Inherited Colon Cancer Syndromes

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2014 ACG Board of Governors/ASGE
Best Practices Course

Hereditary Colon Cancer Syndromes

- Early age of onset (<50 yrs) of manifestations
- Synchronous or cumulative lifetime polyps
- Metachronous or synchronous cancers
- Multiple relatives/generations affected
- Family member with known HCCS

- Any of these should prompt referral for genetic counseling


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Colorectal Cancer

Sporadic

FAP

MYH

Adenoma

CIN

MSI

Lynch Syndrome

CIMP

Serrated Neoplasm

MLH1 promotor methylation

BRAF mutation

MSI

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Chromosomal Instability

APC/β-catenin

KrAS

TP53, PIK3CA, loss of 18q

Normal mucosa

Aberrant crypt focus

Early adenoma

Late adenoma

Invasive cancer

EGFR, COX2

Increasing CIN

Pino MS, et al. NEJM 2010;339;1277

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CpG Island Methylation (CIMP)

Gene Expression

Gene Silencing

Microsatellite Instability

- Repeated nucleotide sequences called "microsatellites"
- 4 DNA Mismatch Repair (MMR) Genes: MLH1, MSH2, MSH6, PMS2
- DNA nucleotide replication errors repaired by MMR Proteins

MLH1 PMS2
MSH2 MSH6

Boland CR, Gastroenterology 2010;138:2073
## Hereditary CRC Syndromes

<table>
<thead>
<tr>
<th>Autosomal Dominant</th>
<th>Autosomal Recessive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch Syndrome</td>
<td>MYH associated polyposis</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis</td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td></td>
</tr>
<tr>
<td>Juvenile Polyposis Syndrome</td>
<td></td>
</tr>
<tr>
<td>PTEN Hamartoma Tumor Syndrome (Cowden’s syndrome, Bannayan-Ruvalcaba-Riley Syndrome)</td>
<td></td>
</tr>
<tr>
<td>Hereditary Mixed Polyposis Syndrome</td>
<td></td>
</tr>
</tbody>
</table>

## Hereditary CRC Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Polyp Type</th>
<th>Gene Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch Syndrome</td>
<td>Adenomatous</td>
<td>MMR</td>
</tr>
<tr>
<td>FAP and attenuated FAP</td>
<td>Adenomatous</td>
<td>APC</td>
</tr>
<tr>
<td>MYH Associated Polyposis</td>
<td>Adenomatous</td>
<td>MYH</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>Hamartomatous</td>
<td>STK11</td>
</tr>
<tr>
<td>Juvenile Polyposis Syndrome</td>
<td>Hamartomatous</td>
<td>SMAD4 or BMPR1A</td>
</tr>
<tr>
<td>PTEN Hamartoma Tumor Syndrome</td>
<td>Hamartomatous</td>
<td>PTEN</td>
</tr>
<tr>
<td>Mixed Hyperplastic Polyposis Syndrome</td>
<td>Mixed</td>
<td>SCG5</td>
</tr>
</tbody>
</table>
Case 1

• 50 year old female: Second opinion
• No personal/family hx of cancer; 53 yo brother with polyps
• Colonoscopy 3 yrs prior for abnormal BMS, normal
• 3 mos ago EGD normal, screening colonoscopy:
  – Hepatic Flexure: 3mm and 10mm sessile polyp : tubular adenoma
  – Rectum: 2, small polyps: hyperplastic polyp, lymphoid aggregate
  – Cecum: Polypoid tissue, cannot be safely removed

• Recommendation: See a surgeon

Case 1
What is the next most appropriate step?

1. Surgical Consult for segmental colectomy
2. Surgical consult for total colectomy
3. Repeat Colonoscopy
4. Repeat Colonoscopy and EGD
Case 1

- 12 < 5 mm polyps throughout colon: Tubular adenoma
- 3, 8 -10 mm in cecum: 2 snared: TVA
- Submucosal injection, inadequate lift: TVA

Case 1

- EGD: ? manifestations of FAP or MAP
- Esophagus and stomach: normal
- Duodenum: 2, < 5 mm flat polyps: TA
- Papilla, normal appearing including biopsy
Case 1

What is the next most appropriate step?

1. Surgical Consult for segmental colectomy
2. Repeat Colonoscopy one year, sulindac
3. Genetic counseling

Genetic Counseling

- Patients with unusual phenotype
- Risk assessment
  - 3 generation family history; age and cause of death and cancer
- Education session
- Informed Consent for genetic testing
  - R, B, A and insurance coverage, out of pocket
- Providing results
- Recommended FU for proband and family
Genetic Testing in Polyposis Syndromes

- ≥10 cumulative lifetime adenomas
- > 20 adenomas for Medicare
- CRC < 50 yrs
- Desmoids
- Relatives of known APC or MYH mutation carriers (or other polyposis syndromes)

Colon Polyp Burden in FAP/MAP

- AFAP
- MAP
- FAP

0 adenomas 100 adenomas 1000 adenomas

Oligopolyposis

Gastroenterology 2001;121:195-7
NEJM 2003;348:791-99
Gastroenterology 2004;127:444-51
Gastroenterology 2004;127:9-16

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Prevalence of *APC* and *MUTYH* mutations by lifetime adenoma Burden

![Graph showing prevalence of APC and MUTYH mutations by lifetime adenoma burden.](image)


**Case 1**

**Total colectomy with ileo-rectal anastomosis**
- Well differentiated adenocarcinoma in cecum at appendiceal orifice
- **TOTAL OF 6 TUBULAR ADENOMAS and MULTIPLE AND PROMINENT POLYPOID LYMPHOGLANDULAR COMPLEXES**

**COMMENT: pT1pN0**
Case 1: Follow Up

- Genetic counseling and testing
  - APC mutation testing *negative*
  - MYH mutations: Y165C and R231H
- Diagnosis: MYH associated polyposis
- Management recommendations
  - Inform family members
    - Offer genetic counseling and testing
  - Surveillance for polyposis

MYH associated polyposis (MAP)

- Autosomal recessive syndrome of adenomas and CRC
- Due to bi-allelic mutations in the MYH gene
- Colon features similar to attenuated FAP
- Extra-colonic features similar to FAP
- Board tip: Polyposis with recessive inheritance
Autosomal Recessive Inheritance (MAP)

Each child has a 25% chance of inheriting both MYH gene mutations (affected), a 50% chance of inheriting at least one MYH gene mutation, and a 25% chance of inheriting no MYH gene mutations.

FAP

- Due to APC mutation
- Affects 1:10,000 individuals
  - 30% cases de novo
- 60-100% risk of CRC

1Nieuwenhuis MH Cr Rev Onc Hem 2007;61:153
Gastric features of FAP/MAP

• Fundic gland polyposis
  – Prevalence: 88%
  – 50% with low grade dysplasia
  – 3% HGD, > 10 mm- resect

• Gastric adenomas
  – Prevalence: 10%
  – Usually antrum- resect

• Gastric Cancer: Rare

Duodenum in FAP/MAP

• Duodenal adenomas: 100%
• Adenomatous papilla¹:
  – 54% if normal appearance
  – 89% if abnormal appearance

• Periampullary/Duodenal cancer: 2-36%²
  – When occurs, all die of malignant disease
  – Cancer risk based upon stage of duodenal polyposis

¹Burke C, GIE 1999;49:358
²Groves C Gut 2002;50:636
Staging of Duodenal Polyposis

<table>
<thead>
<tr>
<th>No. of polyps</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>1-4</td>
<td>5-20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Polyp size (mm)</td>
<td>1-4</td>
<td>5-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Histology</td>
<td>Tubular</td>
<td>TVA</td>
<td>Villous</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Spigelman AD. Lancet 1989;2: 783

<table>
<thead>
<tr>
<th>Stage</th>
<th>Points</th>
<th>Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1-4</td>
<td>0%</td>
</tr>
<tr>
<td>II</td>
<td>5-6</td>
<td>2.3%</td>
</tr>
<tr>
<td>III</td>
<td>7-8</td>
<td>2.4%</td>
</tr>
<tr>
<td>IV</td>
<td>9-12</td>
<td>36%</td>
</tr>
</tbody>
</table>

Gut 2002;50:636

Extra-intestinal features of FAP/MAP

- Desmoid tumors (15%)
- Thyroid carcinoma (2-15%)
- Adrenal adenoma (7-13%)
- Osteomas (50-90%)
- Supernumerary teeth (11-27%)
- CHRPE (70-80%)
- Soft tissue tumors (50%)
  - Lipoma, fibroma, sebaceous cysts
- Hepatoblastoma (<2%)

Thyroid Cancer in FAP/MAP

- Ultrasound and palpation in 192 pts
  - Thyroid cancer: papillary
    - 3% FAP
    - 15% MAP
  - Mean age: 44 yrs (35–60)
  - Size: 15 mm (range 6–23 mm)
  - Physical exam unreliable


UGI Surveillance FAP/MAP

<table>
<thead>
<tr>
<th>Stage</th>
<th>Interval</th>
<th>Method</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5 yrs</td>
<td>EGD/D</td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>3 yrs</td>
<td>EGD/D</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1 yr</td>
<td>EGD/D</td>
<td>Celecoxib 400 BID/Polyp eradication</td>
</tr>
<tr>
<td></td>
<td>3 yrs</td>
<td>Pill Cam</td>
<td></td>
</tr>
<tr>
<td>IV*</td>
<td>6 mo</td>
<td>EGD/D</td>
<td>Pancreas sparing duodenectomy</td>
</tr>
<tr>
<td></td>
<td>3 yrs</td>
<td>Pill Cam</td>
<td></td>
</tr>
</tbody>
</table>

D= duodenoscopy with bx of papilla
* Preferred approach is preventive surgery

Prophylactic Duodenal Surgery
Pancreas sparing Duodenectomy


Surveillance of FAP/MAP

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Procedure</th>
<th>Age (yrs)</th>
<th>Interval (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic FAP</td>
<td>FS or colonoscopy*</td>
<td>10-15</td>
<td>1</td>
</tr>
<tr>
<td>aFAP/MAP</td>
<td>Colonoscopy*</td>
<td>18-20</td>
<td>1-2</td>
</tr>
<tr>
<td>Surgical Consult</td>
<td>Colonoscopy*</td>
<td>When polyps detected</td>
<td></td>
</tr>
<tr>
<td>Post operative</td>
<td>FS or pouchoscopy</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Thyroid Ultrasound</td>
<td>Late teens</td>
<td>1</td>
</tr>
<tr>
<td>Duodenum</td>
<td>EGD- duodenoscopy</td>
<td>25</td>
<td>Based upon stage</td>
</tr>
</tbody>
</table>

NCCN guidelines v2 2013
FAP/MAP Surgery

- **Indications:**
  - Symptoms present, advanced adenomas or excess polyp burden
  - Severe polyposis
    - Total colectomy and ileorectal anastomosis (desmoids or low rectal burden)
    - Proctocolectomy and IPAA (if rectal burden high)
  - Oligopolyposis (< 100 polyps)
    - Colectomy and IRA

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Chemoprevention of FAP/MAP

- **Adjunct to endoscopy**
- **Oligopolyposis:** Intact colon
- **High rectal polyp burden post operative**
  - Sulindac 150-200 mg BID - 50% reduction
  - Celecoxib 400 mg BID - 28% reduction
  - Steinbach G, NEJM 2000;342:1947
- **Duodenal polyposis**
  - Celecoxib 400 mg BID
Hereditary Non Polyposis Colon Cancer

- ≥ 3 relatives with CRC
- 1 FDR to other 2
- ≥ 2 successive generations
- 1 CRC diagnosed < 50 yrs

Mutations found in 50%
40% with LS don’t meet clinical criteria

Vasen HF et al, Dis Colon Rectum 1991

CRC in Lynch Syndrome

- Lifetime Risk: Varies by genotype
- Median age: 45 years
- Location: Usually right sided
- Pathology: Distinctive
- Recurrence: 40% at 20 yrs

Bonadonna V et al. JAMA 2011;2304
Tumor Microsatellite Instability Testing

NR21  BAT25  Mono27

Normal Tissue

Tumor Tissue

Immunohistochemistry

MLH1  MSH2

Can be done on formalin fixed, archival tumor specimens.

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Courtesy Jennifer Hunt MD
Hereditary Non Polyposis Colon Cancer

HNPCC

Lynch Syndrome

Familial CRC Type X

MSI

Germline MMR Mutation

No MSI or MMR mutation

Lynch Syndrome

Extra-Colonic Cancer Risks

Koornstra JJ et al. Lancet Oncology 2009;10:400-408

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## Cancer Risk
**Lynch Syndrome vs Type X**

<table>
<thead>
<tr>
<th>Site of Cancer</th>
<th>SIR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lynch (MSI or MMR) (N=1855)</td>
<td>Type X (No MSI) (N=1567)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>6.1*</td>
<td>2.3*</td>
</tr>
<tr>
<td>Uterus</td>
<td>4.1*</td>
<td>0.8</td>
</tr>
<tr>
<td>Stomach</td>
<td>4.6*</td>
<td>1.4</td>
</tr>
<tr>
<td>Kidney</td>
<td>2.6*</td>
<td>0.9</td>
</tr>
<tr>
<td>Ovary</td>
<td>2.0*</td>
<td>1.5</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>7.6*</td>
<td>1.6</td>
</tr>
<tr>
<td>Ureter</td>
<td>9.0*</td>
<td>2.9</td>
</tr>
</tbody>
</table>

* Compared to SEER


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## Segmental Colectomy and CRC in Lynch Syndrome

![Graph showing CRC Risk for Segmental Colectomy Cohort](Gut%202011%3A60%3A950-957)
Universal CRC Testing for LS

- 1066 patients, 2.2% had LS
- 19.5% had MSI, 11% were LS
- Phenotype:
  - 43% diagnosed > 50 years
  - 22% did not Amsterdam II or revised Bethesda guidelines

### Germline Testing Results in 21 Proband’s Relatives

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Tested</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td>54</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Second degree</td>
<td>22</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>≥ Third degree</td>
<td>41</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>117</td>
<td>52</td>
<td>65</td>
</tr>
</tbody>
</table>

Hampel H et al. NEJM 2005;352;18

LS Screening Method

Cleveland Clinic → Resected CRC

- Genetic testing If appropriate

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Chemoprevention and Lynch Syndrome

![Graph showing the effect of aspirin on CRC incidence over time.](image)


Quick Risk Assessment Tool

- Do you have FDR with any of the following < age 50:
  - CRC
  - Uterus, ovary, stomach, small intestine, urinary tract, bile ducts, pancreas or brain cancer
- Have you had any of the following diagnosed < age 50?
  - CRC
  - Colorectal polyps
- Do you have 3 or more relatives (FDR, SDR) with CRC?

- Yes to questions: Refer for genetic assessment
  - Identifies 77% of high risk patients
  - 95% of Lynch patients (+ mutation)

Kastrinos et al. Am J Gastro 2009;104:
Gastroenterologists and MSI Testing

- Requires
  - Endoscopic bx of target lesion (adenoma or cancer) and normal tissue
- When to consider MSI testing during colonoscopy
  - Pts with CRC (plan operation)
  - Pts with proximal, >9 mm adenoma, <40 years old
  - Pts with adenoma/CRC and FHx suspicious for HNPCC

<table>
<thead>
<tr>
<th>Adenoma Size</th>
<th>MSI-H</th>
<th>Abnormal IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 mm (N=22)</td>
<td>32%</td>
<td>38%</td>
</tr>
<tr>
<td>5-9 mm (N=7)</td>
<td>29%</td>
<td>57%</td>
</tr>
<tr>
<td>&gt; 10 mm (N=6)</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Yurgelun MB, Cancer Prev Res 2012:5;574

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Surveillance in Lynch Syndrome

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Interval</th>
<th>Age to begin</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>1-2 yrs</td>
<td>20-25 yrs</td>
<td>Strong</td>
</tr>
<tr>
<td>Endometrial Bx, TVUS</td>
<td>1 yr</td>
<td>30-35 yrs</td>
<td>Insufficient</td>
</tr>
<tr>
<td>EGD</td>
<td>3-5 yrs</td>
<td>30-35 yrs</td>
<td>Insufficient</td>
</tr>
<tr>
<td>UA</td>
<td>1 yr</td>
<td>25-30</td>
<td>No comment</td>
</tr>
<tr>
<td>Hysterectomy/BSO</td>
<td>After childbearing</td>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>

Or 2-5 yrs earlier if relative was < 25 years

NCCN 2013 www.nccn.org
Sanford R. Weiss, MD
Center for Hereditary Colorectal Neoplasia