Practical Approach to Genetic Syndromes in CRC

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Objectives

• Recognize clues suggestive of a genetic CRC syndrome
• Formulate diagnostic and management plan for patients with Lynch Syndrome and FAP/MAP
Hereditary Colon Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch Syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Colon, endometrial, ovarian, gastric, urinary tract, small bowel, brain and skin (sebaceous) neoplasms</td>
</tr>
<tr>
<td>Li Fraumeni</td>
<td>TP53</td>
<td>Childhood cancers, sarcoma, leukemia, brain tumors, breast cancer, colon cancer</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis</td>
<td>APC</td>
<td>Adenomas, CRC, thyroid cancer, osteomas, soft tissue tumors, desmoid tumors</td>
</tr>
<tr>
<td>MYH-Associated Polyposis</td>
<td>MUTYH*</td>
<td>Adenomas, colon cancer, thyroid cancer</td>
</tr>
<tr>
<td>NTHL1- associated polyposis</td>
<td>NTHL1*</td>
<td>Adenomas (oligopolyposis), endometrial, CRC</td>
</tr>
<tr>
<td>Polymerase proofreading associated polyposis</td>
<td>POLE, POLD1</td>
<td>Adenomas (oligopolyposis), endometrial, brain cancer</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11</td>
<td>Mucocutaneous pigmentation, hamartomas, breast, GI, pancreatic, and rare GYN/testicular cancers</td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td>PTEN</td>
<td>Hamartomas, skin lesions, macrocephaly, breast, thyroid, and endometrial cancers, CRC</td>
</tr>
<tr>
<td>Juvenile Polyposis Syndrome</td>
<td>BMPR1A, SMAD4</td>
<td>Hamartomas, colon cancer, SMAD4 –HHT overlap</td>
</tr>
</tbody>
</table>

Pathways to CRC

- Sporadic CRC
- FAP
  - Microsatellite Stable (MSS)
  - Adenoma
    - Microsatellite Instability (MSI)
    - Lynch Syndrome
- MAP
- Sessile Serrated Polyp
  - MSI
  - BRAF mutation
  - MLH1 methylation
CpG Island Methylation (CIMP)

- Normal colon epithelium: Gene Expression
- Colorectal cancer: Gene Silencing
- Turns off MLH1

Microsatellite Instability

- Repeated nucleotide sequences called “microsatellites”
- DNA fidelity maintained by Mismatch Repair Proteins (MMR)

MLH1 PMS2
MSH2 MSH6

Boland CR, Gastroenterology 2010;138:2073
Mismatch Repair Protein Function

Normal MMR: TCGAC
AGCTG

Defective MMR: TCTAC
AGATG

Etiology:
1. MLH1 promoter methylation
2. Germline MMR mutation-Lynch Syndrome

Nucleotide mismatch

Microsatellite Stable (MSS)

Microsatellite Instability (MSI)

Tumor MSI Testing

NR21

BAT25

Mono27

Normal Tissue

Tumor Tissue

MSI-H: \( \geq 2/5 \) (30%) consensus MSI sequences
Lynch Syndrome

- Causes up to 5% CRC
- Defined as: a **germline mutation** in a MMR gene
  - **MLH1** and **MSH2**: 90%
    - **EPCAM**: mutation silences transcription of MSH2
  - **MSH6**: 10%
  - **PMS2**: 6%
CRC in Lynch Syndrome

- Lifetime Risk: Varies by genotype
- Median age: 45 years
- Location: Right (72%)
- Pathology: Distinctive
- Recurrence: 40% at 20 yrs

<table>
<thead>
<tr>
<th>Age</th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>6</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>50</td>
<td>14</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>60</td>
<td>28</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>70</td>
<td>41</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td>80</td>
<td>49</td>
<td>52</td>
<td>18</td>
</tr>
</tbody>
</table>

Age Specific Risk, % (95% CI)

Bonadona V et al. JAMA 2011;2304

Clinical Criteria for HNPCC

- Amsterdam Criteria I
  - >3 relatives with CRC
  - 1 FDR to other 2
  - >2 successive generations
  - 1 CRC diagnosed <50 yrs
  - FAP excluded

Lynch Syndrome Mutations found in 50%

Your patient age 38

- = unaffected
- = affected CRC

Vasen HF et al, Dis Colon Rectum 1991
Clinical Criteria for HNPCC

**Extra-Colonic Cancer LS Risks**

- >3 relatives with HNPCC-associated cancer (CRC, endometrial, small bowel, ureter, or renal pelvis)
- 2 generations affected
- 1 FDR to other two
- Age <50

**Amsterdam Criteria II**

- Sensitivity 22%, Specificity 98%

Vasen H, Gastroenterology 1999;116:1453–8

Universal Testing of CRC for MSI

*Recommended by:*

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)


U.S. Multi-Society Task Force

Giardiello FM, Am J Gastro 2014;109:1159

ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes

Approach To Tumor Testing for LS

- **Tumor Testing MSI/IHC**
  - Loss MLH1
    - **BRAF mutation (+) and/or MLH1 promoter methylation (+)**
      - Sporadic Cancer
        - Follow cancer specific guidelines
    - Loss MSH2, MSH6, PMS2
      - Germline testing directed by IHC

- Manage patient and family according to test results

Giardiello FM, Am J Gastro 2014

Approach to Tumor Testing in CRC/HNPCC

- **HNPPCC**
  - **MSI**
    - No Germline Mutation
      - Lynch Like Syndrome
    - Germline MMR Mutation
      - Bi-allelic Somatic MMR
  - **No MSI**
    - Familial Colorectal Type X

Cancer Risk in MSS AC I Families

<table>
<thead>
<tr>
<th>Site of Cancer</th>
<th>SIR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>161 AC-1 families</td>
<td>MSI-H (N=1855)</td>
<td>No MSI Familial CRC Type X</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>

* P<0.001 Compared to SEER


Post op CRC recurrence in Lynch Syndrome

- Extended colectomy (IRA or ISA) vs segmental colectomy
- FU: 11 years
- CRC recurrence: 0% in extended colectomy cohort

Parry S, et al Gut 2011;60:950-957
HNPCC Management

- Genetic counseling and testing
- Surveillance
  - Familial CRC Type X
    - Colonoscopy every 3-5 years
  - Lynch Syndrome
    - Colonoscopy and Extra-colonic Cancer screening
    - Prophylactic GYN surgery after childbearing
    - Extensive colon surgery if CRC diagnosed

Surveillance in LS

<table>
<thead>
<tr>
<th>Organ</th>
<th>Age to Begin</th>
<th>Method</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>20-25 yrs*</td>
<td>Colonoscopy</td>
<td>1-2 yrs</td>
</tr>
<tr>
<td>Uterus/Ovary</td>
<td>30-35 yrs</td>
<td>TVUS, Endometrial Bx</td>
<td>1-2 yrs</td>
</tr>
<tr>
<td></td>
<td>After childbearing or age 40</td>
<td>TAH-BSO</td>
<td></td>
</tr>
<tr>
<td>Stomach/SB</td>
<td>30-35 yrs</td>
<td>EGD-bx H pylori</td>
<td>2-3 yrs</td>
</tr>
<tr>
<td>Urothelium</td>
<td>30-35 yrs</td>
<td>Urinalysis</td>
<td>1 yr</td>
</tr>
</tbody>
</table>

*Or 10 years younger than the youngest age of the affected relative (2-5 yrs if relative <25 yrs)

### Adenomatous Polyposis Syndromes

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

**MAP**
- Due to bi allelic *MUTYH* mutations
- Autosomal recessive
- Usually <100 polyps
- 2-3% population carriers
- 60% risk of CRC

### Extra-intestinal features of FAP/MAP
- Desmoid tumors (15%)
- Thyroid carcinoma (2-17%)
- Adrenal adenoma (7-13%)
- Osteomas (50-90%)
- Supernumerary teeth (11-27%)
- CHRPE (70-80%)
- Soft tissue tumors (50%)
  - Lipoma, fibroma, sebaceous cysts
- Hepatoblastoma (<2%)
Gastric features of FAP/MAP

- Fundic gland polyposis
  - Prevalence: 88%
  - Histology
    - LGD: 41%
    - HGD: 3%

- Gastric adenomas
  - Prevalence: 10%
  - Usually antrum

- Gastric Cancer: Increasing

Duodenum in FAP/MAP

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

- Periampullary/Duodenal cancer: 2-36%²
  - Cancer risk based upon stage of duodenal polyposis

¹Burke C, GIE 1999;49:358
²Groves C Gut 2002;50:696
Staging of Duodenal Polyposis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Points</th>
<th>Cancer Risk</th>
<th>EGD Interval*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1-4</td>
<td>0%</td>
<td>2-3 y</td>
</tr>
<tr>
<td>II</td>
<td>5-6</td>
<td>2.3%</td>
<td>1-3 y</td>
</tr>
<tr>
<td>III</td>
<td>7-8</td>
<td>2.4%</td>
<td>6-12 m</td>
</tr>
<tr>
<td>IV</td>
<td>9-12</td>
<td>36%</td>
<td>3-6 m, Surgical Evaluation</td>
</tr>
</tbody>
</table>

Groves C Gut 2002;50:636

Genetic Testing in Adenomatous Polyposis Syndromes

- History of >10 cumulative adenomas
- Family history FAP/MAP
- History of adenomas and extracolonic manifestations
  - duodenal adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium (CHRPE), epidermal cysts, osteomas
- Genetic testing for APC and MUTYH mutations

## Colorectal Phenotype and Genotype

![Graph showing the relationship between cumulative adenoma count and mutation prevalence.](image)


## 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>puberty</td>
<td>1</td>
</tr>
<tr>
<td>aFAP/MAP</td>
<td>Colonoscopy*</td>
<td>18-20</td>
<td>1-2</td>
</tr>
<tr>
<td>Post operative</td>
<td>FS or pouchoscopy ileoscopy</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>25-30</td>
<td>Based on stage</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>AFP and ultrasound</td>
<td>B – 7</td>
<td>6 months</td>
</tr>
</tbody>
</table>
