

## Hereditary Colorectal Cancer Syndromes

GI Cancer Risk Evaluation Program (GI CREP): for appointments call 215-898-0154 or visit our website at <http://www.med.upenn.edu/gastro/GICancerRiskEvalProgram.shtml> or place an order for [consult for cancer risk evaluation program](#) or [genetics](#) via EPIC

Comprehensive cancer risk evaluation will be performed by Dr. Anil Rustgi or Dr. Tim Hoops and our genetic counselors  
We also see familial forms of pancreatic cancer, gastric cancer, Barrett's esophagus, and esophageal cancer

### **Lynch Syndrome:**

Hereditary Non-polyposis Colorectal Cancer (HNPCC) or Lynch Syndrome is a highly penetrant autosomal dominant disorder caused by germline mutation in genes involved in DNA mismatch repair (MMR). Germline testing for the most commonly affected genes, MLH1, MSH2, MSH6, and PMS2, are commercially available.

#### A) Clinical diagnosis:

##### Amsterdam II Criteria (must meet all):

Families or individuals that meet these criteria should be suspected as having Lynch syndrome and germline testing should be considered.

- 3 or more family members with HNPCC-related cancers\*, one of whom is a first degree relative (parent, sibling, offspring) of the other two
- 2 consecutive affected generations
- 1 or more of the HNPCC-related cancers\* diagnosed <50 years
- FAP has been excluded (see below for diagnosis of FAP)

##### Revised Bethesda Guideline (must meet one):

Patients who meet these criteria should have their colorectal tumor tested for the presence of microsatellite instability (MSI) and those with microsatellite unstable cancers should have germline MMR gene testing.

- Colorectal cancer (CRC) diagnosed <50 years
- 2 HNPCC cancers\*\* in one person (can be 2 primary CRC)
- CRC with MSI-H<sup>◆</sup> histology (tumor infiltrating lymphocytes, Crohn's like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern) diagnosed <50 years
- CRC or HNPCC-associated tumors\*\* diagnosed under age 50 years in at least 1 first-degree relative
- CRC or HNPCC-associated tumor\*\* diagnosed at any age in 2 first- or second-degree relatives (aunts, uncles, grandparents, grandchildren, nieces, nephews, or half-siblings).

\*Colorectal, endometrial, stomach, small intestine, renal pelvis/ureter.

\*\* Same as above with addition of ovarian cancer, pancreatic cancer, hepatobiliary malignancies, brain tumors (predominantly glioblastoma as seen in Turcot syndrome), sebaceous tumors and keratocanthomas as seen in Muir-Torre syndrome.

◆ MSH-H in tumor specimen refers to characteristic genomic instability in two or more of the five National Cancer Institute (NCI)-recommended panel of microsatellite loci.

Abbreviations- HNPCC, hereditary non-polyposis colorectal cancer; MSI-H, microsatellite instability high; CRC, colorectal cancer.

#### B) Screening and management (there are no consensus guidelines):

##### Surveillance:

- Colonoscopy .....Every 1-2 yrs starting at age 20-25
- Upper endoscopy.....Every 1-2 yrs starting at age 20-25
- Gyn exam/endometrial sampling.....Every 1-2 yrs starting at age 25-30
- Transvaginal ultrasound (+/- CA-125).....Every 1-2 yrs starting at age 25-30
- Urinalysis with cytology (+/- abdominal ultrasound).....Every 1-2 yrs starting at age 25-30 (especially in individuals with personal or family history of Transitional Cell Carcinoma of the bladder)

##### Surgical management:

At time of colectomy consider subtotal colectomy or complete proctocolectomy instead of segmental resection of colorectal tumor. Consider hysterectomy and bilateral oophorectomies post completion of childbearing years.

C) Request for MSI/IHC testing on tumor specimens at Hospital of University of Pennsylvania:

Testing should be requested through the Department of Pathology and Laboratory Medicine. MSI testing can be requested on molecular surgical pathology form, available at the link below, and faxed to 215-614-1986. Immunohistochemistry (IHC) testing can be requested separately or by contacting the molecular pathology fellow. For additional testing questions contact the office of Dr. Antonia Sepulveda, Director of Surgical Pathology at the University of Pennsylvania.

<http://www.uphs.upenn.edu/path/LabServices/mp/pages/MolecularOncologyRequestForm806.pdf>

**Familial Adenomatous Polyposis (FAP):**

FAP is an autosomal dominant condition caused by a germline mutation in the tumor suppressor gene Adenomatous Polyposis Coli (APC), and genetic testing is commercially available. Approximately 30% of patients have no family history and APC mutations, and such individuals are thought to have “de novo” mutations. Attenuated FAP (AFAP) is a milder variant with fewer adenomas and later onset of disease.

A) Clinical diagnosis of classic FAP (must meet one):

- >100 colorectal adenomatous polyps
- <100 adenomatous polyps AND a relative with FAP

Other clinical features may include: gastric polyps (fundic gland and antral adenomas), duodenal adenomatous polyps, osteomas, supernumerary teeth and/or dental odontomas, epidermoid cysts, adrenal gland adenomas, congenital hypertrophy of the retinal pigment epithelium (CHRPE), follicular or papillary thyroid cancer, brain tumors (primarily medulloblastoma), duodenal/ampullary carcinoma, gastric carcinoma, and childhood hepatoblastoma.

B) Clinical diagnosis of Attenuated FAP (must meet one):

Note: There is no consensus on the exact diagnostic criteria.

- Ten to 99 colonic adenomatous polyps
- A personal history of CRC before age 60 years and a family history of multiple adenomatous polyps

C) Screening and management (there are no consensus guidelines):

The following general recommendations are made for individuals at risk for classic FAP:

- Birth-7yrs.....Physical exam, serum alpha- fetoprotein, +/- abdominal ultrasound yearly to evaluate for hepatoblastoma.
- 12 yrs .....Colonoscopy every 1-2 years until surgery

Note: APC genetic testing is recommended to confirm the clinical diagnosis in all affected individuals and their family members. There are no standard guidelines for age at which to initiate germline genetic testing. If polyps are found, the surgery recommended is proctocolectomy

Guidelines for follow-up of individuals with confirmed diagnosis of classic FAP:

- Yearly physical exam
- Upper endoscopy every 1-2 years or surveillance per Spigelman classification of duodenal polyposis & inspection of ampulla of Vater (+/- endoscopic ultrasound, EUS)
- Flexible sigmoidoscopy every 6 months for those with intact rectum
- Flexible sigmoidoscopy every 6 months to 1 year for patients with ileoanal pouch
- Thyroid exam annually +/- thyroid ultrasound every 1-2 years (refer for biopsy if nodule > 10mm or >5 mm and characteristics associated with malignancy) especially in women 15-35 years of age, concomitant CHRPE, or family history of thyroid cancer.
- CT of abdomen/pelvis every 1-2 years for those with history of desmoid tumors

**MYH-Associated Polyposis (MAP):**

MAP is an autosomal recessive syndrome due to biallelic mutation in the base excision repair gene, MYH. Germline genetic testing is commercially available. The clinical syndrome is similar to attenuated FAP with no detected germline APC mutation.

A) Clinical diagnosis:

- History of >10 adenomas or >15 cumulative adenoma in 10 years AND
- Family history of polyps consistent with recessive inheritance
- Negative APC germline testing

Extracolonic features: include gastroduodenal polyps, duodenal carcinoma, osteomas, breast carcinoma in female carriers, CHRPE, dental cysts, and sebaceous gland tumors.

B) Screening (there are no consensus guidelines):

**Surveillance:**

- Colonoscopy .....Every 2-3 years starting at age 20-25
- Upper endoscopy .....Starting at age 25

Note: The frequency of repeated endoscopies depends on the location and histology of polyps.

**Surgical management:**

Recommendations are individualized based on clinical and endoscopic findings.

**Peutz-Jeghers Syndrome (PJS):**

PJS is an autosomal dominant disease due to mutation in the tumor suppressor gene LKB1/STK11. Genetic testing is commercially available. Approximately 15-50% of affected individuals have no known family history. PJS is characterized by numerous pigmented spots on the lips and buccal mucosa as well as the tendency to develop multiple hamartomatous polyps throughout the gastrointestinal (GI) tract. Early in life patients develop recurrent bouts of small bowel intussusceptions, obstruction and GI bleeding that may require bowel resection. Individuals with PJS have markedly increased lifetime risk of multiple cancers including colon, small intestine, stomach, esophagus, pancreas, breast, lung, uterus, cervix, and ovary.

A) Clinical diagnosis:

- Histopathologically confirmed Peutz-Jeghers type hamartomatous polyps AND
- At least two of the following:
  - Positive family history of PJS
  - Mucocutaneous pigmentation
  - Small bowel polyposis

B) Screening (there are no consensus guidelines):

Surveillance:

- Colonoscopy .....Every 1-2 years starting at age 10
- Upper endoscopy .....Every 1-2 years starting at age 10
- Small bowel follow-through ..... Every 1-2 years starting at age 10
- Mammogram +/- breast MRI .....Yearly starting at age 20-25
- Pelvic exam, transvaginal u/s (+/-CA-125).....Yearly starting at age 35
- Endometrial sampling and Pap smear.....Yearly starting at age 30-35
- Endoscopic ultrasound/MRCP (+/- CA19-9, CEA).....Every 2 years starting at age 25

Note: in selected cases initiation of close surveillance maybe recommended at an age younger than indicated above

**Familial Juvenile Polyposis (FJP):**

FJP is an autosomal dominant childhood-onset highly penetrant disease that is characterized by distinct hamartomatous polyps throughout the GI tract, GI bleeding, diarrhea, protein-losing enteropathy, and increased risk of CRC. This is a genetically heterogeneous syndrome and germline mutations in a number of cell signaling molecules including SMAD4, PTEN, and BMPR1A have been described. Genetic testing is available at select laboratories.

A) Clinical criteria (must meet one):

- More than five juvenile polyps of the colorectum
- Multiple juvenile polyps throughout the GI tract
- Any number of juvenile polyps and a family history of juvenile polyps

B) Screening (there are no consensus guidelines):

Surveillance:

- Colonoscopy .....Every 1-2 years starting at age 10
- Upper endoscopy .....Every 1-2 year starting at age 10
- Small bowel follow-through.....Every 1-2 year starting at age 10

Note: Given the known association between SMAD4 mutation and hereditary hemorrhagic telangiectasia (HHT), screening for occult arteriovenous malformations in organs with life threatening hemorrhagic consequences maybe considered. In selected cases surveillance maybe started at an age younger than indicated above.

**On-line resources:**

- **GeneReviews through the National Center for Biotechnology Information (NCBI):**  
<http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=GeneTests>
- **Genetics Home References through the National Institute of Health (NIH):**  
<http://ghr.nlm.nih.gov>