Hereditary Colorectal Cancer Syndromes

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Living Beyond Cancer A-Z
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Hereditary CRC Syndromes

- Objectives are to discuss the:
  - Most common Hereditary CRC syndromes
  - Suspicion and diagnostic approach for Hereditary CRC syndromes
  - Indications and genetic tests available
Colorectal Cancer

Family History Red Flags

- Early age of diagnosis (<50 years for CRC)
- More than one primary cancer
- Multiple affected relatives
- Clear pattern of inheritance
- Rare cancer or unusual cancer
  - Male breast Ca
- Bilateral cancers in paired organs
- Non-cancerous features
Syndromes Associated with Polyps

Colonic Polyps

Hamartomatous Polyps
- Juvenile Polyposis Syndrome
- Peutz-Jeghers Syndrome
- Cowden Syndrome
- Hyperplastic
- Serrated

Adenomatous Polyps
- Few (<10)
  - Sporadic
  - Familial CRC
  - HNPCC-Lynch syndrome
- Moderate (<100)
  - Attenuated FAP
  - MYH-Associated Polyposis (MAP)
  - HNPCC/LS
  - POLE/POLD1
- Numerous (>100)
  - FAP
  - MYH (MAP)
# Hereditary CRC Syndromes

<table>
<thead>
<tr>
<th>Family History</th>
<th>Gene(s)</th>
<th>Age CRC dx (med)</th>
<th>Polyps</th>
<th>Extra-colonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch (HNPCC)</td>
<td>MMR, EPCAM</td>
<td>45</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>FAP/AAPC</td>
<td>APC</td>
<td>39/54</td>
<td>++++</td>
<td>Yes</td>
</tr>
<tr>
<td>MutYH</td>
<td>MYH</td>
<td>+/- 50’ s</td>
<td>+…+++</td>
<td>+/-</td>
</tr>
<tr>
<td>PPAP</td>
<td>POLD1 POLE</td>
<td>+/- 50’ s</td>
<td>+…+++</td>
<td>Yes POLD1 No</td>
</tr>
<tr>
<td>Hereditary Mixed Polyposis</td>
<td>GREM1</td>
<td>+/- 50’ s</td>
<td>HP/Ad/ SSA</td>
<td>?</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11/ LKB1</td>
<td>+/- 40</td>
<td>Hamartomas</td>
<td>Yes</td>
</tr>
<tr>
<td>Juvenile Polyposis</td>
<td>SMAD-4 BMPR1-A</td>
<td>68% by age 60</td>
<td>++++ JP</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyperplastic Polyposis</td>
<td>+/-</td>
<td>Undefined</td>
<td>++++ HP</td>
<td>No</td>
</tr>
<tr>
<td>Cowdens</td>
<td>PTEN</td>
<td></td>
<td>+++</td>
<td>Yes</td>
</tr>
<tr>
<td>NTHL1</td>
<td>NTHL1</td>
<td></td>
<td>+…+++</td>
<td>Yes</td>
</tr>
</tbody>
</table>
# Familial Adenomatous Polyposis

**Natural History**

<table>
<thead>
<tr>
<th>Event</th>
<th>Mean age</th>
<th>Adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>33 yrs.</td>
<td>15% at age 10</td>
</tr>
<tr>
<td>Adenoma dx</td>
<td>36 yrs.</td>
<td>50% at age 16</td>
</tr>
<tr>
<td>CR Cancer dx</td>
<td>39 yrs.</td>
<td>75% at age 20</td>
</tr>
<tr>
<td>Death due to CRC</td>
<td>42 yrs.</td>
<td>90% at age 30</td>
</tr>
</tbody>
</table>

- 1:7,500-8,000 live births
- ~25% no family history
- Extracolonic manifestations

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Bussey HJR. Familial Polyposis Coli 1975

St. Marks
Attenuated Adenomatous Polyposis Coli
# Extracolonic Manifestations FAP

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Reported Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundic gland polyps</td>
<td>12-85%</td>
</tr>
<tr>
<td>Gastric Ca</td>
<td>0.6%</td>
</tr>
<tr>
<td>Duodenal adenomas</td>
<td>50-90%</td>
</tr>
<tr>
<td>Duodenal cancer</td>
<td>~ 5%</td>
</tr>
<tr>
<td>Small bowel adenomas</td>
<td></td>
</tr>
<tr>
<td>Adrenal adenomas</td>
<td>7-13%</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>~ 1%</td>
</tr>
<tr>
<td>Brain tumors</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

## Extracolonic Manifestations FAP

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Reported Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Hypertrophy of the Retinal Pigmented Epithelium (CHRPE)</td>
<td>70-80%</td>
</tr>
<tr>
<td>Osteomas</td>
<td>50-90%</td>
</tr>
<tr>
<td>Dental Anomalies</td>
<td>11-27%</td>
</tr>
<tr>
<td>Epidermoid cysts</td>
<td>50%</td>
</tr>
<tr>
<td>Desmoid tumors</td>
<td>10-15%</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>2-3%</td>
</tr>
</tbody>
</table>

Familial Adenomatous Polyposis
Upper GI Manifestations
Familial Adenomatous Polyposis

CHRPE
Familial Adenomatous Polyposis
Osteomas and Dental Anomalies
Familial Adenomatous Polyposis
Epidermoid Cysts
# Eras in Hereditary Polyposis

<table>
<thead>
<tr>
<th>Era</th>
<th>Approach</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1928-1980’s</td>
<td>Prevention of death from cancer</td>
<td>Colectomy</td>
</tr>
<tr>
<td>1960s-2014</td>
<td>Prevention of cancer itself</td>
<td>Prophylactic colectomy</td>
</tr>
<tr>
<td>1980’s-2014</td>
<td>Prevention of cancer but maintaining QOL</td>
<td>IPAA</td>
</tr>
<tr>
<td>1990s-2014</td>
<td>Making colectomy less scary</td>
<td>Laparoscopic surgery</td>
</tr>
<tr>
<td>1983-2014</td>
<td>Prevention of surgery altogether</td>
<td>Chemoprevention</td>
</tr>
</tbody>
</table>
Familial Adenomatous Polyposis
Prophylactic Surgery

- Total abdominal colectomy and ileorectal anastomosis (TAC-IRA)
- Restorative proctocolectomy (IPAA)
- Total proctocolectomy

Chemoprevention
Familial Adenomatous Polyposis
Chemoprevention
Familial Adenomatous Polyposis

- Sulindac 150 mg BID
- Celebrex 400 mg BID
- Rofecoxib 25 mg QD
- Curcumin 480 mg y quercetina 20 mg TID
- Sulindac 150 mg BID + DFMO (Eflornithine) 75 mg QD (Duodenum)

- Sulindac does not prevent development of polyps in patients with pathogenic variants who have not as of yet developed adenomas

Familial Adenomatous Polyposis
Chemoprevention...Current Trials

- Phase III Eflornithine (DFMO) and Sulindac
  - DFMO + Sulindac
  - DFMO + Placebo
  - Sulindac + Placebo

- Primary outcome
  - Delaying to 1st occurrence of any FAP related event
  - 150 patients randomized
  - 13 centers in US and Europe
MutYH Associated Polyposis:
Clinical Aspects

- Autosomal recessive
- 3-100 adenomas at times more
- ~ 60% MAP polyposis present with CRC
  - mean age 48 (21-70 yrs.)
- Lifetime risk of extraintestinal malignancies 38%
  - Duodenal polyposis (17%) and Ca ~ 4%
  - Ovarian
  - Bladder
  - Skin (SCC, basal cell, melanoma)

HEREDITY WITH REFERENCE TO CARCINOMA
AS SHOWN BY THE STUDY OF THE CASES EXAMINED IN THE PATHOLOGICAL
LABORATORY OF THE UNIVERSITY OF MICHIGAN,
1895-1913 *

ALDRED SCOTT WARTHIN, M.D.
ANN ARBOR, MICH.

Arch Intern Med 1913; 12:546-555
Lynch Syndrome/HNPCC

- Dominant inheritance
- Up to 70-80% Penetrance
- Early onset < 50 y
- Right-sided predominance

- Synchronous and metachronous
- Better prognosis, 80-85% MSI-H
- Pathogical features
- Extracolonic manifestations

Adapted from A. Alonso
Cancer Risk in Lynch Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Colorectal</th>
<th>Endometrial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>MLH1</td>
<td>53-68.7%</td>
<td>33-52%</td>
</tr>
<tr>
<td>MSH2</td>
<td>22%</td>
<td>10%</td>
</tr>
<tr>
<td>MSH6</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>PMS2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cancer Risk in Lynch Syndrome
Tumor Screening

- ~15% de CRC have microsatellite instability (MSI-H)
  - ~1/3 Lynch Syndrome y 2/3 sporadic
IHC for MMR Protein Expression

- Absent of MLH1 expression
  - Sporadic …MLH1 promoter methylation/BRAF mutation
  - Germline mutation MLH1

- Absent of MSH2 expression
  - Germline mutation MSH2
  - 3’ TACSTD1 (EPCAM) mutation leading to MSH2 methylation
  - Virtually diagnostic of HNPCC

- Absent MSH6, PMS2 expression
  - PMS2 may be PMS2 mutation or MLH1* mutation
Multigene Panel in Young CRC Patients

1/2013-6/2016
Ohio Initiative
450 Pts CCR \leq 50
NGS 25 genes
72/450 pts (16%) with 75 pathogenic variants
145/450 pts (32%) VUS

Chemoprevention

Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome


Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial


* Aspirin 600 mg/day for a mean of 25 mos. reduced cancer incidence rate after 55.7 mos. in carriers

Peutz-Jeghers

- Hamartomas GI tract
- LKB1 (STK11) mutations in at least 50%
- Pigmentation
  - Perioral 95%
  - Buccal mucosa, hands, feet, genital region
- Lifetime risk Ca as high as 48%
  - GI, breast, pancreas, biliary tract, gallbladder
  - 2-13% risk small bowel, CRC
  - 5-12% risk ovarian (sex cord) tumors and Sertoli Cell tumors
Juvenile Polyposis Syndrome

- **Definition***
  - ≥ 3 juvenile polyps in colon
  - JP throughout GI tract
  - Any number of JP polyps in pt with a family hx of JPS

- **SMAD4, BMPR1-A**
- Associated congenital defects
  - Cardiac, GU, skeletal, mental retardation, macrocephaly, etc

- **CRC risk**
  - 68% by age 60**
- Gastric and duodenal Ca risk

Hereditary Colorectal Cancer

- In spite of all the advances, the management in Hereditary Colorectal Cancer Syndromes must be individualized.

- The most important aspect of the management is the clinical history, including a detailed family history, and the physical examination.