Heredity and Colorectal Cancer: Genetic Testing and Cancer Screening

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Colorectal Cancer

- Sporadic (~80%)
- Familial (~15%)
- Hereditary CRC syndromes (~5%)

Adapted from Burt RW et al. Prevention and Early Detection of CRC, 1996
Risk of Colorectal Cancer

- General population: 6%
- Personal history of colorectal neoplasia: 15%–20%
- Inflammatory bowel disease: 15%–40%
- Lynch Syndrome: 70%–80%
- FAP: >95%

Lifetime risk (%)
Hereditary Colorectal Cancer Syndromes

Identifying these conditions helps determine:

- Who is at risk?
- Who may benefit from genetic evaluation?
Hereditary Colorectal Cancer Syndromes

Categorized in two types:

- CRC associated with multiple polyps: Familial Adenomatous Polyposis (FAP)
- CRC associated with few (if any polyps): Lynch Syndrome

Both involve inheritance of gene mutations that are detected in the blood
Key Features to Consider

• Are there multiple relatives with CRC or other cancers?
• Were relatives diagnosed with CRC at a young age?
• How old were you when you were diagnosed with CRC?
• Did you have CRC more than once?
• Have you had multiple cancers?
Family G

- In 1840s, a German man settled in MI
- Died in 1856 at age 60; had 10 children 7 of which died of cancer
- 3rd generation numbered 70; 33 cancer
- 4th generation came to attention of Dr. Aldred Scott Warthin:
  - 1913: "in certain families there is an inherited susceptibility to cancer"
Cancer Family Syndrome
Lynch Syndrome Features

- Striking family history affecting multiple generations
- Early age at CRC diagnosis (mean 45 years)
- Multiple cancers
- Cancers other than the colon:
  - Endometrium
  - Ovary
  - Urinary tract
  - Stomach
  - small bowel
  - sebaceous carcinomas of skin
Lynch Syndrome

- Most common hereditary CRC syndrome
  - 3-4% of all CRC
  - 1 in 35 patients with CRC has Lynch Syndrome
- Lifetime risk of CRC = 70-80%
  - Risk is markedly lower if colonoscopies begin early
- Defective DNA Mismatch Repair
  - *Mutations in MLH1, MSH2, MSH6, PMS2*
Lynch Syndrome Results From Failure of Mismatch Repair (MMR) Genes

Base pair mismatch

Normal DNA repair

Defective DNA repair (MMR+)

AGCTG

TCGAC

TCGAC

AGCTG

AGCTG

TCGAC

AGCTG

AGATG
Identification of Lynch Syndrome

Based strongly on:

• Personal and family history of cancer
• Tumor Testing
Need for Specialized Screening

1- CRC occurs at younger ages in Lynch Syndrome: start screening at 20-25 years

2- A larger proportion of CRC (60%–70%) occur in the right colon: colonoscopy is test of choice

3- Patients with Lynch Syndrome are at increased risk of other cancers: consideration additional screening

4- Rapid growth of polyps and tumors: repeat screening every 1-2 years or consider surgical resection
Surgical Management of Colorectal Cancer Risk in Lynch Syndrome

- Consider compliance with screening, efficacy of screening tests, need for surgical resection
- Subtotal colectomy should be considered if patient not candidate for optimal surveillance
- Subtotal colectomy option given risk of second CRC (20-30% in 10 years)
Surgical Management of Endometrial Cancer Risk in Lynch Syndrome

- Most common extracolonic cancer
- Up to 60% lifetime risk in women
- Prophylactic removal of uterus and ovaries recommended when childbearing is completed
## Associated Lynch Syndrome Cancers

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Surveillance Recommendation*</th>
<th>Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Colonoscopy every 1-2 years</td>
<td>20-25 years</td>
</tr>
<tr>
<td>Endometrium/Ovaries</td>
<td>Transvaginal ultrasound/Endometrial biopsy annually; consider risk reducing TAH/BSO when childbearing completed</td>
<td>30 years</td>
</tr>
<tr>
<td>Stomach</td>
<td>EGD every 2-3 years</td>
<td>30-35 years</td>
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<tr>
<td>Urinary tract</td>
<td>Urinalysis and cytology annually</td>
<td>30-35 years</td>
</tr>
<tr>
<td>Brain</td>
<td>No evidence to support screening</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td></td>
<td></td>
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<tr>
<td>Pancreas</td>
<td></td>
<td></td>
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<tr>
<td>Biliary Tract</td>
<td></td>
<td></td>
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<tr>
<td>CNS</td>
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Familial Adenomatous Polyposis (FAP)

- Classic FAP easily recognizable
- Majority of classic cases due to germline APC mutations
- Risk of cancer is >90% without surgery
- Risk of extracolonic tumors: upper GI, desmoid, osteoma, thyroid
Familial Adenomatous Polyposis (FAP)

- APC gene mutation carriers have >90% risk of developing polyps
- The age at onset is variable:
  - by age 10 years: 15% of carriers manifest adenomas;
  - by age 20 years: 75%; and by
  - By age 30 years, 90% will have presented with FAP.

- Surveillance for carriers and at-risk persons
  - Annual sigmoidoscopy beginning 10-12 years
  - Goal: early detection of polyps, leading to preventive colectomy
Prophylactic Colectomy for FAP

- Timing of colectomy:
  - Individualized
  - Depends on:
    - Polyp burden: number, size, advanced histology
    - Family history of CRC onset
  - NCCN recommendation
    - Patients be managed by physicians or centers with FAP expertise
    - Management be individualized
# FAP surveillance

<table>
<thead>
<tr>
<th>Surveillance Recommendation*</th>
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<tbody>
<tr>
<td>Colon</td>
<td></td>
</tr>
<tr>
<td>Flexible sigmoidoscopy; Annual colonoscopy when polyps detected</td>
<td>10-12 years</td>
</tr>
<tr>
<td>Prophylactic colectomy when increased polyp burden</td>
<td></td>
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<tr>
<td>Duodenum/Ampulla/Stomach</td>
<td></td>
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<tr>
<td>EGD 1-3 years</td>
<td>20-25 years</td>
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<tr>
<td>Thyroid</td>
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<tr>
<td>Annual thyroid palpation +/- ultrasonography</td>
<td>20 years</td>
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<tr>
<td>Brain</td>
<td></td>
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<tr>
<td>No evidence to support screening</td>
<td></td>
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<tr>
<td>Desmoids</td>
<td></td>
</tr>
<tr>
<td>Annual abdominal palpation; If family history consider MRI or CT 1-3 years post colectomy and every 5-10 years thereafter</td>
<td>Variable</td>
</tr>
<tr>
<td>Small bowel polyps/cancer</td>
<td></td>
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<tr>
<td>Consider small bowel evaluation (SBCE, CT/MR enterography) if duodenal polyposis is advanced</td>
<td>Variable</td>
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<tr>
<td>Hepatoblastoma</td>
<td></td>
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<tr>
<td>Liver palpation, abdominal ultrasonography, AFP every 6 months</td>
<td>First 5 years of life</td>
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*Other than colon cancer, screening recommendations are expert opinion rather than evidence-based.
Genetic Evaluation

• Requires a team of
  – Physicians: gastroenterologists and surgeons, gynecologists
  – Pathologists
  – Genetic counselors
• Obtain a complete family tree of three-generations
• Patient Education
Rationale for Genetic Testing for Hereditary Cancer Syndromes

• Determine cancer risk

• Make a plan for individualized cancer screening (i.e. endoscopy)

• Test at-risk individuals and family members
  – Children have a 50% chance of inheriting a gene mutation from a parent known to be a carrier
Red Flags for a Hereditary CRC Syndrome

- Cancer in 2 or more close relatives
- Early age at diagnosis (CRC <50* years)
- Multiple primary tumors
- Constellation of tumors consistent with specific cancer syndrome (eg, colon and uterine)
- Evidence of more than one generation affected
Practicing in the Genetics Era

- Family history is the best screening tool for inherited diseases
- Systematize family history assessment
- Refer for genetic evaluation and counseling
- Address surveillance of multiple cancers
- Incorporate recommendations for family members
- Rapid developments in cancer genetics with new discoveries
Thank you.

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