Too Many Polyps to Count: An Update on Hereditary Polyposis Syndromes

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Disclosures

• None.
Distribution of colon cancers based on family and hereditary risk factors

- **Sporadic** (65-85%)
- **Family Risk** (10-30%)
- **Hereditary Syndrome** (2-3%)

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**Hereditary Polyposis Syndromes**

- **Adenomatous polyposis syndromes**
  - Familial adenomatous polyposis (FAP)
  - MUTYH-associated polyposis (MAP)
  - Polymerase proofreading-associated polyposis (PPAP)
  - NTHL1-associated polyposis (NAP)
- **Hamartomatous polyposis syndromes**
  - Peutz-Jeghers syndrome (PJS)
  - Juvenile polyposis syndrome (JPS)
  - PTEN hamartoma tumor syndrome (PHTS)
    - [Cowden syndrome, Bannayan-Riley Ruvalcaba syndrome]
- **Other important polyposis syndromes**
  - Serrated polyposis syndrome (SPS)
  - Hereditary mixed polyposis syndrome (HMPS)
- **Genetic counseling and genetic testing considerations**
- **Review of some “Polyp Scenarios” and resources**
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Familial adenomatous polyposis (FAP)

- Most common hereditary polyposis syndrome (1 in 10,000 live births)

- Second most common cause of hereditary colon cancer (1% of CRCs)

- Germline mutation of APC

- APC is involved in Wnt-signaling, leads to β-catenin degradation

- Somatic mutation of APC seen in 80% of CRCs

- Autosomal dominant → de novo mutation in ~25% of cases (no family history!)

### Classic FAP versus Attenuated FAP (AFAP)

<table>
<thead>
<tr>
<th></th>
<th>Classic FAP</th>
<th>Attenuated FAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of colonic adenomas</td>
<td>&gt; 100</td>
<td>10-100 (often proximal)</td>
</tr>
<tr>
<td>Decade of life when polyps develop</td>
<td>2nd - 3rd</td>
<td>4th - 5th</td>
</tr>
<tr>
<td>Lifetime risk of developing colorectal cancer without intervention</td>
<td>~100%</td>
<td>70-80%</td>
</tr>
<tr>
<td>Average age of development of colorectal cancer</td>
<td>~40</td>
<td>~50's</td>
</tr>
</tbody>
</table>

Cancer risk of each FAP/AFAP-associated adenoma is similar to sporadic adenomas.

### Extra-colonic manifestations

- GI polyps/cancers
  - Fundic gland polyps → often with LGD
  - Gastric adenomas
  - Duodenal/Ampullary
    - Adenomas (65% risk)
    - Adenocarcinoma (12% risk)
  - Jejunal/ileal adenomas

- Non-luminal tumors
  - Desmoid tumors
  - Thyroid cancer (papillary)
  - Hepatoblastoma
    (in childhood)
  - Medulloblastoma

- Other manifestations
  - Sebaceous cysts
  - Epidermoid cysts
  - Lipomas
  - Osteomas
  - Supernumerary teeth
  - CHRPE (congenital hypertrophy of the retinal pigment epithelium)
The position of the \textit{APC} mutation is important

![Diagram showing the position of the \textit{APC} mutation and associated conditions and codon numbers.]


Colonic management in FAP

- Classic FAP
  - Annual colonoscopy starting between age 10-12
  - Surgery if polyp burden is not manageable by colonoscopy, adenomas > 1cm, adenomas with HGD, or CRC
  - Preferred surgery is TPC with IPAA around age 18
  - Annual pouchoscopy post-TPC

- Attenuated FAP
  - Start colonoscopy screening in late teens-early 20's
  - Colonoscopy every 1-2 years
  - If adenoma burden becomes endoscopically unmanageable then consider colectomy
**Extra-colonic management in FAP**

EGD with forward-viewing and side-viewing endoscope starting at age 18-25 (earlier if colectomy is being considered) → Spigelman staging criteria (number, size, histology, dysplasia)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duodenal Polyposis</th>
<th>Endoscopic surveillance interval</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>4 years</td>
</tr>
<tr>
<td>1</td>
<td>1-4 TAs (&lt; 5mm)</td>
<td>2-3 years</td>
</tr>
<tr>
<td>2</td>
<td>5-19 TAs (&lt; 1cm)</td>
<td>1-3 years</td>
</tr>
<tr>
<td>3</td>
<td>≥ 20 TAs or size ≥ 1cm</td>
<td>6-12 months</td>
</tr>
<tr>
<td>4</td>
<td>Dense polyposis or HGD</td>
<td>3-6 months or surgical evaluation</td>
</tr>
</tbody>
</table>

Consider (although evidence is limited):
- Annual thyroid ultrasound
- Abdominal imaging for desmoids (especially if family history or if symptomatic)
- Small intestinal imaging with capsule endoscopy or small bowel follow through (especially if duodenal polyposis is significant)

**Chemoprevention in FAP**

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SULINDAC FOR COLORECTAL ADENOMAS — GIARDEILLO ET AL.  
1513

TREATMENT OF COLONIC AND RECTAL ADENOMAS WITH SULINDAC IN FAMILIAL ADENOMATOUS POLYPOSIS


THE NEW ENGLAND JOURNAL OF MEDICINE  
May 6, 1993

Rectal polyps (retained rectum or rectal cuff)
- Sulindac - 150mg twice daily
  Reduces adenoma number and size
  May lead to flattening of adenomas → difficulty detecting endoscopically
Duodenal polyps
- Sulindac/Erlotinib
  - 71% decrease in duodenal polyps burden after 6 months
  - Side effects were very debilitating

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MUTYH-associated polyposis (MAP)

- Biallelic germline mutation in MUTYH
- MUTYH is involved in the base excision repair pathway
- Autosomal recessive
- Monoallelic MUTYH found in ~1-2% of the population
- Lifetime CRC risk is ~80%
- CRC risk associated with monoallelic MUTYH is possibly slightly increased, although these patients do not present with polyposis

Typical presentation:
- 10-100 polyps
- Present in the 5th – 6th decade
- Tubular adenomas and serrated adenomas are possible

Colonoscopy should begin at age 20-25, then every 1-2 years
Endoscopically unmanageable polyp burden → consider subtotal colectomy with IRA versus TPC with IPAA (if dense rectal polyposis)
EGD with side viewing scope starting at 30-35 years → follow-up interval based of level of duodenal polyposis (similar to FAP, range 1-4 years)
Consider annual thyroid ultrasound
Other possible cancer risks: skin, ovarian, bladder, breast → no screening recommendations
Can consider genetic testing of spouse or kids of a MAP patient, given the 1-2% population risk of monoallelic MUTYH mutation

Monoallelic MUTYH carriers
Consider colonoscopy at age 40, then at least every 5 years → but this evidence is evolving
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Polymerase Proofreading-associated Polyposis (PPAP)

- Germline mutation in \textit{POLE} or \textit{POLD1}
- Defect in the proofreading subunit of a DNA polymerase
- Autosomal dominant
- Leads to high rates of DNA mutations
- Increased risk of colon cancer, endometrial cancer, as well as other cancers (breast, brain)

\textit{Seshagari, S. Nature Genetics, 2013}
**NTHL1-associated polyposis (NAP)**

**LETTERS**

A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer

Robbert D A Weren1,6, Marjolijn H Ligtenberg1,6, C Marken van der Lee1,6, Richarda M de Vroe5,6, Egzino T P Verweij7,8, Liebeth P Speijl9, Wendy A G van Zutphen3,8, Marjolein C Langman1,6, Christian Gillans2,6, Jayne Y Hehir‐Swol1, Alexander Holscher6, Jay Sterin‐Sauvage1, Evan A Boyle4, Eveline J Kamping5, Iris D Nauta6,7, Bastiaan R J Topp8, Feikja M Nagengast5, Ad Geertsma van Kessel1,11, Joop J M van Kricken1,11, Roland P Kleiner6,8 & Noudine Hoopes‐Rezaie1,6

VOLUME 47 | NUMBER 6 | JUNE 2015

- Germline mutation in NTHL1
- NTHL1 is involved in the base excision repair pathway
- Autosomal recessive
- Increased risk of colon cancer
- Likely an extended spectrum of cancer risk: duodenal, endometrial, skin.

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**PPAP and NAP management**

- Begin colonoscopy at age 25-30
- Repeat colonoscopy every 2-3 years if no polyps, and every 1-2 years if polyps are present
- Endoscopically unmanageable polyp burden → consider surgery

- Given the rarity of these syndromes
  - data is very limited
  - no clear indication for extra-colonic screening at this time
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Peutz-Jeghers syndrome (PJS)

- Leads to Peutz-Jeghers polyps (hamartomas) of the GI tract

- Classic mucocutaneous pigmentation seen in the majority of patients

- Autosomal dominant

- The tumor suppressor STK11 (previously LKB1) is mutated in 50-70% of patients

- 20-30% of patients → de novo mutation

- Clinical diagnosis (at least 2 of the following):
  - ≥ 2 Peutz-Jeghers polyps of small intestine
  - Mucocutaneous hyperpigmentation
  - Family history of PJS

Juvenile polyposis syndrome (JPS)

- Patients develop juvenile polyps (hamartomas) of the GI tract
- Autosomal dominant
- \(BMPR1A\) or \(SMAD4\) is mutated in \(\sim 50\%\) of cases, some patients with a \(SMAD4\) mutation can have hereditary hemorrhagic telangiectasia (HHT)
- Isolated juvenile polyps of the colon are common in children
- Clinical diagnosis (1 of the following):
  - \(\geq 3\) juvenile polyps of the colon
  - Multiple juvenile polyps found throughout the GI tract
  - Any juvenile polyps with a family history of JPS

JPS management

- Colon cancer risk: 40-50%
  - Begin colonoscopy at age 15
  - Repeat every 1-3 years depending on polyp burden

- Gastric cancer risk: 20%
  - Begin EGD at age 15
  - Repeat every 1-3 years depending on polyp burden

- Bleeding risk
  - If patient has a SMAD4 mutation, screen for vascular lesions associated with HHT beginning at age 6 months

PTEN hamartoma tumor syndrome (PHTS)

- Patients develop hamartomas (including ganglioneuromas) of the GI tract as well as a number of other findings (including macrocephaly and skin findings)

- Autosomal dominant

- The tumor suppressor PTEN is the most commonly mutated gene (30-50% of patients)

- Two variants:
  - Cowden syndrome
  - Bannayan-Riley-Ruvalcaba syndrome (BRRS)

- Complicated diagnostic criteria

**PHTS management**

- Increased risk of breast, endometrial, thyroid, kidney, and colorectal cancers

- Colon cancer risk management
  - Colonoscopy starting at age 35
  - If a relative has colon cancer before age 40, then start 5–10 y before the earliest colon cancer
  - Repeat colonoscopy at least every 5 years

- Consider EGD, but guidelines are variable and evidence is weak

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Serrated polyposis syndrome (SPS)

- Previously referred to as “hyperplastic polyposis syndrome”

- Sometimes SPS runs in families, but no causative gene known at this time

- Serrated polyp:
  - Hyperplastic polyp (proximal to sigmoid or ≥ 1cm in the rectosigmoid)
  - SSA
  - Traditional serrated adenoma

- Diagnosis (1 of the following):
  - 5 serrated polyps proximal to sigmoid with at least 2 being ≥ 1cm
  - Any serrated polyp proximal to sigmoid with a 1st degree relative with SPS
  - More than 20 serrated polyps distributed throughout the colon


SPS colon cancer risk

- The colon cancer risk between patients with SPS compared to those with multiple serrated polyps was not statistically different

- Risk was also the same for first degree relatives from these two groups

- Does the diagnostic criteria for serrated polyposis syndrome need to be broadened?
SPS management

- Colon cancer risk management
  - Colonoscopy every 1-3 years
  - Consider surgery if unable to clear all polyps

- First degree family members of patients with SPS
  - Start colonoscopy at the earliest of:
    - Age 40
    - Youngest age when SPS was diagnosed
    - 10 years before SPS-associated colon cancer
  - Repeat every 5 years if no polyps are found
  - If a serrated polyp is found treat as if SPS

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Hereditary mixed polyposis syndrome (HMPS)

- Develop a mixture of hamartomatous, adenomatous (tubular, TV, and serrated), and hyperplastic polyps
- No consensus clinical criteria for diagnosis
- Can present in families meeting Amsterdam criteria and also in families with polyposis
- Autosomal dominant
- Colon cancer risk management
  - Begin colonoscopy at age 25-30
  - Repeat colonoscopy every 2-3 years if no polyps, and every 1-2 years if polyps are present
  - Endoscopically unmanageable polyp burden → consider surgery
- Given the rarity of this syndrome → no clear indication for extra-colonic screening at this time

HMPS genetics

Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1

- Duplication upstream of GREM1 (in the promoter)
  - GREM1 expression
  - ↓BMP signaling
- 40k8 duplication seen in Ashkenazi Jewish families
- 2 other duplications reported
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When to consider sending a patient for genetic evaluation for a polyposis syndrome?

• ≥ 10 adenomas on a single colonoscopy

• ≥ 20 cumulative adenomas (although some would argue for ≥ 15)

• ≥ 10 adenomas with a history of CRC

• ≥ 3 hamartomas

• Family history of a first degree relative with a polyposis syndrome

• You’re just not comfortable with the patient’s polyp burden!
Easy aspects of genetic testing:
- Sample collection → Saliva or blood, multiple good commercial labs
- Decreasing cost → Typically < $1000 for patients
- Quick turnaround → 3-4 weeks

Difficult aspects of genetic testing:
- Genetic counseling → Should be performed by a licensed genetics counselor
- Detailed informed consent → Imperative
  - GINA/Insurance considerations
  - Worry/concern about cancer risk for patient and family members
  - Different types of genetic abnormalities that can be found
- Determining what genes to order testing on
  - Single gene versus multi-gene panel
- Difficult to interpret variants → variant of uncertain significance (VUS)
- Follow-up of uncertain variants → variants can change status at any time
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Polyp scenarios...

If you see a patient with many **tubular, villous, or tubulovillous adenomas**, what are you thinking about?

- FAP (*APC*)
- MAP (*MUTYH*)
- PPAP (*POLE/POLD1*)
- HMPS (*GREM1*)

In the future...
- NAP (*NTHL1*)
Polyp scenarios...

If you see a patient with many **sessile serrated adenomas or atypical hyperplastic polyps**, what are you thinking about?

- SPS (Does the patient meet clinical criteria?)
- MAP (*MUTYH*, especially if non-serrated adenomas are also present)
- HMPS (*GREM1*)

Polyp scenarios...

If you see a patient with many **hamartomatous polyps**, what are you thinking about?

- PJS (*STK11*)
- JPS (*BMPR1A, SMAD4*)
- PHTS (*PTEN*)
- HMPS (*GREM1*)
- Cronkhite-Canada syndrome*

* Non-hereditary
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Thank you

bryson.katona@uphs.upenn.edu

I'M A YOUNG POLYP!!! I'VE GOT MY INVASIVE NEOPLASTIC TRANSFORMATION AHEAD OF ME!!!

DON'T SHARE ME!! I STAY I'M BENIGN.

NO ONE LIKES COLONOSCOPIES.