Lynch Syndrome aka Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

Germline mutations with mismatch repair (MMR) enzymes. Autosomal Dominant
→ defective DNA repair → tons of mutations ("hypermutated") → microsatellite unstable

Most common form of heritable CRC (colorectal cancer)
CRC usually develops before age 50, often with multiple primaries (~80% lifetime risk)
Also at risk for: Endometrial cancer, Upper urinary tract and other GI cancers, and Sebaceous skin tumors

Universal screening of all new CRC. Do IHC first (algorithm below), can also do MSI testing by PCR.
Looking for LOSS of staining. Normal is intact staining of all 4 MMR enzymes.
Lynch-related CRC is more often right-sided and arises from adenomas
(vs. sporadic MMR-deficient tumors, that come from SSP/A’s, and are associated with BRAF V600E mutations and then MLH-1 promoter hypermethylation and MLH1 loss of expression)

Universal Testing in ALL newly diagnosed CRC:

MMR-IHC

MMR Intact → Probably NOT Lynch (sporadic)
MSH2, MSH6, or PMS2 Deficient → Probably Lynch
MLH1 Deficient (with PMS2)

Methylation

Sporadic
MLH1 Methylation testing
No Methylation
Methylation

BRAF Mutation
No BRAF

BRAF Testing

MLR-deficient CRC:
Associated with high-grade, mucinous differentiation, and lymphocytic infiltrates (hypermutated state is immunogenic).

Better survival compared to MMR-intact CRC (probably due to host response). Automatically approved for anti-PDL1 therapy.

Peutz-Jeghers

Mutation in the STK11/LKB1 gene on chromosome 19
Can be sporadic or inherited

Classic polyps are Hamartomas (non-neoplastic)
Most frequent in small intestine, can remove with polypectomy
Multilobated, may have papillary or frond-like surface
Arborizing smooth muscle
Generally cytologically bland epithelium
Often pedunculated → cause intussusception

Also see: Mucocutaneous melanotic macules (lips and oral mucosa)
Increased risk of many cancers
(e.g., Stomach, Colon, Pancreas, Breast, etc...)
Ovarian SCTAT’s, Sertoli cell tumors, Cervical adenoma malignum
Familial Adenomatous Polyposis  

**Germline mutation in APC gene. Autosomal Dominant**

- **Tumor suppressor → Loss leads to lots of tumors**
- Hundreds of colorectal adenomas carpeting colon, more on left side
- Almost complete penetrance
- Mean age of CRC diagnosis: 40 yrs (so often prophylactic colectomy in 20’s)

Also at risk for duodenal and gastric adenomas (less cancer risk though)
- Need to undergo regular surveillance upper endoscopies also

First morphologic finding: **Single dysplastic crypts** (”unicryptal adenoma”)

**Variants:**
- **Attenuated FAP** – Less than 100 adenomas, right-sided, older age of presentation and CRC. Mutation in different part of APC gene.
- **Gardner’s** – FAP with prominent extraintestinal manifestations (including: Desmoid tumors, Osteomas, Epidermoid cysts, Papillary thyroid carcinoma (classically the cribriform-morular variant variant), and nasopharyngeal angiofibromas)
- **Turncot’s** – “Glioma polyposis syndrome.” FAP with brain tumor (usu. Medulloblastoma)

MYH-Associated polyposis

**Autosomal recessive** (need biallelic germline mutations for phenotype)

- MYH gene involved in base excision repair → defects result in APC and RAS mutations
- Multiple adenomas (usu. < 100), may have extraintestinal manifestations of FAP
- Increased risk of CRC, usu. Right side, even in absence of polyps

Hereditary Diffuse Gastric Cancer

- Most common mutation: **CDH1 (E-cadherin). Autosomal Dominant**
  - E-cadherin is important for cell adhesion and tumor suppression
  - Mutation causes uncontrolled growth of poorly-cohesive cells
- Many families have other mutations, so use clinical criteria often

>70% risk of gastric cancer by 80 yrs
- Endoscopic surveillance is likely inadequate as invisible in situ
- Many get prophylactic gastrectomies
- Women at increased risk for lobular breast cancer

**Classic finding:**  **Signet ring carcinoma in situ**
- Signet ring cells above basement membrane
- Pagetoid spread
- Can then progress to invasive, diffuse gastric cancer
- **Often Multifocal**

Q: What other tumor has loss of E-cadherin?
A: Lobular breast cancer! Makes sense, right?
**Juvenile Polyposis**

* JP's can be sporadic (much more common, esp. if few) or Hereditary

Defined as ≥5 Juvenile polyps, or any number if positive family history

Germline mutations in **SMAD4 or BMPR1A**

Present with bleeding → anemia

Usu. 50 – 200 polyps

Can develop dysplasia and CRC. Age or CRC ~35 yrs

Need increased surveillance

Polyps are pedunculated with cystically dilated cysts

Loose, edematous with inflamed stroma and ulceration

**Cronkhite-Canada**

Uncertain etiology (NOT clearly genetic), **Non-familial**

Often older male (~50 yo)

**Hamartomatous polyps and protein-losing enteropathy**

**Diffusely** nodular mucosa throughout GI tract

Broad, sessile polyps with edema and cystic dilations

In stomach, look like HP. In colon, look like JP

“Ectodermal” manifestations: onychodystrophy, alopecia, cataracts, glossitis, vitiligo

Increased risk of colon cancer, but PLE is often more dangerous!

**COWden Syndrome**

*Think of this cow*

PTEN mutation. Autosomal dominant

Tumor suppressor → lots of different tumors

*Other PTEN syndromes include: Bannayan-Riley Ruvalcaba syndrome and Lhermitte-Duclos disease*

Get:

Multiple **hamartomas** (mouth, GI tract)

**Thyroid carcinoma** (usually Follicular)

**Breast Cancer** (high risk)

**Endometrial Cancer**

Trichile **MMO000**mas

Lipomas

**Esophagus**: Glycogen acanthosis

**Stomach**: Polyps that often resemble HP’s

**Colon**: **Stroma-rich polyps** with cystically dilated glands

Can mimic JP’s.

Can contain **Adipocytes** in lamina propria (relatively unique)

Can get **ganglioneuromatous** polyps

Uterine Cancer

(“because of the bow... get it?”)

Thyroid Cancer

Breast CA
Is it a Hamartoma?

Polyp with:
- Epithelial hyperplasia,
- Dilated & distorted glands,
- Lamina propria edema,
- Chronic inflammation

Does it have a prominent smooth muscle component?

Yes

Does it have:
- Arborizing smooth muscle,
- Smooth Muscle wisps in the lamina propria,
- Lobular configuration of glands?

Yes

Peutz-Jeghers Polyp

No

Are there other cell types present?
- Adipocytes
- Nerves

Yes

Consider Cowden Syndrome
- (and other PTEN syndromes)

No

Hamartomatous polyp

Consider Cowden Syndrome

Are there other cell types?
- Adipocytes
- Nerves

Yes

Most likely Hyperplastic polyp or Inflammatory polyp

No

Most likely Juvenile Polyp or Inflammatory polyp

Background not sampled

Nonspecific: Hamartoma vs Hyperplasia

DDX: Hyperplastic/inflammatory polyps, Prolapse polyp, Juvenile polyp, Peutz-Jegher’s polyp, etc...

Background identical to polyps

Ganglion cells & Nerves

Adipocytes

See either of these?
Think Cowden syndrome

Can confirm there are adipocytes (and not air) with S100 IHC