Objectives

- Detect clinical characteristics of hereditary cancer syndromes.
- Elicit family history and refer patients for genetic evaluation when indicated.
- Address patient expectations about genetic counseling and testing for hereditary cancer predisposition.

Question #1

Which of the following cancers has the highest proportion of hereditary cases?

A. Breast  
B. Ovarian  
C. Endometrial  
D. Colorectal
Question #2
Which of the following cancers is most commonly seen in association with colon cancer in a hereditary cancer predisposition syndrome?
A. Breast
B. Thyroid
C. Prostate
D. Uterine

Question #3
Which of the following combination of cancers in a family history is not suggestive of a hereditary cancer predisposition syndrome?
A. Breast, ovarian, melanoma
B. Colon, ovarian, pancreatic
C. Breast, endometrial, prostate
D. Breast, thyroid, renal

Outline
- Cancer: sporadic, familial, hereditary
- Family history features
- Hereditary susceptibility to:
  - Breast cancer
  - Ovarian cancer
  - Endometrial cancer
  - Colorectal cancer
- Pathological characteristics
- Guidelines for genetic evaluation referral
- Hereditary cancer gene panel tests

Sporadic vs Familial vs Hereditary Cancer
- HEREDITARY 5-10%
- FAMILIAL 15-20%
- SPORADIC 70-80%
Sporadic Cancer

- Sporadic mutations that accumulate over a lifetime in cells
- Influenced by environmental factors
- Not passed to family members
- Genetic testing is not indicated

Familial Cancer

- Inherited component
  - Multiple genes involved?
  - Clustering of cancer without a specific pattern
  - Family members may have an elevated risk
  - Genetic testing is not indicated

Hereditary Cancer

- 5-10% of breast cancers
- Inherited single gene defect
- Autosomal dominant inheritance
- Genetic testing is available for some but not all cases

Hereditary Cancer Susceptibility-Suggestive Features

- Young age of onset
- Multiple affected relatives in ≥2 generations
- Hx of related cancers
- Specific pathology
- Paternal family history
- Ethnicity

This slide addresses cultural/linguistic competence requirements.
Hereditary Breast Cancer – Suggestive Features

- Age of onset: <50 yo
- Multiple primary breast cancers
- Breast and ovarian cancer
- Male breast cancer
- Pathology:
  - Invasive carcinoma
  - TNBC: ER- PR- HER2 -

KPSC Referral Guidelines

- Breast cancer dx ≤45 or TNBC ≤60
- Bilateral or multiple primary breast cancers
- Patient with both breast and ovarian cancers
- Breast cancer dx ≤50 and Ashkenazi Jewish
- Breast cancer dx ≤50 and 1° relative with breast or ovarian cancer
- Male breast cancer

KPSC Referral Guidelines

Family history (same side) of:
- 1° or 2° relative with multiple breast primaries or both breast and ovarian cancer
- Breast cancer in at least two 1° or 2° relatives on same side of family, one dx ≤50
- Breast cancer in at least one 1° or 2° relatives plus ovarian cancer in at least one 1° or 2° relatives
- Ashkenazi Jewish and one 1° or 2° relatives with breast or ovarian cancer
- Male breast cancer in 1° or 2° relative

Breast Cancer Susceptibility Genes

The slide addresses cultural/linguistic competence requirements.
**Breast Cancer Susceptibility Genes**

- **BRCA1**, **BRCA2**, **TP53** are well characterized.
- Other actionable genes: **PTEN**, **STK11**, **CDH1**
- Newer genes (15 and counting) — limitations:
  - Uncertain/unknown penetrance
  - Lack of specific management recommendations

**Gene Reviews — Updated 9-2013**
http://www.ncbi.nlm.nih.gov/books/NBK1247/

**Hereditary Breast/Ovarian Cancer (HBOC) syndrome**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Mutation Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>BRCA1</strong></td>
</tr>
<tr>
<td>Breast</td>
<td>50%-80%</td>
</tr>
<tr>
<td>Second primary breast</td>
<td>27% within 5 yrs</td>
</tr>
<tr>
<td></td>
<td>40%-50% at 20 yrs</td>
</tr>
<tr>
<td>Ovarian</td>
<td>24%-40%</td>
</tr>
<tr>
<td>Male breast</td>
<td>1%-2%</td>
</tr>
<tr>
<td>Prostate</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1%-3%</td>
</tr>
</tbody>
</table>

**Cowden Syndrome**

Aka PTEN Hamartoma Tumor Syndrome:
- Breast cancer
- Endometrial cancer
- Thyroid cancer (follicular)
- GI hamartomas
- Mucocutaneous lesions
- Macrocephaly

**Li-Fraumeni Syndrome**

Germline **TP53** gene mutation
- Breast cancer
- Bone & soft tissue sarcoma
- Acute leukemia
- Brain tumor
- Adrenocortical carcinoma
- Choroid plexus carcinoma
<table>
<thead>
<tr>
<th>Hereditary Breast Ovarian Cancer (HBOC) syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/BRCA2</td>
</tr>
<tr>
<td>10-15% of unselected cases</td>
</tr>
<tr>
<td>Epithelial ovarian carcinoma – mainly papillary serous</td>
</tr>
<tr>
<td>Fallopian tube carcinoma, primary peritoneal carcinoma</td>
</tr>
<tr>
<td>Lynch syndrome (formerly known as HNPCC)</td>
</tr>
<tr>
<td>Epithelial ovarian carcinoma</td>
</tr>
<tr>
<td>2-3% of unselected cases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serous carcinoma</th>
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</thead>
<tbody>
<tr>
<td>ovary, fallopian tube, or peritonium</td>
</tr>
<tr>
<td>dx ≤60</td>
</tr>
<tr>
<td>Ashkenazi Jewish any age</td>
</tr>
<tr>
<td>Both breast and ovarian/fallopian tube/peritoneal cancers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cowden syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime risk 28%</td>
</tr>
<tr>
<td>Average onset 38-46 yo</td>
</tr>
<tr>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>Lifetime risk 25-60%</td>
</tr>
<tr>
<td>Average onset 48-62 yo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aka Hereditary Non-polyposis Colorectal Cancer (HNPCC) syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common hereditary colon cancer susceptibility syndrome (2-4% of all CRC)</td>
</tr>
<tr>
<td>Autosomal dominant inheritance</td>
</tr>
<tr>
<td>Caused by germline mutations in mismatch repair (MMR genes)</td>
</tr>
</tbody>
</table>
### Lynch Syndrome Genes

- **MLH1**: 50%
- **MSH2**: 40%
- **MSH6**: 7-10%
- **PMS2**: <5%
- **Other**: 1%

### Lynch Syndrome

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Lynch Syndrome (MLH1 and MSH2 heterozygotes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk</td>
</tr>
<tr>
<td>Colon</td>
<td>52%-62%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>25%-40%</td>
</tr>
<tr>
<td>Stomach</td>
<td>6%-13%</td>
</tr>
<tr>
<td>Ovary</td>
<td>4%-12%</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>1.4%-4%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>1%-4%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>2%-6%</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>1%-3%</td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>1%-9%</td>
</tr>
</tbody>
</table>

### Lynch Syndrome Gynecological Cancers

- **Ovarian cancer**
  - 2-3% of unselected cases
  - 4-12% risk in mutation carriers
- **Endometrial cancer**
  - 2-5% of unselected cases
  - 25-60% risk in mutation carriers
- **Pathology**
  - Epithelial carcinomas
  - No specific histological type dominates

### Lynch Syndrome Pathology

- Colon cancer pathological features:
  - Poor differentiation
  - Tumor-infiltrating lymphocytes
  - Mucinous
  - Signet ring or cribriform histology

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Lynch Syndrome Diagnosis

- Clinical Criteria
  - Amsterdam I Criteria
  - Amsterdam II Criteria
- Prediction Models
  - MMRpro
  - PREMM1, 2, 6
  - MMRpredict
- Genetic testing
  - Microsatellite instability (MSI) testing
  - Immunohistochemistry for MMR proteins
  - Molecular genetic analysis for MMR gene mutations

Lynch Syndrome Detection

- Clinical criteria
  - Low utilization
  - Low sensitivity
- Genetic testing
  - Molecular genetic testing – cost prohibitive
  - MSI testing – not specific enough, requires molecular laboratory
  - IHC – inexpensive, readily available, specific

Universal Lynch syndrome screening

- Recommended by EGAPP group of CDC in 2009
- Evaluate every case of colorectal tumor by MSI and/or IHC for MMR gene defect

Tumor Testing for Lynch Syndrome by Level of Cancer Program


NCI-CCC: NCI-designated Comprehensive Cancer Center
Cm-CCC: Community Hospital Comprehensive Cancer Program
Cm-CP: Community Hospital Cancer Program
Universal Lynch Screening at KPNC

- Pilot site started in 4/2011
- Currently expanded to 60% of facilities
- Goal of 100% role out by Fall of 2014
- 4/11-12-13 screened 681 cases
- Overall mutation positive rate 2.1%
- Positive IHC, no germline mutation 0.9%

SCKP Colorectal Cancer Referral Guidelines

- CRC dx <50 yo
- Multiple primary CRC
- CRC & endometrial CA
- Multiple cases of CRC on same side of family
- CRC & endometrial CA on same side of family
- CRC & any of the following: other GI cancers, ovarian, urinary or biliary tract
- Polyposis (≥10 colorectal adenomas) at any age
- Colorectal polyps dx <40
- Sebaceous adenoma or carcinoma

Gene Panel Tests

A test that uses next-generation sequencing technology to analyze multiple genes simultaneously.
- Cardiomyopathy panels
- Neuromuscular disorders
- X-linked intellectual disability panels
- Hearing loss panels
- Cancer predisposition panels
Cancer Gene Panel Tests

**General** – collection of genes related to several different hereditary cancer predisposition syndromes

**Site-specific** – collection of genes related to hereditary predisposition to a specific cancer type (e.g. breast cancer)

**Actionable** – collection of genes related to hereditary cancer predisposition that are well defined and have specific management recommendations

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**Promise of**
- Efficiency through cost effectiveness and time savings
- Elimination of diagnostic dilemmas

**Utility**
- Families with cancer history consistent with several different syndromes
- Patients with negative genetic test for the most likely syndrome

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Limitations of Panel Tests

- No clear guidelines for patient eligibility
- Unresolved reimbursement issues

- Variants of Uncertain Significance (VUS)
  - Genetic variant that may or may not be associated with a cancer risk
  - High rate
  - VUS in multiple genes

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Limitations of Panel Tests

- Moderately penetrant genes
  - No established clinical management guidelines

- Novel genes
  - Unknown cancer spectrum
  - Limited cancer risk data
  - No management guidelines

- Mutations in multiple genes
  - Uncertain cancer risks
  - Mutation in a gene inconsistent with clinical history
  - Uncertain clinical management
### Summary
- Only 5-10% cancers are related to a hereditary susceptibility
- Personal and family history features help identify those at risk for hereditary cancer susceptibility
- Common cancers can be part of different susceptibility syndromes
- Follow regional referral guidelines for genetic evaluation
- New cancer gene panels have promise and limitations

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References

- http://www.nccn.org
- http://www.genetests.org/disorders