Clues to Hereditary Polyposis Syndromes

- Early age of onset
- Numerous relatives affected
- Unusual number or pathology of polyps
- Multiple organs affected
- Synchronous or metachronous lesions
Recognizing Hereditary CRC Syndromes

- Obtain personal and family history with sufficient information to develop a preliminary determination of familial cancer risk
  - First and second degree relatives
- Minimum data to gather:
  - History of benign and malignant tumors
  - Age at onset and pathology of polyps/tumors
- Recommended for all patients seen in outpatient gastroenterology and endoscopy practices


Risk Assessment Tool

1. Do you have FDR with any of the following < age 50?
   1. CRC
   2. Uterus, ovary, stomach, small intestine, urinary

Yes to all
Identifies 95% of LS patients

1. CRC
2. Colorectal polyps
3. Do you have >3 FDR or SDR with CRC?

Kastrinos et al. Am J Gastro 2009;104:
### Polyposis Syndromes

#### Colon Polyp Type and Mutation

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Polyp Type</th>
<th>Gene Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP and attenuated FAP</td>
<td>Adenomatous</td>
<td>APC</td>
</tr>
<tr>
<td>MYH Associated Polyposis</td>
<td>Adenomatous, Serrated, Lymphoid Follicles</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>Hereditary Mixed Polyposis Syndrome</td>
<td>Mixed Polyp</td>
<td>SCG5</td>
</tr>
<tr>
<td>Polymerase Proofreading Associated Polyposis</td>
<td>Adenomatous</td>
<td>POLE and POLD1</td>
</tr>
<tr>
<td>Serrated Polyposis Syndrome</td>
<td>Serrated</td>
<td>None known</td>
</tr>
</tbody>
</table>

### Polyposis Syndromes

#### Tumor Phenotype

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Tumor Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP</td>
<td>Colon, duodenal, thyroid, brain cancers; hepatoblastoma, desmoids, osteomas, lipomas, fibromas, CHRPE</td>
</tr>
<tr>
<td>MAP</td>
<td>As above</td>
</tr>
<tr>
<td>PPAP</td>
<td>Colon, duodenal, endometrial and brain</td>
</tr>
<tr>
<td>PJS</td>
<td>Breast, pancreas, colon, small bowel, lung cancers; gonadal tumors, mucocutaneous pigmentation</td>
</tr>
<tr>
<td>JPS</td>
<td>Colon, Gastric and SB cancers, Hereditary Hemorrhagic Telangiectasia (SMAD4)</td>
</tr>
<tr>
<td>CS</td>
<td>Breast, thyroid, uterine, renal cell, colon cancers; macrocephaly, skin lesions, glycogen acanthosis- esophagus</td>
</tr>
<tr>
<td>SPS</td>
<td>Colon polyposis and colon cancer</td>
</tr>
</tbody>
</table>
Pathways to CRC

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
Adenoma Burden

MAP

AFAP

FAP

0 adenomas 100 adenomas 1000 adenomas

Colorectal Phenotype and Genotype

Gastric features of FAP/MAP

- Fundic gland polyposis
  - Prevalence: 88%
  - Histology
    - LGD: 38%
    - HGD: 3%

- Gastric adenomas
  - Prevalence: 10%
  - Usually antrum

- Gastric Cancer: Increasing

Duodenal features of FAP

- Duodenal adenomas
  - Prevalence: 100%
- Adenomatous papilla\(^1\)
  - 54\% if papilla appears normal
  - 89\% if papilla appears abnormal
  - TIP: EGD with papilla bx to help establish diagnosis
- Periampullary/Duodenal cancer
  - Risk based upon duodenal polyposis stage

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

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

Table adapted from: Spigelman AD. Lancet 1989;2: 783

<table>
<thead>
<tr>
<th>Stage</th>
<th>Points</th>
<th>Cancer Risk</th>
<th>EGD Interval*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0%</td>
<td>4 yrs</td>
</tr>
<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</td>
</tr>
</tbody>
</table>

*Syngal S, Am J Gastroenterol 2015; 110:223

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%)
### 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>18-20/25-30</td>
<td>1-2</td>
</tr>
<tr>
<td>Surgical Consult</td>
<td></td>
<td></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>20-25</td>
<td>Based on stage 6 mos -4 yrs</td>
</tr>
</tbody>
</table>

NCCN guidelines Genetic/Familial High Risk Assessment Colorectal. version 1.2015

### Indications for Genetic Testing in Adenomatous Polyposis

- Individuals with >10 cumulative adenomas
- Family history polyposis syndromes
- History of adenomas and FAP-type extracolonic manifestations
  - duodenal/ampullary adenomas
  - desmoid tumors
  - papillary thyroid cancer
  - congenital hypertrophy of the retinal pigment epithelium
  - epidermal cysts, osteomas
- Testing should include APC and MUTYH mutation analysis.

Serrated Polyposis Syndrome (SPS)

- WHO criteria:
  1. >5 SP above sigmoid, >2 are >10 mm
  2. >1 SP above sigmoid and FDR with SPS
  3. >20 SP distributed throughout the colon

- Age at Diagnosis: 56 yrs

- Prevalence CRC at diagnosis: 28%
  - Metachronous CRC: 1.5% -6.5%\(^2\) within 5 years

- No known extracolonic cancers

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Lack of Recognition of SPS

- 529 patients referred for resection of polyp \(\geq\) 2 cm
- 20 (4%) met WHO criteria for SPS
  - 9 met criteria on index exam. 11 on FU exams
- 40% unrecognized by expert endoscopist

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<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>Spain</th>
<th>Netherlands</th>
<th>Poland</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Pts</td>
<td>205,949</td>
<td>6,091</td>
<td>1,426</td>
<td>12,361</td>
</tr>
</tbody>
</table>

Detection Rates on Colonoscopy

- Baseline: 0.03% Spain, 0.5% Netherlands, 0.1% Poland
- Follow up: ND Spain, 0.3% Netherlands, ND Poland

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1 Snover, et al. WHO Classification of tumours of the digestive system. Berlin: Springer-Verlag; 2010
CRC in SPS

- 434 SPS patients in Netherlands, UK
- 29% had CRC
  - 52% before SPS diagnosis
  - 47% at SPS diagnosis
  - 1.4% during surveillance of SPS
- Median follow-up 3.2 years; colonoscopy interval 1.2 years
- Risk Factors for CRC
  - SSPs with dysplasia, presence of advanced adenomas
  - Combined WHO criteria 1 and 3

<table>
<thead>
<tr>
<th>CRC Features</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecum/Ascending</td>
<td>31.5%</td>
</tr>
<tr>
<td>Transverse</td>
<td>17%</td>
</tr>
<tr>
<td>Descending</td>
<td>4.2%</td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td>48%</td>
</tr>
</tbody>
</table>


SPS Surveillance

Colonoscopy Recommendations

- Affected Individuals: Every 1-3 years<sup>1-3</sup>
  - Remove polyps ≥5 mm
- First Degree Relatives<sup>3</sup>: Every 5 years
  - Begin at the earlier of the following:
    - 10 years < age of relative with SPS cancer
    - Age 40
    - At age of onset of SPS in family

<sup>1</sup> Syngal S, Am J Gastro 2015; 110:223; <sup>2</sup>Lieberman D, Gastro 2012;143:844; <sup>3</sup>NCCN.org V1 2016
Indications for Genetic Testing in SPS

- No genetic cause identified
- Genetic testing not currently recommended
- Testing for MUTYH mutations may be considered for SPS patients with concurrent adenomas and/or a family history of adenomas

Traditional Genetic Testing

• Utilizes Sanger sequencing and large rearrangement analysis
• Testing often limited to single gene or 1-2 high-risk, well known syndromes
• Variant of uncertain significance rate is low
• Results take 2-3 weeks

Next Generation Sequencing

• Whole genome or many genes analyzed at once
• Testing relatively inexpensive
• Used for panel genetic testing
• Variants of uncertain significance common
Commercial Gene Cancer Panel

Genes and Associated Cancer Risks

- BRCA1, BRCA2
- MLH1, MSH2, MSH6, PMS2, EPCAM
- STK11
- APC, BMPRIA, SMAD4
- MUTYH
- CDKN2A, CDK4
- TP53
- PTEN
- CDH1
- PALB2, ATM
- CHEK2
- NBN
- BARD1
- BRIPI, RAD51C
- RAD51D

Approach to Genetic Evaluation for Hereditary CRC Syndromes

- Genetic counseling of patient and family
  - Education, informed consent for testing, costs, disclosure
- Test affected family member first

<table>
<thead>
<tr>
<th>Mutation detected</th>
<th>Mutation not detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test “at risk” relatives</td>
<td>No test available for relatives</td>
</tr>
<tr>
<td>- Positive: Patient affected</td>
<td>- Follow patient and relatives according to phenotype</td>
</tr>
<tr>
<td>- Perform high risk screening</td>
<td></td>
</tr>
<tr>
<td>- Negative: Patient unaffected</td>
<td>- Perform average risk screening</td>
</tr>
</tbody>
</table>