GENETIC COUNSELING FOR BREAST CANCER

Anne Heun, MS, CGC • Unity Point Health – Des Moines • Throckmorton Surgical Symposium 2016
Outline

- High risk genes
- Moderate risk genes
- Appropriate referrals or testing candidates
- Medical management
Cancer Breakdown

BREAST CANCER TYPE BREAKDOWN

- Sporadic, 70-80%
- Familial, 15-20%
- Hereditary, 5-10%
  
  *BRCA1, BRCA2* mutations can explain 25-50% of hereditary cancer cases
# BRCA1 and BRCA2

## Risk of Cancer in Individuals With a BRCA1 or BRCA2 Mutation

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>General Population (No Mutation)</th>
<th>Individuals With Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BRCA1</td>
</tr>
<tr>
<td>Breast</td>
<td>12%</td>
<td>50-80%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1-2%</td>
<td>24-40%</td>
</tr>
<tr>
<td>Male Breast</td>
<td>0.10%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Prostate</td>
<td>15% (N. Europe Origin)</td>
<td>up to 30%</td>
</tr>
<tr>
<td></td>
<td>18% (African American)</td>
<td>1-3%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>0.50%</td>
<td>1-3%</td>
</tr>
</tbody>
</table>
BRCA1 and BRCA2

- **BRCA1**
  - Risk for second primary: 83% lifetime
  - More likely to be triple negative - 8.5-28% of those with -/-/- have BRCA1 mutation

- **BRCA2**
  - Risk for second primary: 62% lifetime
  - Breast cancers most likely to have ER+/PR+/HER2- histology
CDH1

- Hereditary diffuse gastric cancer
- 39-52% risk of invasive lobular breast cancer
- Main risk is for diffuse gastric cancer
  - 67-83% lifetime risk, average age 38
- Can present in some families with only lobular breast cancer
PTEN

- Cowden syndrome or PTEN Hamartoma Tumor syndrome
- Characterized by benign growths and elevated cancer risks
  - Macrocephaly, autism
  - Colon polyps (adenomas, hamartomas) in 92%
  - Skin lesions, particularly trichilemmomas, oral papillomas, acral keratoses
  - Lhermitte-Duclos disease
# Cowden Syndrome Cancer Risks

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>25-50%</td>
<td>85%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3-10%</td>
<td>35%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>5-10%</td>
<td>28%</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>Unknown</td>
<td>34%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Unknown</td>
<td>6%</td>
</tr>
<tr>
<td>Colon</td>
<td>Unknown</td>
<td>9%</td>
</tr>
</tbody>
</table>
PALB2

- Partner and Localizer of BRCA2

- Increased risks of breast cancer (women)
  - Risk dependent upon family history

- Other cancer risks? Pancreatic, male breast?

- Higher risk of triple negative cancers?
Table 4. Risk of Breast Cancer for Female PALB2 Mutation Carriers, According to Family History of Breast Cancer.

<table>
<thead>
<tr>
<th>Age</th>
<th>Cumulative Risk (95% CI)</th>
<th>Mean Estimate without Family History Taken into Account</th>
<th>Mother Unaffected at 50 Yr of Age, Maternal Grandmother Unaffected at 70 Yr of Age*</th>
<th>Mother with Breast Cancer at 35 Yr of Age*</th>
<th>Sister and Mother with Breast Cancer at 50 Yr of Age*</th>
<th>Mother and Maternal Grandmother with Breast Cancer at 50 Yr of Age*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 yr</td>
<td>0.4 (0.3–0.7)</td>
<td>0.3 (0.2–0.6)</td>
<td>0.8 (0.5–1.1)</td>
<td>0.9 (0.6–1.2)</td>
<td>0.7 (0.5–1.0)</td>
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<tr>
<td>35 yr</td>
<td>2 (1.0–2.4)</td>
<td>1 (0.9–2.2)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
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<tr>
<td>40 yr</td>
<td>4 (3–6)</td>
<td>3 (2–5)</td>
<td>7 (5–10)</td>
<td>8 (6–11)</td>
<td>7 (5–9)</td>
<td></td>
</tr>
<tr>
<td>45 yr</td>
<td>8 (5–12)</td>
<td>7 (5–11)</td>
<td>14 (9–20)</td>
<td>16 (12–21)</td>
<td>13 (10–18)</td>
<td></td>
</tr>
<tr>
<td>50 yr</td>
<td>14 (9–20)</td>
<td>13 (8–18)</td>
<td>23 (16–31)</td>
<td>27 (21–33)</td>
<td>22 (17–29)</td>
<td></td>
</tr>
<tr>
<td>60 yr</td>
<td>26 (19–35)</td>
<td>24 (18–33)</td>
<td>40 (31–51)</td>
<td>46 (38–54)</td>
<td>40 (32–48)</td>
<td></td>
</tr>
<tr>
<td>65 yr</td>
<td>31 (23–42)</td>
<td>29 (22–39)</td>
<td>47 (37–58)</td>
<td>53 (45–61)</td>
<td>46 (38–55)</td>
<td></td>
</tr>
<tr>
<td>70 yr</td>
<td>35 (26–46)</td>
<td>33 (25–44)</td>
<td>52 (41–63)</td>
<td>58 (50–66)</td>
<td>51 (42–60)</td>
<td></td>
</tr>
<tr>
<td>75 yr</td>
<td>40 (30–51)</td>
<td>38 (28–48)</td>
<td>57 (46–68)</td>
<td>63 (55–71)</td>
<td>56 (47–65)</td>
<td></td>
</tr>
<tr>
<td>80 yr</td>
<td>44 (34–55)</td>
<td>41 (32–53)</td>
<td>61 (50–72)</td>
<td>67 (59–75)</td>
<td>61 (51–69)</td>
<td></td>
</tr>
</tbody>
</table>

* Data are predicted breast-cancer risks obtained from the most parsimonious model, which allows for the residual familial aggregation effects in PALB2 mutation carriers and noncarriers.
Li-Fraumeni syndrome

**VERY HIGH cancer risks**
- Lifetime risk for ANY cancer for women: 93%
- Lifetime risk for ANY cancer for men: 70%
- Risk of cancer by age 30 for women: 50%
- Risk of breast cancer for women by age 50: 50%

**Core cancers:** adrenocortical carcinomas, brain tumors, sarcomas (bone and soft tissue), breast
Genetic testing indicated for all women diagnosed with breast cancer ≤ 35 yr
- 5-7% of BRCA negative women with breast cancer diagnosed at age 35 or under

Important to identify in making surgical decisions
- Patients should avoid radiation therapy unless necessary
STK11

- Peutz-Jeghers syndrome
  - Presents in childhood with oral mucocutaneous pigmentation
    - Can disappear by adulthood
    - Also on hands and feet
- Small bowel intussusceptions
<table>
<thead>
<tr>
<th>Site</th>
<th>% Lifetime Risk</th>
<th>Screening Procedure and Interval</th>
<th>Initiation Age (y)</th>
</tr>
</thead>
</table>
| Breast             | 45%–50%         | • Mammogram and breast MRI annually<sup>c</sup>  
• Clinical breast exam every 6 mo | ~ 25 y            |
| Colon              | 39%             | • Colonoscopy every 2–3 y                                                                         | ~ Late teens       |
| Stomach            | 29%             | • Upper endoscopy every 2–3 y                                                                        | ~ Late teens       |
| Small intestine    | 13%             | • Small bowel visualization (CT or MRI enterography baseline at 8–10 y with follow-up interval based on findings but at least by age 18, then every 2–3 y, though this may be individualized, or with symptoms) | ~ 8–10 y          |
| Pancreas           | 11%–36%         | • Magnetic resonance cholangiopancreatography or endoscopic ultrasound every 1–2 years            | ~ 30–35 y         |
| Ovary<sup>c</sup>  | 18%–21%         | • Pelvic examination and Pap smear annually  
• Consider transvaginal ultrasound | ~ 18–20 y         |
| Cervix Uterus      | 10%             |                                                                                                  |                    |
|                    | 9%              |                                                                                                  |                    |
| Testes             |                 | • Annual testicular exam and observation for feminizing changes                                   | ~ 10 y            |
| Lung               | 15%–17%         | • Provide education about symptoms and smoking cessation  
• No other specific recommendations have been made |                    |
ATM

- Studies on penetrance provide wildly different breast cancer risk estimates (based on population?)
  - Some quote 2-4 fold increase in risk
  - Others report up to 60% lifetime risk

- Other cancer risks?

- In recessive form, hereditary ataxia-telangiectasia
CHEK2

- Founder mutation: 1100delC
  - Most data based upon this mutation

- 2-4-fold increased risk of female breast cancer in heterozygous carriers

- 4-7 fold increased risk of female breast cancer in homozygotes

- Other cancers? Colon, prostate?
Mutation Population Prevalence

- BRCA1: ~1:300
- BRCA2: ~1:800
- ATM: 1% Northern Europeans
- CHEK2: 1% Northern Europeans
- CDH1: <1:100,000
- PALB2: ?, <1%
- STK11: 1:25,000
- PTEN: 1:200,000
- TP53: 1:20,000

Estimates changing as more people are testing.
Others

- BARD1, BRIP1, MRE11A, NBN, RAD50, RAD51C, RAD51D, ABRAXAS, GEN1, NF1, XRCC2, FANCC, SMARCA2…

- Still lacking evidence regarding risk estimates

- No medical management recommendations available for breast cancer screening
Identifying Appropriate Patients

- An individual with a breast cancer diagnosis meeting any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Early-age-onset breast cancer
  - Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 y
  - Two breast cancer primaries in a single individual
  - Breast cancer at any age, and
    - ≥1 close blood relative with breast cancer ≤50 y, or
    - ≥1 close blood relative with invasive ovarian cancer at any age, or
    - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or
    - From a population at increased risk
  - Male breast cancer
  - An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
  - An individual with a personal and/or family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract
- An individual with an ovarian cancer
Identifying Appropriate Patients

- An individual with no personal history of cancer but with
  - A close relative with any of the following:^{d,f}
    - A known mutation in a cancer susceptibility gene within the family
    - ≥2 breast cancer primaries in a single individual
    - ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
    - Ovarian^{e} cancer
    - Male breast cancer
  - First- or second-degree relative with breast cancer ≤45 y
  - Family history of three or more of the following (especially if early onset^{b} and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer^{i}, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations^{g,h} and/or macrocephaly, hamartomatous polyps of GI tract^{h}

A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment

Heather Hampel, MS, LGC¹, Robin L. Bennett, MS, LGC², Adam Buchanan, MS, MPH³, Rachel Pearlman, MS, LGC¹, and Georgia L. Wiesner, MD⁴; for a Guideline Development Group of the American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and of the National Society of Genetic Counselors Practice Guidelines Committee
Referral Guidelines

Breast cancer, female

- Breast cancer dx at age ≤50
- Triple-negative breast cancer dx at age ≤60
- ≥2 primary breast cancers in the same person
- Ashkenazi Jewish ancestry and breast cancer at any age
- ≥3 cases of breast, ovarian, pancreatic, and/or aggressive prostate cancer in close relatives, including the patient
- Breast cancer and one additional LFS tumor (Table 5) in the same person or in two relatives, one dx at age ≤45
- Breast cancer and ≥1 PJ polyp in the same person
- Lobular breast cancer and diffuse gastric cancer in the same person
- Lobular breast cancer in one relative and diffuse gastric cancer in another, one dx at age <50
- Breast cancer and two additional Cowden syndrome criteria (Table 4) in the same person

Breast cancer, male

- Single case present
High Risk Management

- High risk screening protocol recommended for women with 20% lifetime risk (or higher)
  - Genetic mutation
  - Risk estimate based upon statistical models (Tyrer-Cuzick, Gail, BRCAPro, etc.)
- Annual mammograms, beginning at age 30
- Annual breast MRI, beginning at age 30
  - BRCA mutations: beginning at age 25
- Annual CBEs, monthly SBEs
High Risk Management

- Chemopreventive medications – SERMs and AIs
  - Tamoxifen, raloxifene, anastrazole, exemestane
  - Can reduce risk by up to 45-60%
    - In premenopausal women with intact breast tissue

- Bilateral mastectomies: >90% risk reduction

- Prophylactic bilateral salpingo-oophorectomies
  - Can reduce lifetime breast cancer risk by 50% in premenopausal women, BRCA2>BRCA1
Increased Risk:

Prior history of breast cancer

Women ≥35 y with 5-year risk of invasive breast cancer ≥1.7%

OR

Women who have a lifetime risk >20% based on history of LCIS or ADH/ALH

OR

Women who have a lifetime risk >20% as defined by models that are largely dependent on family history

See NCCN Guidelines for Breast Cancer - Surveillance Section

• Annual screening mammogram^h + clinical breast exam^a every 6–12 mo^j
  ▪ to begin at diagnosis but not less than age 30 y
  ▪ Breast awareness^g
  ▪ Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk)

• Annual screening mammogram^h + clinical breast exam^a every 6–12 mo^j
  ▪ to begin at diagnosis but not less than age 30 y
  ▪ Breast awareness^g
  ▪ Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk)
  ▪ Consider annual MRI
  ▪ to begin at diagnosis but not less than age 30 y (based on emerging evidence)

• Annual screening mammogram^h + clinical breast exam^a every 6–12 mo^j
  ▪ to begin 10 years prior to youngest family member but not less than age 30 y
  ▪ Breast awareness^g
  ▪ Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk)
  ▪ Recommend annual breast MRI^l
  ▪ to begin 10 years prior to youngest family member but not less than age 30 y
  ▪ Referral to genetic counseling if not already done

NCCN Guidelines
version 1.2015
Estimating Risks for Unaffected Women

- Multiple models used to estimate risk
  - Personal risk factors, family history
- All have strengths and weaknesses

- Examples:
  - Tyrer-Cuzick
  - Gail
  - BOADICEA
  - Claus
  - BRCAPro
Estimating Risks for Unaffected Women

**Personal:**
- 10-yr risk: 0.7%
- Lifetime risk: 24.6%

**Population:**
- 10-yr risk: 0.4%
- Lifetime risk: 13.4%

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**No BRCA gene:**
- Personal: 99.56%
- Population: 99.68%

**BRCA1 gene:**
- Personal: 0.13%
- Population: 0.12%

**BRCA2 gene:**
- Personal: 0.31%
- Population: 0.20%
# High Risk Management

## NCCN Guidelines

### Version 2.2016

<table>
<thead>
<tr>
<th>Intervention warranted based on gene and/or risk level</th>
<th>Recommend Breast MRI&lt;sup&gt;d&lt;/sup&gt; (&gt;20% risk of breast cancer&lt;sup&gt;e&lt;/sup&gt;)</th>
<th>Discuss Option of RRM</th>
<th>Recommend/Consider RRSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53</td>
<td>BRCA1, BRCA2, CDH1, PTEN, TP53, PALB2</td>
<td>BRCA1, BRCA2, Lynch syndrome&lt;sup&gt;f&lt;/sup&gt;, BRIP1, RAD51C, RAD51D</td>
<td></td>
</tr>
<tr>
<td>Insufficient evidence for intervention&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>BRIP1</td>
<td>ATM, CHEK2, STK11</td>
<td>PALB2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Breast and ovarian management based on genetic test results.

<sup>b</sup> Intervention may still be warranted based on family history or other clinical factors.

<sup>c</sup> Insufficient evidence for any recommendations for breast MRI, RRSO, or RRM include but are not limited to: BARD1, FANCC, MRE11A, MUTYH, NF1, NBN, RAD50, SMARCA, or XRCC2.

RRM: risk-reducing mastectomy
RRSO: risk-reducing salpingo-oophorectomy
Decision Tool for Women with BRCA Mutations

Patient Characteristics
Current Age: Age 25-29
Mutation Status: BRCA1

Screening & Prevention Strategies
For Comparison: No Interventions

Screening
None
Mammogram
Mammo & MRI

Prophylactic Oophorectomy
None
at Age 35
at Age 40

Prophylactic Mastectomy
None
None
None

Probability of Outcomes

By Age 70:
- 14 out of 100 women died from other causes
- 5 out of 100 women died from ovarian cancer
- 5 out of 100 women died from breast cancer
- 4 out of 100 women are alive with ovarian cancer of which 1 also had breast cancer
- 18 out of 100 women are alive after breast cancer
- 54 out of 100 women are alive and never had breast or ovarian cancer

http://brcatool.stanford.edu
Challenges

- Penetrance estimates
  - Mutation specific?
  - Ethnicity specific?
  - Family specific?

- Variable expressivity

- Lack of data for “newer” genes

- Variants of uncertain significance
Questions?

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