Hereditary Cancer Syndromes

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Outline

- Lynch Syndrome (previously HNPCC)
- Familial adenomatous polyposis (FAP) and Attenuated FAP
- MUTYH-associated polyposis (MAP)
- Hamartomatous polyposis syndromes
  - Peutz-Jeghers syndrome
  - Juvenile polyposis syndrome
  - Cowden syndrome
  - Bannayan-Riley-Ruvalcaba Syndrome

Lynch Syndrome

-The most common hereditary form of colon CA.

-2-4% of all colon CA

-Autosomal Dominant with incomplete penetrance

-Germline mutation in 4 different mismatch repair (MMR) genes

-1:1,000-1:3,000 are carriers for MMR gene mutations

-100,000-300,000 Americans have Lynch

-Associated cancers include colon (50-80% lifetime risk), endometrium (40-60%), Stomach (11-19%), Ovary (9-12%), hepatobiliary tract (2-7%), upper urinary tract (4-5%), pancreatic (3-4%), small bowel (1-4%), CNS (1-3%)

Lynch Syndrome

- Colon CA: Lymphocyte infiltration, medullary growth pattern and a signet ring (mucinous) differentiation
- Mostly proximal colon CA
- High level of microsatellite instability
- MMR genes: hMSH2 and hMLH1 70% of cases, hMSH6 14% cases, hPMS2 15%. Also EPCAM (not a MMR gene but inactivates hMSH2 genes in 1%)

Diagnosis of Lynch Syndrome

Amsterdam criteria II for Lynch syndrome

There should be at least three relatives with a Lynch syndrome-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter or renal pelvis)

All of the following criteria should be present

1. One should be a first-degree relative of the other two
2. At least two successive generations should be affected
3. At least one should be diagnosed before the age of 50 years
4. Familial adenomatous polyposis should be excluded in colorectal cancer case(s), if any
5. Tumors should be verified by pathological examination

Revised Bethesda guidelines for MSI testing

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age
2. Presence of synchronous, metachronous colorectal, or other Lynch syndrome-related tumors,*regardless of age
3. Colorectal cancer with the MSI-H histology,**diagnosed in a patient who is less than 60 years of age
4. Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch syndrome-related tumor, with one of the cancers being diagnosed under age 50 years
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors, regardless of age

*Lynch syndrome-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract, and brain (usually glioblastoma) tumors, sebaceous gland adenomas, keratoacanthomas, and carcinoma of the small bowel; **Presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern

Diagnosis of Lynch Syndrome

- Previously used Amsterdam criteria and Bethesda guidelines
- Most cost effective: perform tumor testing when any of the Bethesda guidelines are identified
  - Start with MSI and/or immunohistochemistry testing . 90% will have high MSI so very sensitive but specificity lower as 15% of sporatic cancers have high MSI. IHC helps identify the MMR gene that most likely has the mutation.
  - Additional tumor testing for the BRAF mutation and the hMLH1 promotor methylation analysis can identify sporatic cancer.
  - If BRAF absent then testing for the MMR gene mutation can confirm the syndrome.
  - Confounding factor: 6% of Lynch has no MSI-H (MSH6)
- If tumor tissue is not available could consider molecular testing of the family member diagnosed with Lynch syndrome to identify the MMR gene but not usually recommended as less cost effective.

Prediction Models to Guide Testing

Online calculators of risk include: MMRpredict model, MMRpro model , and **PREMM model**

http://premm.dfci.harvard.edu/

Proband Information *"Proband" refers to the individual being evaluated. Ideally, this individual should have a cancer diagnosis.*
Proband Sex: Male /Female
Number of Separate Colorectal Cancers: None One Two or more
If one, what was the age at diagnosis? If two or more, what was the youngest age at diagnosis? *(if unknown, estimate)*
Has the Proband had Endometrial Cancer? No Yes
What was the youngest age at diagnosis? *(if unknown, estimate)*
Has the Proband had another Lynch syndrome-associated cancer? No Yes
Other Lynch-syndrome associated cancers include ovary, stomach, small intestine, urinary tract/kidney, bile ducts, glioblastoma multiforme (brain), sebaceous gland tumors, and pancreas.

Relatives Information - First Degree**(Only from affected side of family)**
How many first-degree relatives have had colorectal cancer? None One Two or more
If one, what was the age at diagnosis? If two or more, what was the youngest age at diagnosis? *(if unknown, estimate)*
How many first-degree relatives have had endometrial cancer? None One Two or more
If one, what was the age at diagnosis? If two or more, what was the youngest age at diagnosis? *(if unknown, estimate)*
Have any first-degree relatives had another Lynch syndrome-associated cancer? No Yes

Relatives Information - Second Degree**(Only from affected side of family)**
How many second-degree relatives have had colorectal cancer? None One Two or more
If one, what was the age at diagnosis? If two or more, what was the youngest age at diagnosis? *(if unknown, estimate)*
How many second-degree relatives have had endometrial cancer? None One Two or more
If one, what was the age at diagnosis? If two or more, what was the youngest age at diagnosis? *(if unknown, estimate)*
Have any second-degree relatives had another Lynch syndrome-associated cancer? No Yes

Then calculates a percentage risk based on above answers:

***If the overall predicted probability is ≥ 5%, referral for genetic evaluation and/or molecular testing of tumor sample for microsatellite instability (MSI) or immunohistochemistry (IHC) testing should be considered. When a tumor sample is not readily available, germline sequencing should be considered in patients with ≥ 5% risk (National Comprehensive Cancer Network [NCCN] Guidelines Version 2.2012, Colorectal Cancer Screening).**

Management of Lynch Syndrome

-Screening colonoscopy starting at 20-25 years old and Q1-2 years.

-Subtotal colectomy with ileorectal anastamosis with the appearance of colon cancer then annual rectal surveillance.

-Prophylactic hysterectomy and bilateral salpingo-oophorectomy after childbearing age

-If family member has negative MMR then colonoscopy q5 years beginning 10 years before youngest family member

-CAPP2 trial- long term ASA (600mg/day) use can decrease CRC by 63% in Lynch syndrome, CAPP3 determining optimal dose

FAP

- Second most common inherited syndrome
- Autosomal dominant inheritance
- Hundreds to thousands of colonic adenomas beginning in early adolescence
- Male=female
- 1% of all colon CA, prevalence 1 in 10,000 births
- APC gene mutation (germ line mutation in tumor suppressor gene)
- 100% risk of colon CA, average age of CRC is 39 if untreated, 95% will develop CRC by age 50
- Variants: Turcot, Gardner and aFAP

FAP

- Gastric fundic gland polyps in 50% patients and can be diffuse, adenomas are less common in the stomach. Lifetime risk of gastric cancer 1%.
- Duodenal adenomas in >50%, duodenal cancer 2nd most common malignancy, lifetime risk 4-12%.
- Other benign growths: osteomas, epidermoid cysts, fibromas, dental abnormalities, desmoids.
- Gardner Syndrome: FAP with osteomas, sebaceous cysts, thyroid CA, epidermoid cysts
- Turcot syndrome: FAP with brain tumors

Attenuated FAP

- Fewer adenomas (<100) and later onset of CRC at approximately age 55.
- More proximal colon tumors
- Can still develop extracolonic manifestations of FAP

Management of FAP

- Screening:

  -APC gene testing.

  -If patient is APC mutation positive then family should get APC gene testing.

  -If the genetic mutation is unknown or the affected family member is unavailable then a negative APC gene mutation is considered inconclusive.

  -aFAP-same as FAP but fewer patients have a detectable mutation

  -Gene carriers or family members with inconclusive results begin annual endoscopic surveillance at age 10-12 and continue 1-2 years. (yearly once adenomatous polyps develop)

  -Patient's with aFAP should always be screened with full colonoscopy because of higher frequency proximal polyps. Can begin in late teenage years.

Duodenal adenomas in FAP

Table II. Spigelman's Clasiffication

	1	*2*	*3*
N° of polyps	1-4	5-20	>20
Size	1-4	5-10	>10
Histology	Tubular	Tubulovellous	Vellous
Dysplasia	Mild	Moderate	Severe

Staging according to score: Stage 0: 0 points; stage I: 1-4 points; stage II: 5-6 points; stage III: 7-8 points; stage IV: 9-12 points.

Spigelman stage	Endoscopic frequency	Chemoprevention	Surgery
Stage 0	4 years	No	No
Stage I	2–3 years	No	No
Stage II	2–3 years	+/−	No
Stage III	6–12 months	+/−	+/−
Stage IV	6–12 months	+/−	Yes

Stage IV: recommend duodenectomy given high rate of high grade dysplasia and periampullary CA

Management of FAP

- Colectomy considered if >20 adenomas, when adenomas >1cm, or when advanced histology.
- Total proctocolectomy (TPC) and ileostomy or proctocolectomy with ileal pouch-anal anastomosis (IPAA).
- Colectomy and ileorectal anastomosis (IRA) isn't recommended because of high risk of rectal CA but can be considered in patients with milder disease
- Sulindac/NSAIDs: have been used to delay development of rectal/duodenal adenomas but have not been found to prevent CA
- Annual endoscopy with IPAA/IRA required (to examine remaining rectal tissue)
- Thyroid US yearly

MAP- MUTYH associated polyposis

- Autosomal recessive form of FAP
- MUTYH gene produces an enzyme responsible for DNA repair. Mutations lead to an accumulation of mutations in the APC gene leading to a form of FAP
- Normally fewer than 100 polyps but can be up to 1,000 polyps
- Can result in CA even without polyps
- Includes extracolonic manifestations of FAP
- Screening similar to aFAP- c-scope + EGD Q1-2 years, polyps are usually less dense so surgery may not be required

Hamartomatous Polyposis Syndromes

- Hamartoma: proliferation of subepithelial cells native to the tissue of origin.
- Adenoma: epithelial in origin
- HPS:
  - account for <0.5% of all colorectal CA
  - High rate of malignancy

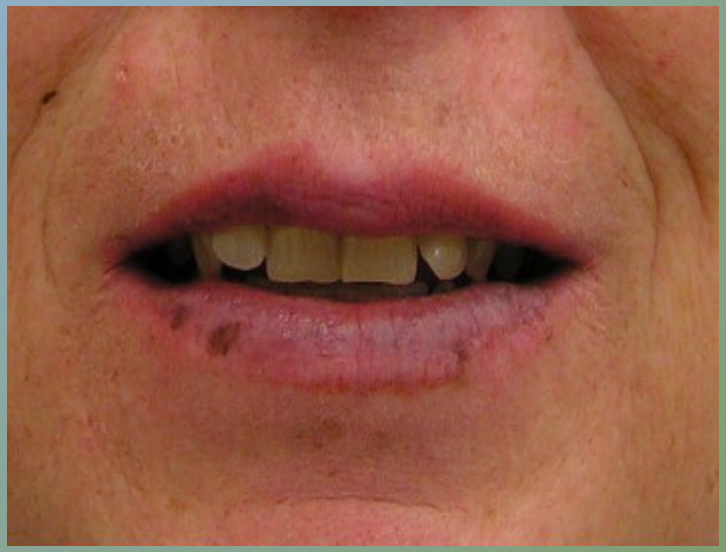
Peutz-Jeghers Syndrome

- Mutation in STK11 tumor suppressor gene, autosomal dominant and de novo
- Mucocutaneous pigmentation (lips, buccal mucosa, periorbital but also fingers, soles, labia, intestinal mucosa). Fades with aging.
- Hamartomatous polyps throughout GI tract: most frequently in small intestine (jejunum) up to 90%, 30% will get in colon, 25% will get gastric polyps
- Presenting symptoms: 50% present by age 20.
  - Classic presentation- early teens with intussusception, SBO and GI bleeding resulting in anemia

Diagnosis

*2 or more of the following features:
-2 or more PJS polyps of the small intestine
-Pigmentation of the mouth, lips, nose, eyes, genitalia and fingers
-Family history of PJS

*85-90% of developing any CA (GI or associated)
*GI (70%), Breast (45-50%), pancreas (11-36%), lung, ovary, cervix, uterus, testes



Peutz–Jeghers associated pigmented macules.

PJS screening recommendations

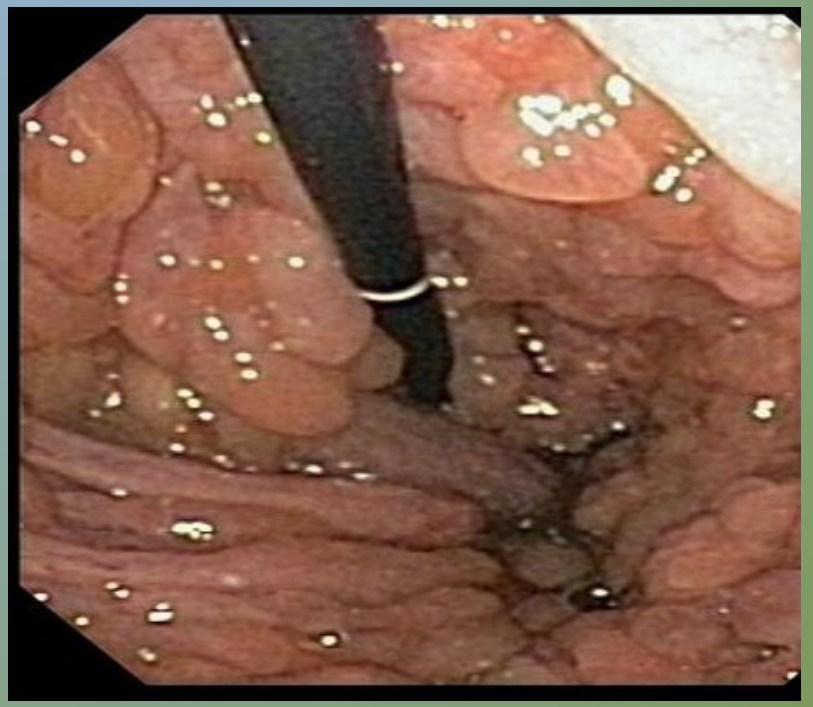
- Colonoscopy + EGD Q2-3 years, beginning in late teens
- Annual mammogram and breast MRI beginning age 25
- Screening Q1-2 years with pancreatic imaging (MRCP or EUS) by age 30
- Annual pelvic exam/PAP smear and US by age 20
- Small bowel imaging (Abdominal CT with contrast, SBFT, or capsule) beginning at age 8-10
- Annual testicular exam/ultrasound beginning at age 10

Juvenile Polyposis

- Multiple juvenile polyps (mucous retention polyps) in the GI tract
- Usually presents prior to age 20
- 15% have congenital cardiac abnormalities and a subset have GI and/or pulmonary AVMs
- Overall risk of any GI malignancy 50%
- One of the following criteria:
  - At least 3-5 juvenile polyps of the colon
  - Multiple polyps found throughout the GI tract (most prominent in colon)
  - Any number of juvenile polyps in an individual with a family history of JPS

Juvenile Polyposis

- Autosomal Dominant
- SMAD4 and BMPR1A: genes associated with JPS and part of the TGF-B signaling pathway
- SMAD4 associated with higher rate of gastric polyposis
- Recommended PTEN testing to r/o Cowden given overlap
- Screening: colonoscopy and EGD start at age 15, repeat annually if polyps, if no polyps then Q2-3 years.
- If polyp burden can't be managed endoscopically then need surgery of affected site
- No recs for pancreas/SB surveillance

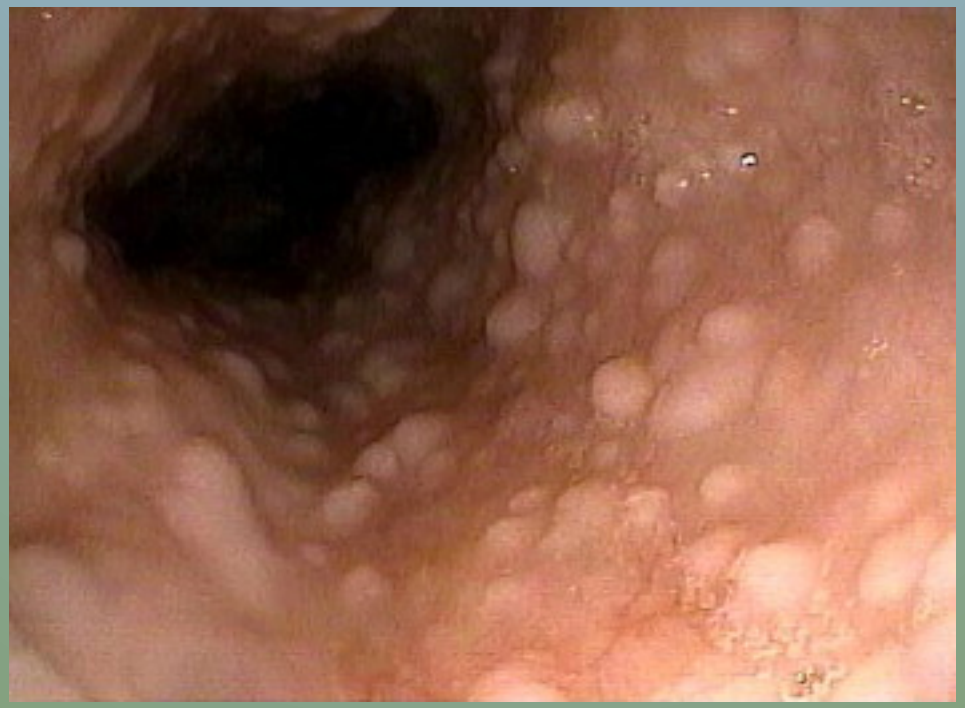


Gastric polyposis in JPS due to SMAD4 mutation.

Cowden Syndrome

- Autosomal Dominant
- PTEN mutation
- Noncancer associations: Facial trichilemmommas, mucocutaneous papules, goiter, fibrocystic breast disease, cerebellar gangliocytomas
- Increased risk for breast cancer and papillary thyroid cancer, risk for CRC not well defined.
- Juvenile polyps most frequent lesion in the colon stomach and small bowel and tend to be asymptomatic. Glycogenic acanthosis in the esophagus.

Cowden Syndrome



Glyocogenic acanthosis associated with Cowden syndrome.

Bannayan-Riley-Ruvalcaba Syndrome

- Same phenotypic spectrum as Cowden Syndrome
- PTEN gene mutation
- No consensus criteria developed for the diagnosis BRRS
- Same associated features of Cowden but GI polyps are more symptomatic
- Pigmented macules of glans penis, mental retardation and assorted congenital abnormalities
- Genetic testing for PTEN for patient and family

Question 1

An 18F w/ FH of FAP presents to your clinic to discuss her GI cancer screening recommendations. She is asymptomatic at present. She informs you that her mother had hundreds of colorectal polyps at the age of 35 and died of CRC but did not undergo genetic eval. The pt has undergone genetic testing and no mutation in either the APC or MUTYH genes were found. She has recently undergone a flex sig and found to have no colorectal polyps. Which is the next best step in management?

A. The pt had a negative genetic test for both polyposis genes and is therefore not at an increased risk for CRC. No further CRC surveillance indicated until age 50.

B. Colonoscopy annually starting at age 25

C. Flex sig in 1 year

D. Upper endoscopy for eval of gastroduodenal polyps now

E. Abdominal MRI to screen for abdominal desmoid tumor

Question 1 Answer

- C. flex sig in 1 year.
- Pt had inconclusive genetic testing and her mother was not tested so a true negative can only be obtained if another at-risk family member tests positive for a mutation. In at-risk pts with indeterminate results, pt should be offered a flex sig or colonoscopy every 12 months starting age 10-12 and continue til 35-40 if negative. EGD (forward and side viewing) recommended at time of onset of colonic polyps or around age 20-25 (whichever comes first)

Question 2

- A 32F presents to clinic for eval of IDA and hematochezia that has been attributted to hemorrhoids. On c-scope she is found to have a 3 cm ulcerated sigmoid adenocarcinoma and 30 3-7mm adenomas throughout the colon. She informs you that her sister was recently dx with CRC at age 38 and had 8 adenomas on her first c-scope. Germline testong for APC mutation is negative. Which is the next best step in eval?
- A. Germline testing for mutations in MLH1, MSH2, MSH6, and PMS2 genes
- B. No further genetic eval necessary
- C. Germline testing for mutation in STK11 gene
- D. Germline testing for mutations in MUTYH gene
- E. Tumor microsatellite instability testing

Question 2 answer

- D. testing for MUTYH gene mutation

Multiple colorectal adenomas attributable to FAP which is autosomal dominant or MAP (MUTYH associated polyposis) which is autosomal recessive. A and E would be done if considering for lynch syndrome which would not have a large number of polyps as in FAP/MAP. STK11 is associated with Peutz Jeghers which has hamartomatous polyps.

Question 3

- A 49AAM presents with h/o 5 months of hematochezia. C-scope demonstrates a 5cm cecal adenocarcinoma and one 5mm adenoma in transverse colon. He reports that his mother had three 5-6mm adenomas on her only c-scope at age 60. He has no other FH of cancer or polyps. Based on his history, you order tumor immunohistochemistry and MSI testing. The tumor is MSI high and has loss of MSH2 and MSH6 and intact expression of MLH1 and PMS2. No germline mutations in MSH2 or MSH6 are detected on genetic testing. Which is the next best management step?
- A. Full sequencing for MLH1
- B. Full sequencing for PMS2
- C. No further eval for lynch syndrome is indicated as this is likely a sporadic CRC
- D. Tests for MLH1 hypermethylation and BRAF testing should be performed to confirm this is a sporadic CRC
- E. Genetic testing for an EPCAM mutation

Question 3 Answer

- E. genetic testing for EPCAM

- Results could be due to lynch syndrome. EPCAM deletions lead to methylation of the MSH2 promoter and silencing of the gene. Silencing leads to a pattern on MSH2 and MSH6 loss on immunohistochemistry. The presence of high MSI and loss of expression of 2 MMR proteins indicates presence of lynch syndrome and not sporadic CRC and therefore MLH1 hypermethylation and BRAF testing not indicated

References

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