Welcome to Master Class for Oncologists

Miami, FL
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Session 3:
9:15 AM - 10:00 AM

Diagnosis, Genetics, and Management of Hereditary Gastrointestinal Cancers

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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Dr Sapna Syngal has no relationships to disclose.

Off Label/Investigational Discussion

Hereditary Syndromes in GI Cancer

- Hereditary colorectal cancer
  - Familial adenomatous polyposis (FAP)
  - Hereditary nonpolyposis colorectal cancer (HNPCC)
  - Hamartomatous polyposis syndromes
- Hereditary pancreatic cancer
- Hereditary gastric cancer
- GI cancers associated with other hereditary syndromes

How is Management of Hereditary Cancers Different than Sporadic Cancers?

- Screening and surveillance post-treatment of primary cancer
- Surgical management of cancer
- Surveillance for associated cancers
- Screening and surveillance of family members
- Reproductive counseling

How Can Genetic Evaluation Help?

- Clinically determine if a hereditary cancer syndrome exists
  - Detailed pedigree
  - Confirmation of cancer diagnoses in probands and family members
- Genetic testing and interpretation of results
- Coordination of post-cancer care
- Counseling of family members
Causes of Hereditary Susceptibility to CRC

- Sporadic (65%–85%)
- Familial (10%–20%)
- Hereditary nonpolyposis colorectal cancer (HNPCC) (5%)
- Familial adenomatous polyposis (FAP) (1%)
- Rare CRC syndromes (< 0.1%)

Risk of Colorectal Cancer (CRC)

- General population: 5%
- Personal history of colorectal neoplasia: 15%–20%
- Hamartomatous polyposis syndromes: 15%–40%
- HNPCC mutation: 70%–80%
- FAP: > 95%

Audience Response Question

Case A
A 45-year-old presents with rectal bleeding. Colonoscopy reveals a sigmoid cancer and numerous (approximately 40-50) polyps. There is no family history of polyps or cancer. What is the least likely diagnosis?

1. Familial adenomatous polyposis
2. Attenuated familial adenomatous polyposis
3. MYH associated polyposis
4. Lynch syndrome

Clinical Features of FAP

- Estimated penetrance for adenomas and cancer > 90%
- Risk of extracolonic tumors (upper GI, desmoid, osteoma, thyroid, brain, other)
- Recognition of phenotype is easy in an affected individual
- Majority of classic cases due to germline APC mutations

MYH Gene Mutations as Another Cause of Hereditary Colon Cancer Associated with Multiple Polyps

- Involved in base excision repair
- Dysfunction leads to increase in rate of G to T transversions following DNA oxidative damage
- Mutational hotspots:
  - White, Northern Europeans: Y165C
  - (66/76 mutant alleles = 87%): G382D
  - Indian/Pakistani: E466X

MYH: A New Paradigm in Inherited Colon Cancer Risk

- Autosomal dominant (FAP, HNPCC)
- Autosomal recessive (MYH)
Variations of Classic Phenotypes are Common

- De novo germline mutations occur in ~30% of FAP cases
- Attenuated forms of polyposis occur – suspect if > 10 adenomas

Approach to the Patient with CRC and Multiple Polyps

- Detailed family history
- Age of onset (REFER IF AGE < 50)
- Quantify number of polyps (REFER IF > 10)
- Upper endoscopy to rule out gastric, duodenal, ampullary adenomas (REFER IF PRESENT)
- Define size and location of polyps (stomach, small intestine vs colon)
- Confirm histology
- Genetic evaluation based on results

FAP Management

- Appropriately-timed colectomy
- Surveillance of rectal segment every 6-12 months if subtotal colectomy
- Upper tract surveillance 1-3 years
  - Duodenoscope in addition to regular EGD
  - Biopsy even if endoscopically normal
- Chemoprevention largely used for rectal remnants and upper tract polyps
- No proven role for primary chemoprevention

FAP Family With APC Mutation

Prenatal Genetic Testing in Patients With FAP

- Prenatal testing is available for APC mutation carriers:
  - Amniocentesis
  - Chorionic villous sampling (CVS)
  - Preimplantation genetic diagnosis (PGD)
- Can reveal whether an embryo or fetus is affected with FAP

Prenatal Counseling is Part of Care of APC Mutation Carriers
Case A
A 45-year-old presents with rectal bleeding. Colonoscopy reveals a sigmoid cancer and numerous (approximately 40-50) polyps. There is no family history of polyps or cancer.

What is the least likely diagnosis?
1. Familial adenomatous polyposis
2. Attenuated familial adenomatous polyposis
3. MYH associated polyposis
4. Lynch syndrome

Case B
A 35-year-old presents with a cecal carcinoma and no other polyps. Family history is notable for mother with endometrial cancer at age 45 and a brother with colon cancer at age 42. Which of the following statements is false?
1. The tumor is likely to be microsatellite unstable.
2. Immunohistochemical analysis of the tumor should be done to look for loss of expression of the APC gene.
3. Subtotal colectomy should be considered.
4. He may carry a germline mutation in a mismatch repair gene.

Clinical Features of HNPCC (Lynch Syndrome)
- Early but variable age at CRC diagnosis (~45 years)
- Multiple primary cancers
- Tumor site in proximal colon predominates
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors

Mismatch Repair Failure Leads to Microsatellite Instability (MSI)

HNPCC Results From Failure of Mismatch Repair (MMR) Genes

Contribution of Gene Mutations to HNPCC Families
Surveillance Recommendations for HNPCC Patients

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Intervention</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Colorectal cancer</td>
<td>Colonoscopy</td>
<td>Begin at age 20–25, repeat every 1–2 years</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>Transvaginal ultrasound</td>
<td>Annually, starting at age 25–35</td>
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<td></td>
<td>Endometrial aspirate</td>
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Cancer Genetics Study Consortium Task Force Recommendations

Prophylactic Surgery Options for HNPCC-Associated Mutation Carriers

- Colon cancer options include subtotal colectomy vs total colectomy (esp. important at time of CRC diagnosis!)
- Uterine and ovarian cancer options include hysterectomy and oophorectomy
- Individual patient decisions dependent on compliance with screening, efficacy of screening tests, need for surgical resection

How Can Genetic Testing Benefit My Family?

- No identified mutation in family
  - Colon Ca, 52
  - Colon Ca, 47
- Microsatellite stable
  - No mutation found
- Inconclusive

- Family with known mutation
  - Colon Ca, 52
  - Colon Ca, 47
  - Endometrial Ca, 47
  - MSH2 +
- Inconclusive
- Informative

Revised Bethesda Guidelines

- Colorectal cancer under age 50
- Synchronous or metachronous colorectal or HNPCC-associated tumor
- CRC with 1 or more FDR* with CRC or other HNPCC tumor, with 1 diagnosed before age 50
- CRC with 2 or more relatives with CRC or other HNPCC tumor, regardless of age at diagnosis

The PREMM1,2 Model (Prediction of MSH2 and MLH1 Mutations)

- 1941 consecutive, unrelated probands who submitted blood samples for full gene sequencing of MSH2 and MLH1 to Myriad Genetics Laboratories, Inc. beginning November 2000.
- Samples from 50 states and 4 continents
- Samples submitted by:
  - Oncologists (36%)
  - Genetic counselors (28%)
  - Gastroenterologists (17%)
  - Surgeons (7%)
  - Gynecologists (6%)
  - Internists (4%)

1. Proband history
   - Presence of colon cancer, other HNPCC cancer and/or adenomas
   - Age of onset
2. Family history
   - Presence of colon or other HNPCC cancer
   - Youngest age at diagnosis

www.dfci.org/premm
Google “premm”
Isolated Early-Onset Colorectal Cancer

Amsterdam Criteria II

Amsterdam Criteria II (Earlier Age of Onset)

Lynch Syndrome – Who Should be Referred?

Audience Response Question

Case B
A 35-year-old presents with a cecal carcinoma and no other polyps. Family history is notable for mother with endometrial cancer at age 45 and a brother with colon cancer at age 42. Which of the following statements is false?

1. The tumor is likely to be microsatellite unstable.
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3. Subtotal colectomy should be considered.
4. He may carry a germline mutation in a mismatch repair gene.
Hereditary Pancreatic Cancer

- Hereditary Breast/Ovarian Cancer
  - BRCA1/2
- Familial Atypical Multiple Mole Melanoma: FAMMM
  - p16
- HNPCC/Lynch Syndrome
  - Mismatch Repair (MLH1, MSH2, MSH6)
- Hereditary pancreatitis
  - Cationic trypsinogen gene

Pancreatic Cancer Risk in other Genetic Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene(s)</th>
<th>Lifetime Risk, % (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Peutz-Jeghers Syndrome (PJS)</td>
<td>STK11</td>
<td>38 (N/A)</td>
</tr>
<tr>
<td>Familial Atypical Mole Melanoma (FAMMM)</td>
<td>CDKN2A</td>
<td>17 (3, 30)</td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer (HBOC)</td>
<td>BRCA1</td>
<td>1.2 (0.8, 1.6)</td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer (HBOC)</td>
<td>BRCA2</td>
<td>2.1 (1.2, 3.0)</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>MLH1, MSH2, MSH6</td>
<td>3.88 (1.52, 6.63)*</td>
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*adjusted for ascertainment

Management Options for High-Risk Individuals

- Screening with endoscopic ultrasound
- Screening with imaging (dedicated pancreatic protocol CT or MRI/MRCP)
- Aggressive evaluation and management of precancerous lesions (ie, IPMNs)
- In rare instances, prophylactic pancreatectomy

Hereditary Gastric Cancer

- Hereditary Diffuse Gastric Cancer
  - Lifetime risk of gastric cancer > 60%
  - Screening is ineffective and prophylactic total gastrectomy is recommended for mutation carriers
  - Association with lobular breast cancer
  - CDH-1/E-cadherin gene mutations found in some families (autosomal dominant)

Hereditary Pancreatic Cancer: Who should be Referred?

- BRCA1/2 mutation carriers with a family history of pancreatic cancer
- More than two pancreatic cancers on the same side of the family
- Association of pancreatic with colon cancer, melanoma, breast cancer, or other GI tumors if one is at age < 50
<table>
<thead>
<tr>
<th><strong>Hereditary Gastric cancer: Who Should be Referred?</strong></th>
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<tbody>
<tr>
<td>• Isolated diffuse gastric cancer at age &lt; 45</td>
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<tr>
<td>• More than one diffuse gastric cancer on the same side of the family at any age</td>
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<tr>
<td>• Association of gastric cancer and lobular breast cancer</td>
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<th><strong>Family History Assessment by Oncologists</strong></th>
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<tr>
<td>• 433 patients at first visit for treatment of CRC</td>
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<td>• Physician documentation and patient self-reports compared</td>
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<tr>
<td>• Family history accurately obtained in 64% of patients</td>
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<tr>
<td>• Total numbers of family cancers inversely related to accuracy (OR 0.5, P &lt; 0.001)</td>
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<tr>
<th><strong>Family History Assessment in Clinical Practice</strong></th>
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<tr>
<td>• Often not comprehensive</td>
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<tr>
<td>• Frequently limited to first-degree relatives because of time constraints or unreliable information</td>
</tr>
<tr>
<td>• Restricted to include only certain cancer types</td>
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<tr>
<td>• eg, “Any history of colon cancer in your family?”</td>
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<tr>
<td>• Relationship between different cancers (eg, colon and endometrial CA) may be missed</td>
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<tr>
<th><strong>When to Suspect a Hereditary Cancer Syndrome</strong></th>
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<tr>
<td>• Cancer in two or more close relatives (on same side of family)</td>
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<tr>
<td>• Early age at diagnosis (CRC &lt; 50, adenoma &lt; 45)</td>
</tr>
<tr>
<td>• Multiple primary tumors</td>
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<tr>
<td>• Multiple (&gt; 10) adenomas</td>
</tr>
<tr>
<td>• Constellation of tumors consistent with specific cancer syndrome (eg, colon and uterine or ovarian, pancreatic and breast, gastric, and lobular breast)</td>
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<th><strong>What Is Genetic Discrimination?</strong></th>
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<tr>
<td>• Social or economic discrimination based on one’s hereditary predisposition to disease</td>
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<tr>
<td>- Denial of access to or increased cost of insurance</td>
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<tr>
<td>- Loss of employment, educational, or other opportunities</td>
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<tr>
<td>• No data to support that genetic discrimination issues play a major role related to cancer predisposition testing</td>
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<th><strong>GENETIC MALPRACTICE</strong></th>
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<tr>
<td>• Failure to make diagnosis and use proper diagnostic tools</td>
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<tr>
<td>• Failure to recommend adequately aggressive cancer surveillance</td>
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<tr>
<td>• Failure to recommend surveillance or prophylactic surgery for associated cancers</td>
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<tr>
<td>• Failure of “duty to warn” family members</td>
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Cancer Screening in the Genetics Era

- Family history is still the best screening tool for inherited diseases
- Systematize family history assessment and evaluation
- Referral for genetic counseling when necessary
- Address surveillance of multiple cancers
- Incorporate (and document) recommendations for family members

Questions & Answers

?