Cancer Genetics Case Studies
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Outline
• Review the Red Flags of Hereditary Cancer Syndromes
• Highlight 2 Common Hereditary Cancer Syndrome Cases
• Present 1 Case that Highlights the Use of Molecular Diagnostics
• Introduce the ETSU Cancer Risk Evaluation Service

Red Flags of Hereditary Cancer Syndromes
• Cancer diagnosed at an unusually young age (e.g. breast/colon before age 50);
• Multiple close family members with either the same type of cancer or related cancers (e.g. breast/ovary or colon/endometrial);
• 2 or more primary cancers in the same person
Red Flags of Hereditary Cancer Syndromes, cont.

- Certain rare cancers or tumors (e.g. medullary thyroid ca, retinoblastoma, hepatoblastoma, male breast cancer)
- Other features associated with a hereditary cancer syndrome (e.g. multiple colon polyps)

Hereditary Breast Ovarian Cancer

Case #1

How Much Breast and Ovarian Cancer Is Hereditary?

- Breast Cancer: 15-20% Sporadic, 5-10% Family clusters, 5-10% Hereditary
- Ovarian Cancer: 5-10% Sporadic, 5-10% Hereditary
Causes of Hereditary Susceptibility to Breast Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Contribution to Hereditary Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>20%–40%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>10%–30%</td>
</tr>
<tr>
<td>Undiscovered genes</td>
<td>30%–70%</td>
</tr>
</tbody>
</table>

**BRCA1**
- Tumor suppressor gene on chromosome 17
- Autosomal dominant transmission
- Protein has role in genomic stability
- ~500 different mutations reported

**BRCA1-Associated Cancers:**
- Breast cancer 50%–85% (often early age at onset)
- Second primary breast cancer 40%–60%
- Ovarian cancer 15%–45%
- Possible increased risk of other cancers (e.g., prostate, colon)

**BRCA2**
- Tumor suppressor gene on chromosome 13
- Autosomal dominant transmission
- Protein has role in genomic stability
- ~300 different mutations reported
BRCA2-Associated Cancers: Lifetime Risk

- Breast cancer (50%–85%)
- Male breast cancer (6%)
- Ovarian cancer (10%–20%)
- Increased risk of prostate, laryngeal, and pancreatic cancers (magnitude unknown)

Other Genetic Conditions Associated With Increased Breast Cancer Risk

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li-Fraumeni</td>
<td>TP53</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
</tr>
<tr>
<td>Muir-Torre</td>
<td>MSH2, MLH1</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
</tr>
</tbody>
</table>

Features That Indicate Increased Likelihood of Having BRCA Mutations

- Multiple cases of early onset breast cancer
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer

Other Cancer Associated with BRCA1 or BRCA2 Mutations

- Absolute risk likely to be higher than 10%
  - Prostate cancer
- Absolute risk 10% or lower
  - Male breast cancer
  - Fallopian tube cancer
  - Pancreatic cancer
- Risk association unclear
  - Colon cancer
  - Gastric cancer
  - Melanoma
  - Other sites
BRCA1: Clinicopathological Findings in Mutation Carriers vs. Sporadic Cases

- Breast Cancers in Mutation Carriers
  - Medullary histology more common
  - Less likely to observe DCIS by itself or associated with invasive cancers
  - High rate of ER/PR/Her2 negativity
  - High nuclear grade
  - Basaloid cell type by microarray
  - erbB-2 positivity less common
  - p53 overexpression
- Ovarian Cancer in Mutation Carriers
  - Exclusively epithelial origin
  - Mostly high grade, serous histopathology
  - Mucinous histology rare

BRCA2: Clinicopathological Findings in Mutation Carriers vs. Sporadic Cases

- Breast cancers in mutation carriers
  - No typical phenotype emerging, unlike the features observed with BRCA1 mutation-associated tumors
  - ER and PR profiles are similar to those for sporadic cancers (most are ER positive)
- Ovarian cancers in mutation carriers
  - Exclusively epithelial origin
  - Mostly high grade, serous histopathology
  - Mucinous or borderline neoplasms uncommon

Case #2

Lynch Syndrome/HNPCC
Risk Factors for Colorectal Cancer (CRC)

- Aging
- Personal history of CRC or adenomas
- Dietary patterns
- Inflammatory bowel disease
- Family history of CRC
- Hereditary colon cancer syndromes


Risk of Colorectal Cancer (CRC)

<table>
<thead>
<tr>
<th>General population</th>
<th>Personal history of colorectal neoplasia</th>
<th>Inflammatory bowel disease</th>
<th>HNPCC mutation</th>
<th>FAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>6%</td>
<td>10%–20%</td>
<td>15%–40%</td>
<td>70%–80%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>


Causes of Hereditary Susceptibility to CRC

- Sporadic (65%–85%)
- Rare CRC syndromes (<1.0%)
- Hereditary nonpolyposis colorectal cancer (HNPCC) (2.3%)
- Familial adenomatous polyposis (FAP) (1%)
- Familial (10%–30%)

Modified with permission from the American Gastroenterological Association, Clinical Teaching Project: Colorectal Neoplasia II: Genetics and Prevention.
Consider hereditary colon cancer if...

- Cancer in 2 or more close relatives (on the same side of the family)
- Early age at diagnoses (CRC<50, adenoma<45)
- Multiple primary tumors
- Multiple (>10) adenomas
- Constellation of tumors consistent with specific cancer syndrome (e.g. colon, uterine, or ovarian)

Clinical Features of HNPCC

- Early but variable age at CRC diagnosis (~45 years)
- Few adenomas
- 70% lifetime risk
- Tumor site in proximal colon predominates
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors, brain

Genetic Features of HNPCC

- Autosomal dominant inheritance
- Penetrance ~80%
- Genes belong to DNA mismatch repair (MMR) family
- Genetic heterogeneity (MLH1, MSH2, MSH6, PMS1, PMS2)

Amsterdam Criteria I

- Three or more relatives with verified CRC in family
- At least two successive generations
- One CRC diagnosed by age 50
- FAP excluded
- Failure to meet these does not exclude HNPCC
Amsterdam Criteria II
- Three or more relatives with verified HNPCC associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis) in family
  - Any combination of histologies in three different relatives
  - One case a first-degree of the other two
- At least two successive generations affected
- One or more cancer cases by age 50
- FAP excluded
  - Failure to meet these criteria does not exclude HNPCC

Bethesda Criteria (pt is affected)
- Amsterdam criteria met
- Patient is younger than 50
- Pt has multiple HNPCC-associated tumors
- Pt has >1 FDR who had an HNPCC-related tumor at age <50
- Pt has > 2 FDR or SDR with HNPCC related tumors at any age
- The patient is < 60 and has CRC that has microscopic characteristics that are indicative of MSI

Lynch Syndrome Variants
- Turcot Syndrome
  - hereditary syndrome of multiple CRC and primary brain tumors
- Muir-Torre Syndrome
  - Typical features of HNPCC with sebaceous gland tumors and keratoacanthomas

Lynch Syndrome- Conclusions
- HNPCC is the most common cause of hereditary CRC
- MMR mutation carriers are at risk of extracolonic tumors
- Guidelines exist to help identify individuals appropriate for genetic testing
- Genetic analysis is medically necessary care
  - Colonoscopies reduce CRC incidence and mortality in carriers
  - Extracolonic screening and risk reducing options are available
Testing for Lynch Syndrome

- Tumor Analysis-
  - Screening tests which evaluate for characteristics of Lynch syndrome in the tumor
  - Proceed with tumor analysis if meet Bethesda or Amsterdam Criteria or patient is under 50 at diagnosis
  - MSI/IHC
- Germline genetic testing
  - Diagnostic test
  - Proceed with germline testing if tumor testing positive or if Amsterdam Criteria met
  - MLH1, MSH2, MSH6, PMS2

Mismatch Repair Failure Leads to Microsatellite Instability (MSI)

- Microsatellite instability leads to the addition of nucleotide repeats
- MSI on colon cancer tissue
  - 10-15% of sporadic tumors have MSI
  - 90% of HNPCC tumors have MSI at multiple loci

Immunohistochemistry (IHC)

- Method used to evaluate for the presence or absence of proteins in tumor tissue
- Lack of staining may indicate a MMR defect
- Helpful in determining strategy for germline testing
- (Tests will read: normal expression or e.g. MSH2 absent)

Case #3
Molecular Diagnostics

- Rapidly growing, dynamic area being integrated into many areas of medicine
- Familiarization with the basics of these methodologies is important to fully understand a test result
- Analysis and interpretation of some unique alterations can be challenging
- An open line of communication between clinicians and labs is beneficial for optimizing diagnostic capabilities

ETSU Cancer Risk Evaluation Service

What we offer:

- Patients complete a 3 generation FHQ and return it to C for evaluation, risk modeling, and pedigree construction:
  - BRCAPro, CRCAPRO, BOADICEA, Myriad, etc., PREMM1,2, MMRPro
- Patient/family presents for cancer genetic counseling (CGC) (2 or 3 part visit)
  1. 1 hour session- education
  2. Testing can be offered the day of testing or deferred to next visit;
  3. In-person disclosure session

Which patients may benefit from CGC?

- Individuals with a personal and/or family history suspicious of hereditary cancer susceptibility;
- Members of a family with a known syndrome
- Individuals with extreme cancer anxiety, even in the absence of heightened risk;
- Individuals considering GT;

Which patients may benefit from CGC? (continued)

- Individuals with questions about cancer risk in offspring or extended family;
- High-risk individuals including those with a known syndrome who have questions about treatment, prevention, and screening;
- Individuals who have undergone testing with a provider but want a more detailed discussion about results/interpretation.
Indications for CGC referral-
HBOC

- One or more of the following:
  - BRCA1/2 mutation identified in the family
  - Breast cancer <50 y/o
  - Ovarian ca at any age in patient or FDR
  - Breast and ovarian ca in same pt. or FDR at any age
  - 2 or more breast primaries in patient or FDR
  - 2 or more cases of breast/ov cancer in FDRs or SDRs if 1 is under 50 or bilateral
  - 3 or more cases of br/ov cancer in FDRs or SDRs at any age
  - Male breast cancer at any age
  - Ashkenazi Jewish ancestry and any of the following: br ca <50, ov ca or male brca at any age, 2 or more cases of br or ov cancer in FDRs or SDRs

Indications for CGC referral- Lynch Syndrome (HNPCC)

One or more of the following

- CRC<50 y/o
- Endometrial Ca <50 y/o
- 3 FDRs or SDRs with any HNPCC associated cancer (CRC, endometrial, stomach, ovary, sm. Bowel, pancreas, ureter, or renal pelvis)
- 2 or more HNPCC associated cancer isn a single FDR or SDR
- IHC for MMR proteins (MLH1, MSH2, MSH6, PMS2 demonstrating absence of one or more proteins in tumor
- MSI in HNPCC associated tumor
- MLH1, MSH2, MSH5 or PMS2 gene mutation identified in family

POLYPOSIS: 10 or more colorectal polyp of any histology

Components of CGC

- Identification and referral of high-risk individuals
- Evaluation of individual/family’s needs
- Collection of pertinent family, medical and personal information
- Creation of personal risk profile
- Provision of cancer risk education and counseling
- Pre-test genetic counseling
- Genetic testing (when appropriate)
- Post-test disclosure and risk management strategy recommendations
- Facilitation of referrals to appropriate specialists
- Long-term surveillance

What happens post-disclosure?

- Patients and care providers identified receive a disclosure letter detailing:
  - Test results
  - Preventive surgery recommendations
  - Surveillance recommendations
  - Information for family members
  - If needed, identification of other CGC programs out-of-state for extended family
Current Practice Sites

• ETSU Student/University Health
  – Suite 160, Nicks Hall

• Pikeville Medical Center
  – Leonard Lawson Cancer Center, Pikeville, KY