Hereditary Breast and Ovarian Cancer and Genetic Testing

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Breast Cancer

- Breast cancer is one of the most common forms of cancer among women (40,290 in 2015).
- It is second only to lung cancer as a cause of cancer deaths in American women,
- One-third of women with breast cancer die from breast cancer,
- One out of every eight women will be diagnosed with breast cancer in 2015.
Breast Cancer Risk Factors

All women are at risk.

- Age
- Family Risk
- Not having children
- Birth control pills
- Hormone replacement therapy
- Controllable
- Uncontrollable
- Obesity
- Exercise
- Breastfeeding
- Alcohol
Breast Cancer Risk Factors: Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>By age 30</td>
<td>1 out of 2,000</td>
</tr>
<tr>
<td>By age 40</td>
<td>1 out of 233</td>
</tr>
<tr>
<td>By age 50</td>
<td>1 out of 53</td>
</tr>
<tr>
<td>By age 60</td>
<td>1 out of 22</td>
</tr>
<tr>
<td>By age 70</td>
<td>1 out of 13</td>
</tr>
<tr>
<td>By age 80</td>
<td>1 out of 9</td>
</tr>
<tr>
<td>Lifetime risk</td>
<td>1 out of 8</td>
</tr>
</tbody>
</table>

Family History as a Risk Factor

Breast Cancer

- 70% Sporadic
- 15–20% Family clusters
- 5–10% Hereditary

Ovarian Cancer

- 90% Sporadic
- 5–10% Hereditary
Compare Hereditary vs. Sporadic Cancer

- A younger age at the onset of cancer
  - Generally < 50 years of age

- Multiple primary cancers:
  - Breast
  - Ovarian
  - Other
**Causes of Hereditary Susceptibility to Breast Cancer**

5–10% of breast cancers can be attributed to inherited factors.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Contribution to Hereditary Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>BRCA1</em></td>
<td>20–40%</td>
</tr>
<tr>
<td><em>BRCA2</em></td>
<td>10–30%</td>
</tr>
<tr>
<td><em>TP53</em></td>
<td>&lt;1%</td>
</tr>
<tr>
<td><em>PTEN</em></td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Undiscovered genes</td>
<td>30–70%</td>
</tr>
</tbody>
</table>
• **BRCA1** (for **BR**east **CA**ncer gene 1) was described in 1990 on chromosome 17 and isolated in 1994.

• **BRCA2** was isolated on chromosome 13 in late 1994.
Passing on Risk: Autosomal Dominant

Each child has 50% risk of inheriting a familial mutation.

Legend
- **B**: BRCA gene with mutation
- **b**: Normal BRCA gene

- **Normal BRCA genes (bb)**
  - **Bb**
  - **bb**

- **BRCA mutation (Bb)**
  - **Bb**
  - **bb**

- **Susceptible BRCA gene**
  - **Susceptible BRCA gene**
  - **Population risk**
  - **Susceptible BRCA gene**
  - **Population risk**
Consequences of Having a *BRCA* Mutation

<table>
<thead>
<tr>
<th></th>
<th><em>BRCA</em> Mutation Carriers</th>
<th>In General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Cancer ♀</strong></td>
<td>50–85%</td>
<td>11%</td>
</tr>
<tr>
<td><em>BRCA1 &amp; BRCA2</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ovarian Cancer</strong></td>
<td>40–60%</td>
<td>1–2%</td>
</tr>
<tr>
<td><em>BRCA1</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ovarian Cancer</strong></td>
<td>10–20%</td>
<td>1–2%</td>
</tr>
<tr>
<td><em>BRCA2</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breast Cancer ♂</strong></td>
<td>≤6%</td>
<td>Rare</td>
</tr>
<tr>
<td><em>BRCA2</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other BRCA+ Related Cancers

Slight risk for other cancers

• Shown to be increased in carriers:
  – Pancreatic
  – Melanoma
  – Stomach
  – Colon
  – Prostate
  – Male breast cancer
Who Should Be Tested?

• Multiple family members with breast cancer
• A family member with primary cancer in both breasts
  – Especially if manifested before age 50
• A family member with ovarian cancer
• A family member with male breast cancer
• A family member with an identified BRCA1 or BRCA2 mutation
• Jewish ancestry
BRCA1 and BRCA2 Mutations

- **BRCA1**: 1873 mutations
  - Point mutations: 1574 (84%)
  - Large deletions/duplications: 299 (16%)

- **BRCA2**: 1597 mutations
  - Point mutations: 1523 (95%)
  - Large deletions/duplications: 74 (5%)
Three mutations in *BRCA1* and 2 account for 97% of *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish individuals:

- *BRCA1*: 185delAG, 5382insC
- *BRCA2*: 6174delT
Hereditary Breast/Ovarian Cancer Testing

- Ashkenazi Jewish \((BRCA1\) and \(BRCA2\)), 3 Mutations (2011958)

- Breast and Ovarian Hereditary Cancer Syndrome \((BRCA1\) and \(BRCA2\)) Sequencing and Deletion/Duplication (2011949)

- Breast and Ovarian Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 20 Genes (2012026)
Test Recommendation for Jewish Ancestry

- Test with Ashkenazi Jewish (BRCA1 and BRCA2), 3 Mutations (2011958): sensitivity 97% (PCR/ capillary electrophoresis)

- Negative: Breast and Ovarian Hereditary Cancer Syndrome (BRCA1 and BRCA2) Sequencing and Deletion/Duplication (2011949)

**185delAG**
Testing for High-Risk Individuals

- Breast and Ovarian Hereditary Cancer Syndrome (*BRCA1* and *BRCA2*) Sequencing and Deletion/Duplication (2011949)
  - Sequencing *BRCA1* and *BRCA2* genes: sensitivity 80–84% and 90–95%
  - Deletion/duplication of *BRCA1* and *BRCA2* genes: sensitivity 16% and 5%
Breast Cancer Multi-Gene Panel

- Breast and Ovarian Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 20 Genes (2012026)

- 20 genes associate with increased risk of breast cancer: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53

Next-generation sequencing

Array CGH
Is This Sequence Variant a Mutation?

M18T in *BRCA1*: Is this a mutation or benign?
Publication, computational prediction, database

http://www.arup.utah.edu/
<table>
<thead>
<tr>
<th>Location</th>
<th>Mutation Type</th>
<th>Nucleotide Change</th>
<th>Protein Change</th>
<th>Classification</th>
<th>Posterior Probability</th>
<th>Reference</th>
<th>Secondary Reference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 2</td>
<td>Insertion</td>
<td>c.32_33insC</td>
<td></td>
<td>5 - Definitely pathogenic</td>
<td>&gt;0.99</td>
<td>Szabo (1995) Hum Mol Genet 4: 1811</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 2</td>
<td>Deletion</td>
<td>c.61delA</td>
<td></td>
<td>5 - Definitely pathogenic</td>
<td>&gt;0.99</td>
<td>Thirthagiri (2008) Breast Cancer Res 10; R59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Management of BRCA+ Women

## Prevention and Screening Options

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic surgery</td>
<td>Mastectomy</td>
</tr>
<tr>
<td></td>
<td>Oophorectomy</td>
</tr>
<tr>
<td>Chemoprevention</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Screening</td>
<td>Mammograms</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>Ultrasound</td>
</tr>
<tr>
<td></td>
<td>Clinical breast exams</td>
</tr>
</tbody>
</table>
Current Screening Recommendations for BRCA+ Women

- **Breast**
  - Monthly breast self-exams (begin by age 18)
  - Early clinical surveillance (begin by age 25)
    - Biannual clinical breast exams at a breast center
    - Annual mammography
    - Sonography? MRI?

- **Ovarian: no good options**
  - Transvaginal ultrasound
  - CA-125 blood levels
Conclusion:
Identifying high-risk individuals will help surveillance and prevention of breast/ovarian cancer.
Germline Pharmacogenetics in Breast Cancer

Gwen McMillin, PhD, DABCC(CC,TC)
Medical Director, Toxicology
Co-Medical Director, Pharmacogenetics
Germline vs. Somatic Genetics

**Somatic mutations**
- Occur in *non-germline* tissues
- Cannot be inherited

**Germline mutations**
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

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Mutation in tumor only (for example, breast)

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Mutation in egg or sperm

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All cells affected in offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
Germline Pharmacogenetics

Inherited genes can predict/explain if and how a person will tolerate and respond to a drug:

– Pharmacokinetics, such as drug metabolism
– Pharmacodynamics, such as drug response
Good response

Unconventional dose and/or dosing frequency

Poor response

Sensitivity

No side effects

Resistance

Adverse effects
Drug Metabolism

- Most drugs are metabolized.
- Some drugs require metabolism to be converted to an active form (drug activation); these drugs are called “prodrugs.”

[Chemical structures of Codeine and Morphine showing O-dealkylation process]
• Most drugs are inactivated by metabolism to promote elimination of the drug.

• Drug metabolism is mediated by enzymes; the cytochrome P450 (CYP) family is one of the most clinically significant.
Proportion of Drugs Metabolized by P450 Enzymes

Relationship to Breast Cancer

CYP2D6

- Major enzyme responsible for activation of tamoxifen and some pain drugs
- Major enzyme responsible for inactivation of many drugs, such as antidepressants

CYP2C19

- Minor enzyme responsible for activation of tamoxifen
- Major enzyme responsible for inactivation of many drugs, such as antidepressants and gastrointestinal drugs

Genetic variants can increase, decrease, or obliterate metabolism.
Common Genetic Variants (Alleles)

**CYP2D6**
- **CYP2D6*4** (↓ function)
  - 1–8% of Asians
  - 6–18% of Caucasians and African-Americans
  - 8% of Middle Easterners
- **CYP2D6*1 or 2xN** (↑ function)
  - 1% of Asians
  - 2–3% of Caucasians and African Americans
  - 7% of Middle Easterners

**CYP2C19**
- **CYP2C19*2** (↓ function)
  - 30–35% of Asians
  - 15–20% of Caucasians and African Americans
  - 55% of Oceanians
- **CYP2C19*17** (↑ function)
  - 1–15% of Asians
  - 15–20% of Caucasians and African Americans
  - 2.5% of Oceanians

2015 CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of SSRIs —Supplemental v1.0.
Two Alleles = Genotype

From which phenotype is predicted

- EM = extensive metabolizer = normal
- IM = intermediate = combinations of non-functional and/or reduced function alleles and/or normal alleles
- PM = poor = two non-functional alleles
- UM = ultra-rapid = duplications of functional alleles or alleles that increase expression
Tamoxifen

- Most commonly prescribed anti-estrogen
- Prodrug
- Used since 1971 for breast cancer treatment, adjuvant therapy, prevention, and several other indications
- Annual sales in the U.S. > $500 million
- ~35% of women do not respond
Simplified Schematic of Tamoxifen Metabolism

Tamoxifen (TAM) → N-desmethyl TAM

CYP2D6
(CYP2B6, CYP2C9, CYP2C19, CYP3A)

4-hydroxy TAM → Endoxifen

CYP3A4/5
(CYP2C9 + other CYP isoforms)

CYP3A4/5

SULT1A1
Theoretical Effect of CYP Phenotypes on Activation of Tamoxifen

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>PM</th>
<th>IM</th>
<th>Normal</th>
<th>UM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>PM</td>
<td>IM</td>
<td>Normal</td>
<td>UM</td>
</tr>
<tr>
<td>IM</td>
<td>Little to no active drug</td>
<td>Potentially inadequate active drug</td>
<td>Active drug</td>
<td>More than average amounts of active drug</td>
</tr>
<tr>
<td>Normal</td>
<td>Some active drug</td>
<td>Active drug?</td>
<td>More active drug</td>
<td></td>
</tr>
<tr>
<td>UM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# CYP Phenotype and Amitriptyline Recommendations

## CYP2D6

<table>
<thead>
<tr>
<th>CYP2C19</th>
<th>PM</th>
<th>IM</th>
<th>Normal</th>
<th>UM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>Avoid use</td>
<td>Consider 25% dose reduction; TDM to optimize</td>
<td>Standard dosing</td>
<td>Avoid use</td>
</tr>
<tr>
<td>IM</td>
<td>Avoid use</td>
<td>Consider 50% dose reduction</td>
<td>Standard dosing</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Normal</td>
<td>Avoid use</td>
<td>Consider 25% dose reduction; TDM to optimize</td>
<td>Standard dosing</td>
<td>Avoid use</td>
</tr>
<tr>
<td>UM</td>
<td>Consider alternate drug</td>
<td>Consider alternate drug</td>
<td>Standard dosing</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

[https://www.pharmgkb.org/guideline/PA166105006](https://www.pharmgkb.org/guideline/PA166105006)
CYPs for Other Drugs Used in Treating Breast Cancer Patients

**CYP2D6**
- Antidepressants
  - Paroxetine, venlafaxine
- Other psychiatric drugs
  - Risperidone, atomoxetine
- Analgesics
  - Codeine, tramadol, oxycodone
- Cardiac drugs
  - Flecainide, propafenone

**CYP2C19**
- Antidepressants
  - Citalopram, sertraline
- Gastrointestinal drugs
  - Omeprazole, lansoprazole, rabeprazole
- Cardiac drugs
  - Clopidogrel
- Other misc. drugs
  - Voriconazole, clobazam
Single gene

- CYP2D6: 0051232
  - 14 variants and gene duplication/deletion

- CYP2C19: 0051104
  - 9 variants

Multi-gene DME panel

- Includes CYP2D6, CYP2C19, and CYP2C9 (test code 2008920)

Notes:

- **CYP3A5** will be available with the November 2015 hotline and will be added to the gene panel in 2016.
- A **saliva kit** will be available soon to promote non-invasive (not blood), outpatient collections.
- **Custom interpretation for multi-gene panel** is anticipated for 2016.
Summary and Conclusions

• Germline pharmacogenetic testing can help personalize drug therapy by predicting whether a patient will be able to metabolically activate and inactivate drugs.

• CYP genetic testing is relevant to all breast cancer patients who are prescribed drugs, particularly tamoxifen, antidepressants, and opioid analgesics.