEN</td>
<td>Hamartomas, Adenomas, Hyperplastic, Ganglioneuroma, Inflammatory, Lipoma, Leiomyoma</td>
<td>Autosomal Dominant</td>
<td>Colon: mixed polyposis, Extracolonic: macrocephaly, autism spectrum, glycogenic acanthosis, multi-nodular goiter, trichelemmomas, oral papillomas, cutaneous lipomas</td>
</tr>
<tr>
<td>Serrated Polyposis Syndrome</td>
<td>unknown</td>
<td>Serrated polyps</td>
<td>Unknown</td>
<td>Colon: serrated polyps</td>
</tr>
<tr>
<td>Polymerase Proofreading-associated Polyposis</td>
<td>POLE, POLD1</td>
<td>Adenomas</td>
<td>Autosomal Dominant</td>
<td>Colon: oligopolyposis</td>
</tr>
<tr>
<td>Hereditary Mixed Polyposis</td>
<td>GREM1</td>
<td>Adenomas, Hamartomas, Serrated Polyps</td>
<td>Autosomal Dominant</td>
<td>Colon: mixed histology oligopolyposis</td>
</tr>
<tr>
<td>Lifetime Cancer Risk</td>
<td>Surveillance Recommendations</td>
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<tr>
<td><strong>NON-POLYPOSIS SYNDROMES</strong></td>
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<tr>
<td>CRC: 12%</td>
<td>Colonoscopy every 3-5 years starting 5-10 years before earliest CRC in family</td>
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<tr>
<td>CRC: 100%</td>
<td>Colonoscopy every 1-2 years starting at age 10-15</td>
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<tr>
<td>Duodenal: 4-12%</td>
<td>EGD with side-viewing scope every 1-5 years starting at age 25-30</td>
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<tr>
<td>Thyroid: 1-2%</td>
<td>Thyroid examination annually starting at age 15-20</td>
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<tr>
<td>Hepatoblastoma: &lt;1%</td>
<td>Thyroid ultrasound at baseline and may be offered annually</td>
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<tr>
<td>Medulloblastoma: 1-2%</td>
<td>Annual physical examination</td>
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<tr>
<td>Others: Pancreatic, biliary, distal small bowel</td>
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<tr>
<td>CRC: 69%</td>
<td>Colonoscopy every 1-2 years starting at age 18-20</td>
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<tr>
<td>Duodenal/periampullary: 4-12%</td>
<td>EGD with side-viewing scope every 1-5 years starting at age 25-30</td>
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<tr>
<td>Thyroid: 1-2%</td>
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<tr>
<td>CRC: 80%</td>
<td>Colonoscopy every 1-2 years starting at age 18-20</td>
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<tr>
<td>Duodenal: 4%</td>
<td>EGD at baseline with side-viewing scope, may be repeated at 1-5 year intervals based on duodenal polyp burden</td>
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<tr>
<td>CRC: 40%</td>
<td>Colonoscopy, EGD and video capsule endoscopy every 3 years starting at age 8-18</td>
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<tr>
<td>Breast: 32-54%</td>
<td>Breast MRI and/or mammogram annually starting at age 25</td>
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<tr>
<td>Pancreatic: 11-36%</td>
<td>Pelvic exam and Pap smear annually starting at age 25; transvaginal ultrasound may be offered</td>
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<tr>
<td>Gastric: 29%</td>
<td>Testicular exam and clinical exam for feminization annually from birth to age 15</td>
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<tr>
<td>Small bowel: 13%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ovarian: 21%</td>
<td></td>
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<tr>
<td>Uterine: 9%</td>
<td></td>
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<tr>
<td>Lung: 7-17%</td>
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<tr>
<td>Testes: 9%</td>
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<tr>
<td>Cervix: 10%</td>
<td></td>
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</tr>
<tr>
<td>CRC: 40%</td>
<td>Colonoscopy and EGD every 1-3 years starting at age 12-15</td>
<td></td>
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</tr>
<tr>
<td>Stomach/duodenum: 21%</td>
<td>Capsule endoscopy or CT/MRI enterography may be offered</td>
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<tr>
<td>HHT screening for SMAD4 mutation carriers</td>
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<tr>
<td>Annual physical exam and evaluation for anemia starting at age 12-15</td>
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<tr>
<td>CRC: 9-16%</td>
<td>Colonoscopy and EGD every 2-3 years starting at age 35</td>
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<tr>
<td>Breast: 25-50%</td>
<td>Thyroid exam annually with baseline ultrasound starting at age 15</td>
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<tr>
<td>Thyroid: 3-10%</td>
<td>Mammography and breast MRI, pelvic examinations with endometrial sampling annually starting at age 30-35</td>
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<tr>
<td>Endometrial: 7-17%</td>
<td>Urine analysis annually starting at age 18; urine cytology or renal ultrasound may be offered</td>
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<tr>
<td></td>
<td>Annual physical exam by age 15</td>
<td></td>
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<tr>
<td>CRC: 25-40%</td>
<td>Removal of all polyps &gt; 3-5mm then colonoscopy every 1-3 years based on polyp burden starting by age 40 or younger based on family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRC: increased, but unknown</td>
<td>Uncertain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial: possibly increased with POLD1</td>
<td>May offer colonoscopy every 3 years starting at age 30-35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRC: increased, but unknown</td>
<td>Uncertain</td>
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</tbody>
</table>
there is a near 100% lifetime risk of CRC (average age 39 years). Attenuated FAP (AFAP) is a less severe phenotype characterized by fewer adenomatous polyps (10-100), a later age of onset of adenomas and CRCs and a lower lifetime risk of developing CRC (70%).

Extracolonic Features
A variety of extra-colonic lesions occur in FAP (Table 1) including increased risks of duodenal, thyroid and other cancers. Although desmoid lesions are histologically benign, they are common (≈10%) in FAP and they carry a great deal of morbidity and even mortality due to local compression. Nieuwenhuis et al. found previous abdominal surgery, APC mutations 3’ of codon 1444 and a family history of desmoids were independent predictors of desmoids. Several benign tumors such as fundic gland polyps, osteomas, fibromas, epidermoid cysts among others are also common in FAP (Table 1).

Genetics
FAP and AFAP are autosomal dominant conditions that arise from germline mutations of the Adenomatous Polyposis Coli (APC) gene located on chromosome 5q21-q22. More than 1000 different APC mutations have been identified in FAP and most cause a truncated gene product. There are substantial genotype/phenotypic correlations with the extra-intestinal manifestations, severity of polyposis and survival in FAP.

<table>
<thead>
<tr>
<th>Table 2. Amsterdam II Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least three relatives with a Lynch associated cancer (CRC, endometrial, small bowel, ureter, renal pelvis)</td>
</tr>
<tr>
<td>Two or more successive generations affected</td>
</tr>
<tr>
<td>One or more relatives diagnosed before the age of 50</td>
</tr>
<tr>
<td>One should be first degree relative of the other two</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis should be excluded</td>
</tr>
<tr>
<td>Tumors should be verified by pathologic examination</td>
</tr>
</tbody>
</table>

Adapted from Vasen, HF, Watson, P, Mecklin, JP, et al. “New clinical criteria for hereditary nonpolyposis CRC (HNPCC, LS) proposed by the International Collaborative group on HNPCC.” Gastroenterology 1999; 116:1453. Note: Amsterdam I criteria are identical to Amsterdam II criteria except that they are only in reference to CRC (not all Lynch associated cancers).

<table>
<thead>
<tr>
<th>Table 3. Revised Bethesda Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC diagnosed at age 50 or younger</td>
</tr>
<tr>
<td>Presence of synchronous or metachronous Lynch associated cancer, regardless of age</td>
</tr>
<tr>
<td>CRC with Lynch-like histology (tumor infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern) in patient younger than 60</td>
</tr>
<tr>
<td>CRC in a patient with at least 1 first degree relative with Lynch-associated cancer diagnosed at age 50 or younger</td>
</tr>
<tr>
<td>CRC in a patient with two or more first or second degree relatives with a Lynch-associated tumor, regardless of age</td>
</tr>
</tbody>
</table>

Tumors meeting one or more of these criteria should be tested for Microsatellite Instability. Adapted from Umar A, et al. Revised Bethesda Guidelines for hereditary nonpolyposis CRC (LS) and microsatellite instability. J Natl Cancer Inst. 2004 Feb 18;96(4):261-8.

Management

Screening & Surveillance
Recommendations are to start annual flexible sigmoidoscopy or colonoscopy screening around age 10-12 for classical or severe FAP and annual colonoscopic screening starting around age 20-25 in AFAP. Surveillance for gastroduodenal adenomas and thyroid cancer is summarized in Table 1.

Surgical Management
Appropriately timed colectomy remains the basis of effective management of CRC risk in profuse FAP. AFAP can sometimes be managed, at least temporarily, with careful endoscopic surveillance and polypectomy. Management of duodenal lesions in FAP is individualized. Most practitioners perform surveillance and remove adenomatous lesions endoscopically, reserving surgery for large and/or histologically advanced lesions or cancer.

Chemoprevention
Although chemoprevention is not a substitute for properly timed colectomy, numerous studies have shown that sulindac induces a marked reduction in polyp count and single studies of the selective COX-2 inhibitors celecoxib and rofecoxib showed similar, albeit less dramatic, results and aspirin appears to

(continued on page 48)
MUTYH ASSOCIATED POLYPOSIS (MAP)
The MUTYH gene is a part of the base-excision repair pathway involved in the repair of oxidative DNA damage. Bi-allelic mutations in MUTYH cause an autosomal recessive colonic polyposis syndrome (MUTYH-Associated Polyposis or MAP) with a clinical picture similar to AFAP. Although MAP is classified as an adenomatous polyposis syndrome, serrated polyps are common.\textsuperscript{39} It is becoming clear that the clinical spectrum of MUTYH germline mutations is broad and can even include younger-onset CRC without polyposis.\textsuperscript{40}

**CRC and Other Cancer Risk**
Bi-allelic MUTYH mutation carriers have over a 10 fold increased CRC risk.\textsuperscript{41,42} Patients with MutYH-related CRCs tend to be younger and more likely to have adenomatous polyps and synchronous CRCs than those with sporadic CRC and the cancers are more often right sided and may have an improved survival.\textsuperscript{43} Mono-allelic carriers of MUTYH mutations appear to have a marginally increased CRC risk; OR 1.16, 95% CI 1.00-1.30.\textsuperscript{42}

Duodenal adenomas are common MAP and they can progress to cancer. Risks of ovarian, bladder and skin cancer are also increased (Table 1).\textsuperscript{44}

**Management of MAP**
The screening/surveillance and surgical management of MAP is similar to attenuated FAP and highly dependent on polyp burden (Table 1).

### Table 4. Cowden Syndrome/PTEN Hamartoma Syndrome Testing Criteria\textsuperscript{15,16}

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Autism spectrum disorder</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>CRC</td>
</tr>
<tr>
<td>Follicular thyroid cancer</td>
<td>≥ 3 esophageal glycogenic acanthosis</td>
</tr>
<tr>
<td>Multiple GI hamartomas or ganglioneuromas</td>
<td>Lipomas</td>
</tr>
<tr>
<td>Macrocephaly</td>
<td>Intellectual disability</td>
</tr>
<tr>
<td>Macular pigmentation of glans penis</td>
<td>Papillary or follicular variant of papillary thyroid cancer</td>
</tr>
<tr>
<td>Mucocutaneous lesions</td>
<td>Thyroid structural lesions (adenoma, nodule, goiter)</td>
</tr>
<tr>
<td>• One biopsy proven trichilemmoma</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>• Multiple palmoplantar keratosis</td>
<td>Single GI hamartoma or ganglioneuroma</td>
</tr>
<tr>
<td>• Multifocal or extensive oral mucosal papillomatosis</td>
<td>Testicular lipomatosis</td>
</tr>
<tr>
<td>• Multiple cutaneous facial papules</td>
<td>Vascular anomalies</td>
</tr>
</tbody>
</table>

**Indications for Genetic Testing**
- Two or more major criteria (one must be macrocephaly)
- Three major criteria without macrocephaly
- One major criteria + ≥ 3 minor criteria
- ≥ 4 minor criteria

(continued on page 50)
(continued from page 48)

**POLYMERASE PROOFREADING-ASSOCIATED POLYPOSIS (PPAP)**

Recently, germ-line mutations in the proofreading polymerases POLD1 and POLE have been shown to cause an adenomatous polyposis syndrome and early onset CRC in a few families. The magnitude and spectrum of cancer risks in this syndrome are not yet known and screening guidelines have not been established but colonoscopy screening starting in young adulthood seems reasonable (Table 1).

**HEREDITARY MIXED POLYPOSIS SYNDROME (HMPS)**

Germline mutations in GREM1 cause an autosomal dominant polyposis syndrome characterized by the development of a variety of polyps, including adenomas, hyperplastic or serrated polyps, as well as juvenile polyps and polyps with mixed pathology CRC. The cancer risks, and screening recommendations in this group are uncertain but colonoscopy screening in young adulthood seems reasonable.

**Peutz-Jeghers Syndrome (PJS)**

PJS is an autosomal dominant syndrome that can arise from germline mutations in the serine threonine kinase gene (STK11). It is clinically characterized by classic muco-cutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia or fingers in addition to a histologically distinct type of hamartoma (PJ polyp) of the small and large bowel. The clinical criteria for PJS include any of the following:

- 2 or more histologically confirmed PJ polyps
- Any PJ polyps in an individual who also has characteristic mucocutaneous pigmentation
- Any PJ polyps or characteristic mucocutaneous pigmentation in an individual with a family history of PJS

**Cancer/Intussusception Risks**

Patients with PJS have a very high cumulative risk of any cancer (up to 85%) and of CRC (>50%). Hamartomas are thought to serve as precursors to CRC as focal dysplasia and invasive cancer has been seen within hamartomas. There is also an exceptionally high rate (10%-50%) of extra-colonic cancers in PJS (Table 1) including gastric, small bowel, pancreatic, breast, ovarian, lung, cervical and uterine/testicular cancer. Small bowel hamartomas lead to a high rate of intussusception (up to 65%) that can start in childhood.

**Screening & Management**

The main management goals in PJS include prevention of polyp-related complications that often necessitate surgery (bowel obstruction from intussusception, bleeding) and prevention/early detection of cancer. Screening guidelines (Table 1) vary, but include upper and lower endoscopic screening and imaging of the small bowel with removal of all polyps >1-1.5 cm in size when possible. In women, screening for breast, uterine and ovarian cancer is recommended starting around age 25; in men annual testicular exam starting at age 20.

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around age 10 is generally recommended (Table 1). Some guidelines recommend annual chest radiographs. Discussion of risk reduction surgery (mastectomy, hysterectomy, oophorectomy) is appropriate for women.

**JUVENILE POLYPOSIS SYNDROME (JPS)**

JPS is characterized by the occurrence of juvenile polyps throughout the intestinal tract (although most typically in the colorectum) and carries an increased risk of CRC. The World Health Organization (WHO) diagnostic criteria for JPS require one of the following:

- >5 juvenile polyps (JPs) in the colon or rectum,
- Multiple JPs in the upper gastrointestinal tract or
- Any JP(s) in a patient with a family history of JPS

Genetics

JPS is an autosomal dominant syndrome although de novo mutations are common (~25%). About 60% of patients with JPS have germline mutations in one of two genes in the transforming growth factor-beta (TGF-beta) signaling pathway (SMAD4, BMPR1A). SMAD4 mutation has also been associated with hereditary hemorrhagic telangiectasia (HHT).

Management

**Screening**

Patients with known or suspected JPS should undergo annual physical examination and evaluation for anemia and regular upper endoscopy, small bowel imaging and colonoscopy starting in adolescence or at the time of first symptoms (Table 1) with endoscopic removal of polyps when possible.

**Surgery**

Surgery is generally considered in JPS when the polyps cannot be managed endoscopically, for severe gastrointestinal bleeding, in polyps exhibiting dysplasia or in patients with a strong family history of CRC. The decision between subtotal versus total proctocolectomy is typically made on the basis of the rectal polyp burden. Post-operative endoscopic surveillance is required given the high recurrence rate of polyps in remaining rectal and ileal tissue.

**PTEN HAMARTOMATOUS TUMOR SYNDROME (PHTS)**

Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS) can both be caused by a germline mutation of the phosphatase and tensin homolog (PTEN) gene and thus are both included in the PHTS. PHTS is autosomal dominant with relatively high penetrance (estimated 80%). The PTEN tumor suppressor gene is located on 10q23.3 and encodes a dual-specificity phosphatase that can de-phosphorylate protein and phospholipid substrates.

PHTS is characterized by hamartomatous lesions in multiple organs with a high frequency mucocutaneous lesion including trichilemmomas, acral keratoses, facial papules/oral papillomas, and esophageal glycogenic acanthosis. Although classified as a hamartomatous polyposis syndrome, adenomas, hyperplastic polyps, ganglioneuromas and inflammatory polyps also occur commonly in PHTS.

Cancer Risks in PHTS

PHTS is associated with a marked increased risk of many cancers including breast, colorectal, endometrial, renal, thyroid (Table 1).

Diagnosis

A clinical diagnosis of CS is entertained when individuals meet criteria established by the International Cowden Consortium. Major and minor clinical criteria and a scoring system have been proposed to help identify such patients (Table 4).

Management

**Screening & Surveillance**

Screening recommendations, based on expert opinion, include general physical examination, careful breast, endometrial and colorectal cancer screening starting in young adulthood (Table 1). Discussion regarding prophylactic mastectomy and hysterectomy is recommended on a case by case basis.

**SERRATED POLYPOSIS SYNDROME (SPS)**

SPS (previously called Hyperplastic Polyposis Syndrome) is likely familial but its genetic basis has not yet been defined. SPS is characterized by the presence of multiple serrated polyps of the colon. The clinical
criteria for SPS\textsuperscript{57} include any of the following:
- 5 or more serrated polyps proximal to the sigmoid colon with at least two being greater than 1 cm
- 20 or more cumulative serrated polyps of any size distributed throughout the colon
- 1 or more proximal serrated polyps in an individual with a first degree relative with SPS

Cancer Risk
The CRC incidence in SPS is based on limited data with estimates varying from around 40\% to 70\%.\textsuperscript{58,59} Extra-colonic cancer risks do not appear to be increased in SPS.

Genetics
The genetic basis of SPS has not yet been established but there does appear to be about a 5-fold increased risk of CRC in first degree relatives of patients with SPS.\textsuperscript{56}

Screening & Surveillance
Serial colonoscopy with polypectomy is recommended until all polyps $\geq 5$ mm are removed, then colonoscopy every 1 to 3 years depending on polyp burden. Chromoendoscopy may improve polyp detection in SPS. If polyp burden cannot be managed endoscopically or if high-grade dysplasia is detected, patients should be referred for colectomy.

**GENERAL APPROACH TO GENETIC COUNSELING AND TESTING IN CRC**

**INITIAL CLINICAL EVALUATION**
Clinical evaluation for a potential hereditary CRC syndrome begins much in the same way as any other clinical encounter; with a careful history and physical examination. Primary care providers and general gastroenterologists play an integral role in initial risk assessment to determine which patients would benefit from referral to a genetics specialist.

**History**
Early-onset cancer is a hallmark of the hereditary cancer syndromes. Evaluation of persistent symptoms such as rectal bleeding is important even in young individuals and will occasionally identify a patient with a young-onset cancer due to a hereditary syndrome.

The most critical part of the history in evaluation for a hereditary syndrome is a thorough family history. It is important to obtain at least a cancer family history starting with the proband (the patient being evaluated) and extending to all first, second and selected third degree relatives. For each family member, it is important to document the age of diagnosis of all cancers and colonic polyps with number and histology if possible. It can also be helpful to document any benign conditions known to be associated with hereditary syndromes (such as osteomas, desmoid tumors, epidermoid cysts, etc).

Despite its critical importance in the evaluation of hereditary cancer syndromes, an accurate family cancer history is not obtained and/or used to assess risk and direct CRC screening.\textsuperscript{60-62} In theory, the electronic health record (EHR) systems should facilitate the collection and use of family history data. Although essentially all EHRs have a family history section the information collected varies, it may not be regularly updated and most EHRs have not yet incorporated family history data into clinical decision-making or provided screening alerts based on family history.\textsuperscript{62}

**Physical Examination**
There are occasional instances when hallmark physical examination findings can suggest hereditary risk. Extra-colonic features of FAP that can be found on physical examination include the presence of jaw osteomas, epidermoid cysts or supernumery teeth. Presence of desmoid tumors (intra-abdominal or abdominal wall) can present as a mass. Though detailed ophthalmologic examinations may not be performed routinely, presence of congenital hypertrophy of the retinal pigment epithelium (CHRPE) raises the suspicion of FAP. Thyroid pathology (nodules, hyperplasia) is found in approximately 36\% of all FAP patients.\textsuperscript{63} Sebaceous adenomas or adenocarcinomas may be cutaneous signs of LS. If these features are detected on physical examination, it is important to take a detailed family history and consider referral for genetic evaluation.

**When to Refer to a Genetic Specialist**
It is becoming increasingly complex to determine when a patient is at risk for a specific hereditary cancer syndrome because of the increased number of hereditary CRC syndromes (Table 1) and the broadening and overlapping phenotypes of the syndromes.\textsuperscript{64-67} Thus, in addition to specific clinical findings for each syndrome detailed above, general guidelines can be utilized by primary care or screening endoscopy physicians (Table 5) to prompt a referral to a genetics expert. If a patient meets any of these criteria, it is very reasonable to
refer to a genetics specialist who can expand and verify the cancer family history and then determine the best approach to genetic counseling and testing, if appropriate. Use of a simple screening questionnaire (Figure 1) can help identify these families.

**Role of Genetic Counseling**

Genetic counseling is critical to informed decision making about genetic testing. Pre-test genetic counseling involves: (1) collection (and often times verification by obtaining medical records) of a thorough multi-generation family history, (2) a risk-assessment to determine whether the family history is suggestive of a hereditary condition, (3) selection of what genetic test(s) to offer, (4) selecting which family member is most appropriate to test, (5) review of the suspected syndrome(s) and inheritance patterns, (6) accuracy and potential ambiguity of genetic tests, (7) possibility of genetic discrimination in life/long term care insurance, confidentiality, economic considerations (8) alternatives to genetic testing, (9) plans for how results will be interpreted and disclosed.  

Traditionally, determining which genetic testing to perform was based on the observed inheritance pattern, clinical presentation (polyposis vs non-polyposis) and histology (adenoma vs serrated vs hamartomas). Emerging data on new syndromes and the overlapping phenotype of the known syndromes highlights the risk of missing genetic diagnoses with a single-syndrome evaluation approach: this and the low cost of next-generation gene sequencing has driven the use of cancer gene panels when the clinical diagnosis is in doubt. Panel testing offers the advantages of increased diagnostic yield, decreased cost and decreased anxiety/testing fatigue with sequential testing but insurance coverage of panel testing is highly variable. If a panel testing is recommended, pre-test counseling should include the possibility of unexpected findings (a pathogenic mutation in the gene that wasn’t considered on the basis of the family history), the potential for finding mutations in low penetrant genes that define a genetic risk but don’t change screening recommendations or finding variants of uncertain significance (VUS). VUS are defined as an alteration in the normal sequence of a gene whose association with disease risk is unknown. VUS rates with multi-gene panel testing are typically in the 10 to 30% range.  

Post-test counseling includes estimates of risk and screening recommendations based on the genetic results. Screening recommendations for specific syndromes can be provided (Table 1), the meaning of an unexpected result and the relevance of any VUS can be discussed. If no mutation is found, however, it does not mean that the patient and their family are not at increased cancer risk and screening recommendations should be based on their family history.

**CONCLUSION**

The clinical spectrum of the hereditary colorectal cancer syndromes is broad. In this review, we attempted to describe the major clinical features, to provide estimates of the cancer risks and summarize the range of screening recommendations for the major hereditary CRC syndromes. The goal of this effort is to provide primary care providers and general gastroenterologists with a guide to the identification of patients who should be referred to a genetics service for further evaluation, genetic counseling and possible genetic testing.

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Answers to this month’s crossword puzzle:

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 1. SECRET
 2. CREATION
 3. AMYL
 4. CELLO
 5. HOOD
 6. LET
 7. GALL
 8. MENDEL
 9. EUR
 10. RAYS
 11. REFLEX
 12. OIM
 13. TARA
 14. SOMA
 15. DIAGNOSTIC
 16. ATANA
 17. BACKGROUND
 18. LIFESCIENCE
 19. PROTEOMICS
 20. ALO
 21. OPU
 22. NUCLEOTIDE
 23. EU
 24. USE
 25. CALDO
 26. LATER
 27. RENAL
 28. BD
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