**Genetic Diagnosis & Testing for Hereditary Breast Cancer**

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**Question #1**

Approximately what percentage of breast cancer is hereditary?

1) 90%
2) 50%
3) 42%
4) 5%

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**Question #2**

A patient with a strong family history of breast and ovarian cancer has tested negative for the BRCA genes. Other family members have not had testing. The patient’s:

1) Not at an increased risk for breast or ovarian cancer
2) Cancer risk cannot be determined based on this result
3) Risk is still elevated based on the family history alone
4) BRCA testing should be repeated with 12 hour fasting

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**Question #3**

A patient with a BRCA2 mutation has an elevated risk for all cancers EXCEPT:

1) Breast
2) Ovarian
3) Pancreatic
4) Prostate
5) Thyroid

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**Objectives**

- Assess clinical characteristics and family history for potential hereditary breast cancer risk to reduce the number of delayed diagnoses and refer when appropriate
- Briefly counsel at-risk patients regarding benefits of genetic counseling and what to expect during a consultation
- Participate in coordinated care for patients with hereditary breast cancer

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**Overview**

- Genetics of breast cancer
- Appropriate Referrals for Hereditary Breast Cancer Risk Assessment
- Process of genetic counseling for hereditary breast cancer
- Management for patients with hereditary breast cancer
Cancer Arises From Gene Mutations

**Germline mutations**
- Present in egg or sperm
- Can be passed down a family
- Cause inherited cancer syndromes

**Somatic mutations**
- Occur only in the organ with cancer
- Cannot be passed down

What percentage of cancer is inherited?

- **HEREDITARY**
  - 5%
- **FAMILIAL**
  - 10%
- **SPORADIC**
  - 85%

Sporadic Breast Cancer
- Sporadic mutations that accumulate over a lifetime in the body cells
- May be influenced by environmental factors
- Not passed to family members
- Genetic testing is not indicated

Familial Breast 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 Breast Cancer
- 5% of breast cancer
- Inherited single gene defect
- Autosomal dominant
- Genetic testing is available for some but not all cancers

Hereditary Breast Cancer Genes

- **BRCA1** 20% to 40%
- **BRCA2** 10% to 30%
- **UNKNOWN** 25% to 65%
- **ATM** 4%
- **TP53** <1%
- **PTEN** <1%
- **CHK2** <1%
The BRCA1 and 2 Genes

BRCA1 & BRCA2
Associated Cancers: Lifetime Risk

Breast cancer (often < 50 yrs) (40 – 85%)
Contralateral breast cancer (40 – 60%)
Ovarian cancer (10% – 45%)
Male breast cancer elevated (~6%)
Melanoma, fallopian tube, pancreas & prostate cancers risks can also be elevated

CLC: BRCA1 and BRCA2 in Ashkenazi Jewish Individuals

- 1 in 40 will have mutation in BRCA 1 or 2
- 3 specific mutations account for the majority of carriers
  - BRCA1 187delAG and 5382insC, BRCA2 6174delT
- Ashkenazi Jewish heritage must be identified for accurate assessment of risk and genetic testing

Pathological features of HBOC

Clinical & pathologic presentation
- BRCA1 breast tumors
  - Excess of medullary histology
  - ER, PR, HER2 negative (triple negative)
  - High nuclear grade
- BRCA2 breast tumors
  - No typical phenotype
  - ER & PR profiles similar to sporadic tumors

Other susceptibility genes

Cowden syndrome
- PTEN gene
- Increased risk for malignant and non malignant tumors of the breast, non-medullary thyroid, endometrial, colon and kidney.

Li-Fraumeni syndrome
- TP53 gene
- Core cancers: sarcomas, breast cancer, brain

Other susceptibility genes: Chk2, ATM, Familial?

The cancer genetic counseling visit
BRCAPRO: A case report

**Mutation Probabilities**

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRCA1 or 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.435</td>
<td>0.092</td>
<td>0.428</td>
</tr>
<tr>
<td>Breast</td>
<td>Myel</td>
<td>BRCA1/2 Prob</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.083</td>
</tr>
</tbody>
</table>

- Cancer Risks Breast
  - Male prob = 0.008, lifetime risk = 0.170
  - Female prob = 0.012, lifetime risk = 0.182
  - BRCA1/2 prob = 0.075, risk = 0.499

- Family history of breast or ovarian cancer, ages of diagnosis, ages of death, unaffected individuals

- Limitations: does not incorporate non-breast or non-ovarian cancers, does not consider more distant family members

Begin by Testing Affected Person

- Testing affected person first allows for accurate interpretation of test results on relatives
- Negative result on an unaffected person can never be a true negative

Possible outcomes of testing

- Negative
  - True negative
  - Uninformative
  - Variant of uncertain significance (VUS)
  - Positive

Testing outcomes: Negative

- Reduce potential risk of unidentified familial mutation
- Emphasize residual risk of sporadic cancer
- Provide individualized risk-management plan
- Encourage adherence to population screening guidelines

Testing outcomes: VUS

- Explain that cancer risk associated with mutation is not yet known
- Possibly, test other family members to clarify risk
- Individualize risk assessment
- Individualize risk management. Keep current with clinical research.
Testing outcomes: Positive

<table>
<thead>
<tr>
<th>Risk</th>
<th>Population Risk</th>
<th>BRCA Carrier Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>&lt;0.5%</td>
<td>2 - 3%</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>&lt;0.5%</td>
<td>2 - 20%</td>
</tr>
</tbody>
</table>

BRCA carriers:
- Risk reduction by 90% or more
- Bilateral Salpingo-Oophorectomy (BSO)
- Recommended at age 35-40 yrs or when childbearing complete
- Reduces risk by 90%-95% or more
- Residual risk of primary peritoneal cancer: 1% to 4.3%
- Reduces breast cancer risk in young women

Options for a BRCA Mutation Positive Patient

- Surveillance
  - Breast Cancer
    - Self breast exams
    - Clinical breast exam
    - Mammogram/MRI
  - Ovarian Cancer
    - Annual pelvic exam
    - Annual transvaginal US
    - Annual CA125

- Prophylactic Surgery
  - Breast Cancer
    - Mastectomy
    - Ovarian Cancer
    - Salpingo-oophorectomy

- Chemoprevention
  - Breast Cancer
    - Tamoxifen
    - Oral contraceptives

High risk breast cancer surveillance

- Monthly breast self-exam from age 18
- Clinical breast exam 2-4 times per year (beginning at age 25)
- Annual mammography and MRI
  - Starting at age 25 or individualized based on earliest age of onset in the family
  - Sensitivity: 80% to 92% MRI vs 23% to 33% mammogram
  - Breast MRI is approved as screening modality for women at high risk (BRCA carriers, lifetime risk of over 25%)

Ovarian Cancer Surveillance

- Concurrent trans-vaginal ultrasound, pelvic exam and CA125 every 6 months
- Starting at age 35 or 5 to 10 years earlier than earliest onset in family
- No proven benefit

Chemoprevention for BRCA Carriers

- Breast Cancer
  - Tamoxifen & Raloxifene:
    - One case control study reported ~50% contralateral cancer risk reduction from Tamoxifen use in BRCA1/2 carriers
    - No evidence that Tamoxifen post BSO reduces breast cancer risk
- Ovarian Cancer
  - Oral Contraceptives reduce risk by 50% to 70% with 5 yr use
    - May pose modest increase in risk of breast cancer, especially if taken before age 30
LAMC High Risk Breast clinic

- A multidisciplinary clinic to provide individualized and comprehensive care and management for BRCA 1 and 2 carriers
- Meets every other month
- Patients seen to discuss options for management
- Allows patient to meet with multiple specialists in one visit
- Genetics, Surgery, Gyn-Oncology, Medical Oncology, Plastic Surgery, Radiology, Primary Care, Social Work, Breast Care Coordinator

The role of primary care in cancer genetics

- The expectation:
  - Play a role in risk identification and referral to Genetics
  - Ongoing role in risk management
- The reality:
  - Limited time, knowledge and resources for collecting a family history
  - Inconsistency in recognizing patients appropriate for referral

Identification of women at high risk for hereditary breast cancer

- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis (<50 yrs)
- Multiple primary tumors
- Rare cancers at any age (male breast cancer)
- Groupings of cancers that go together (e.g. breast and ovary)
- Evidence of autosomal dominant inheritance
- Triple negative breast cancer (BRCA 1)
- Ashkenazi Jewish (BRCA 1 or 2)

Referral to Genetics

- Tapestry referral in HealthConnect
- Any patient with personal or family history suggestive of HBOC
- Service available at all medical centers and many satellites
- Important for member to collect as much family history as possible
- Genetic testing is not appropriate for all patients

KP guidelines

- Learn more on our intranet site!
**Case #1**

Abnormal CT and Ultrasound

Referred to Genetics...

187delAG

T3cN1 high grade serous adenocarcinoma of ovary

**Case #2**

BRCA1 Del exons 16-17

Sister was subsequently tested and found to have same mutation

Patient and her sister elected prophylactic surgery

**Cancer Genetics Resources**

National Comprehensive Cancer Network
http://www.nccn.org/index.asp

FORCE: Facing Our Risk of Cancer Empowered:
support group for BRCA1/2 carriers
www.facingourrisk.org

Be Bright Pink
http://www.bebrightpink.com/

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Thank you

I am feeling sick. I should look up my symptoms online.

I have brain cancer.