CANCER RISK ASSESSMENT IN THE COMMUNITY

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Disclosures:
Nothing to disclose
Timeline of Genetic Risk Assessment for Breast Cancer

- Epidemiologic studies identify/quantify risk factors
- BRCA1 cloned on chr 17
- BRCA2 cloned
- Myriad Genetics offers BRCA testing
- Multi-gene panel testing

- 1888: 1st report of Hereditary Breast cancer
- 1970’s-80’s
- 1988: BRCA1 cloned
- 1994: BRCA2 cloned
- ’96
- ’99
- 2005
- 2012
- ‘13

- ASCO guidelines
- NCCN guidelines
- USPSTF guidelines
- USPSTF update
Under-Utilization of BRCA Testing

- 2007: 30% of commercially insured breast cancer patients diagnosed age < 40 had BRCA testing
- 2007-2009: 50% of women with breast cancer in FL and PA (n=3,016) with moderate/high risk of BRCA mutation had testing
- 2005 National Health Interview Survey: 35,116 women without cancer history
  ➢ 1.4% of those meeting criteria for BRCA testing had DNA testing

BRCA1 and BRCA2-Associated Cancers: Lifetime Risks for the Hereditary Breast & Ovarian Cancer Syndrome (HBOC)

- Breast cancer 50%–85% (often early age at onset)
- Second primary breast cancer 40%–50%
- Ovarian cancer 15%–45%

In men breast cancer risk elevated for BRCA2 carriers. Moderate increased risk of other cancers in BRCA2 carriers (prostate, pancreas, melanoma)
INHERITANCE OF CANCER SUSCEPTIBILITY GENES

AUTOSOMAL DOMINANT INHERITANCE

Either parent can pass on a mutation in a breast cancer gene

Chance of inheriting mutation is 50/50

Sons & daughters have equal chance of inheriting a mutation in a breast cancer gene
## Frequency of *BRCA* Mutations

<table>
<thead>
<tr>
<th>Population</th>
<th>Frequency of mutation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>0.25</td>
</tr>
<tr>
<td>Ashkenazi Jews (AJ)</td>
<td>2</td>
</tr>
<tr>
<td>Female breast cancer</td>
<td>5</td>
</tr>
<tr>
<td>Female breast cancer &lt; age 35</td>
<td>10</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>16</td>
</tr>
<tr>
<td>2 or more breast cancers in family under age 50</td>
<td>22</td>
</tr>
<tr>
<td>Breast &amp; ovarian cancer in family</td>
<td>50</td>
</tr>
<tr>
<td>Breast and ovarian cancer in same person</td>
<td>88</td>
</tr>
</tbody>
</table>
BRCA Mutations in Triple Negative Breast Cancer

- N=1,824 triple negative breast cancers unselected for family history
- BRCA1 mutation in 8.3%,
- BCRCA2 mutation in 2.7%
- No family history of breast/ovarian cancer

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<table>
<thead>
<tr>
<th>Family Cancer History</th>
<th>&lt;35</th>
<th>35 to 39</th>
<th>40 to 49</th>
<th>50 to 59</th>
<th>≥ 60</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mutation Carriers</td>
<td>All Patients</td>
<td>Mutation Carriers</td>
<td>All Patients</td>
<td>Mutation Carriers</td>
</tr>
<tr>
<td>BRCA1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No breast, no ovarian</td>
<td>14</td>
<td>91</td>
<td>15</td>
<td>149</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>15.4%</td>
<td></td>
<td>10.1%</td>
<td></td>
<td>6.7%</td>
</tr>
<tr>
<td>BRCA2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No breast, no ovarian</td>
<td>4</td>
<td>91</td>
<td>8</td>
<td>149</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4.4%</td>
<td></td>
<td>5.4%</td>
<td></td>
<td>1.9%</td>
</tr>
</tbody>
</table>
Pancreatic Carcinoma in *BRCA* Mutation Carriers

- Pancreatic cancer risk 2-5 times higher than general population
- Especially in *BRCA2* carriers

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>N</th>
<th>Gene</th>
<th>Cumulative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson-2002</td>
<td>Breast Cancer Linkage Consortium of high risk families</td>
<td>699 families (11,847 individuals)</td>
<td>BRCA1</td>
<td>1.2%</td>
</tr>
<tr>
<td>BCLC-1999</td>
<td>Breast Cancer Linkage Consortium of high risk families</td>
<td>173 families (3,728 individuals)</td>
<td>BRCA2</td>
<td>3%</td>
</tr>
<tr>
<td>Van Asperen-2005</td>
<td>Population-based cohort in Netherlands of all HBOC families</td>
<td>169 families (1,811 individuals)</td>
<td>BRCA2</td>
<td>7% (male), 3% (female)</td>
</tr>
</tbody>
</table>
Cancer Risks in BRCA2 Mutation Carriers

*The Breast Cancer Linkage Consortium*

J Natl Cancer Inst 1999;91:1310-16

- 3047 individuals from 173 families with BRCA2 mutation
- Relative risk PrCa= 4.65
- for men under age 65 RR= 7.33
- Cumulative risk to age 70 = 20-33%

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>N</th>
<th>Gene</th>
<th>Cumulative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leongamornlert</td>
<td>UK cohort of Pr Ca cases (enriched for age &lt; 65 + fam hx)</td>
<td>913</td>
<td>BRCA1</td>
<td>8.6% by age 65</td>
</tr>
<tr>
<td>Kote-Jarai-2011</td>
<td>UK cohort of PrCa cases (enriched for age &lt; 65 + fam hx)</td>
<td>1864</td>
<td>BRCA2</td>
<td>15% by age 65</td>
</tr>
<tr>
<td>Van Asperen-2005</td>
<td>Nationwide cohort in Netherlands of all BRCA2 families (169)</td>
<td>803</td>
<td>BRCA2</td>
<td>17% by age 80</td>
</tr>
<tr>
<td>Thompson-2001</td>
<td>164 BCLC families transmitting BRCA2 mutation</td>
<td></td>
<td>BRCA2</td>
<td>19% by age 80</td>
</tr>
<tr>
<td></td>
<td>OCCR vs. Non-OCCR</td>
<td></td>
<td></td>
<td>33% by age 80</td>
</tr>
</tbody>
</table>
BRCA Mutation Carriers Have More Aggressive Prostate Cancer

- 2019 men w/ PrCA from 2 UK observational cohort studies
- 18 BRCA1/62 BRCA2 carriers & 1940 cases without mutation

<table>
<thead>
<tr>
<th>Feature</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Non-carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade</td>
<td>28%</td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td>T3-T4 tumor</td>
<td>33%</td>
<td>38%</td>
<td>28%</td>
</tr>
<tr>
<td>Lymph node (+)</td>
<td>11%</td>
<td>16%</td>
<td>5%</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>17%</td>
<td>18%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- 5-yr survival: 82% (BRCA+) vs. 96% (BRCA-)
- BRCA2 mutation strong predictor of mortality in multivariable modeling
  HR=3.2 (95% CI; 1.5-6.8)
Patients diagnosed with breast or ovarian cancer

- Predict risk of second malignancies
- Direct treatment (e.g. platinum for br ca, PARP inhibitors for ov ca)
- Facilitate risk assessment for family members

Healthy women with family history of breast/ovarian cancer

- Identify women at very high risk for breast/ovarian cancer so risk-adapted screening/prevention can be initiated
- Identify women who are not at increased risk

**INTERPRETATION OF NEGATIVE TEST DEPENDS ON GROUP**

Importance of Genetic Counseling
Genetic Counseling

Crucial first step in evaluating family history of cancer

NCCN Guidelines Version 1.2017
Breast and/or Ovarian Cancer Genetic Assessment

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Cancer risk assessment and genetic counseling is highly recommended when genetic testing is offered (ie, pre-test counseling) and after results are disclosed (ie, post-test counseling). A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in the counseling of patients.
Obtain detailed family history - construct a pedigree
Determine probability that there is a genetic cause of cancer in the family
Make recommendations regarding DNA testing
Counsel on benefits and potential risks of testing (including privacy legislation)
Order and interpret DNA tests
Determine cancer risks for family members based on test results
Make recommendations for reducing cancer risk

Crucial first step in evaluating family history of cancer
BRCA1/2 TESTING CRITERIA\textsuperscript{a,b}

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious \textit{BRCA1}/\textit{BRCA2} gene mutation
- Personal history of breast cancer\textsuperscript{b} + one or more of the following:
  - Diagnosed \text\leq 45 y
  - Diagnosed \text\leq 50 y with:
    - An additional breast cancer primary\textsuperscript{c}
    - \textgeq 1 close blood relative\textsuperscript{d} with breast cancer at any age
    - \textgeq 1 close relative with pancreatic cancer
    - \textgeq 1 relative with prostate cancer (Gleason score \text\geq 7)
    - An unknown or limited family history\textsuperscript{a}
  - Diagnosed \text\leq 60 y with:
    - Triple negative breast cancer
  - Diagnosed at any age with:
    - \textgeq 2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score \text\geq 7) at any age
    - \textgeq 1 close blood relative\textsuperscript{d} with breast cancer diagnosed \text\leq 50 y
    - \textgeq 1 close blood relative\textsuperscript{d} with ovarian\textsuperscript{e} carcinoma
    - A close male blood relative\textsuperscript{d} with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (eg. Ashkenazi Jewish) no additional family history may be required\textsuperscript{f}
- Personal history of ovarian\textsuperscript{e} carcinoma
- Personal history of male breast cancer
BRCA1/2 TESTING CRITERIA

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative who has breast cancer and/or ovarian carcinoma and who has ≥2 close blood relatives with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian carcinoma
Indications for *BRCA* Testing

- 3 relatives with breast/pancreatic/prostate (Gleason ≥7) cancer at any age
- 2 cases: 1 breast cancer age ≤ 50 plus 1 breast/pancreas/prostate cancer at any age
- 1 case of breast cancer age ≤ 45 or TNBC age ≤ 60, or Jewish at any age, or bilateral breast cancer, first cancer diagnosed age ≤ 50
  OR
- 1 Male breast cancer at any age
- 1 Ovarian cancer at any age
Some Genetic Testing Rules

Goal: determine if a family is transmitting a cancer susceptibility gene

✓ If yes, then determine who in family carries the mutation
✓ Always try to start DNA testing with someone in the family who has had breast or ovarian cancer
✓ If person with cancer has negative test, don’t test relatives who have not had cancer
✓ If first person in family tested has not had breast/ovarian cancer- a negative test result is considered “uninformative”
✓ Sometimes the test result is ambiguous- “Variant of Uncertain Significance”
✓ Do not test individual under age 18
Interpretation of Negative BRCA Test

Personal history of breast/ovarian cancer

- No increased ovarian cancer risk if family hx negative for ov ca (Kauff, JNCI 2005)
- Risk of contralateral breast cancer may still be elevated- depends on age at diagnosis & family history (Shahedi, Cancer 2006; Rheim, Br Ca Res 2012; Reiner, JCO 2013)
- Do **Not** test family members unaffected by breast/ovarian cancer
- Does **NOT** exclude possibility of genetic predisposition

No personal history of breast/ovarian cancer

- True negative= known familial mutation >> No increased risk for breast/ovarian cancer
- Uninformative negative= NO known familial mutation
  - Possible family is transmitting *BRCA* but this individual did not inherit >> not at increased risk
  - Possible familial risk due to non-*BRCA* gene >> still at high risk
  - Assume still at risk, counsel using empiric risk models
  - Consider testing other family members
Breast Cancer Susceptibility Genes

High Penetrance Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cancer Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>Hereditary Breast and Ovarian Cancer (HBOC)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>HBOC (plus prostate, pancreas, melanoma)</td>
</tr>
<tr>
<td>TP53</td>
<td>Li-Fraumeni: sarcomas, breast, leukemia, adrenal, brain</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden’s: hamartomas, breast, thyroid, endometrial, colon</td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz-Jeghers: hamartomatous polyps, GI cancers, breast, pancreas, lung, Gyn,</td>
</tr>
<tr>
<td>CDH1</td>
<td>Hereditary diffuse gastric cancer: stomach, lobular br ca</td>
</tr>
</tbody>
</table>

*Mavaddat, et al. Molecular Oncology 2010, 174-191*
Breast Cancer Genes Involved in DNA Repair

Walsh T, King M-C. *Cancer Cell* 2007;11:103-105
Breast Cancer Susceptibility Genes

## Moderate Penetrance Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Minor allele frequency</th>
<th>Relative Risk</th>
<th>Fraction of Familial Risk Explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>0.003</td>
<td>2-3</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CHEK2</td>
<td>0.004</td>
<td>2-5</td>
<td>5%</td>
</tr>
<tr>
<td>BRIP1</td>
<td>0.001</td>
<td>2-3</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>PALB2</td>
<td>rare</td>
<td>2-4</td>
<td>1-3%</td>
</tr>
<tr>
<td>RAD51C</td>
<td>rare</td>
<td>?</td>
<td>1%</td>
</tr>
</tbody>
</table>

Moderate Penetrance Genes

- Individually account for a small fraction of familial risk
- Act multiplicatively with other susceptibility alleles or as modifier genes
- Cancer phenotype differs from BRCA carriers
- Risk counseling based on genotyping is challenging
Risk of breast cancer in 362 individuals with PALB2 mutation

<table>
<thead>
<tr>
<th>Age</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>
</tr>
<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>
</tr>
<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>
</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>
</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>
</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>
</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>
</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>
</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>
</tr>
</tbody>
</table>

Antoniou, NEJM 2014
Breast Cancer Susceptibility Genes

Genetic Variants that predispose to breast cancer
Multi-Gene Panel Testing

- Next generation DNA sequencing dramatically reduced cost of mutation testing
- “Panel testing” includes simultaneous analysis of multiple genes of interest
- “Phenotypic panels” = high +/- moderate penetrance genes for specific cancer type (e.g. breast, colon, etc.)
- Pan-cancer panels = all known hereditary cancer genes
- Several genetic testing companies offer various gene panels ranging from 5-48 genes
Syndromic Testing vs. Panel Testing
NCCN Statement

• Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome.

• When more than one gene can explain an inherited cancer syndrome, than multi-gene testing, may be more efficient and/or cost-effective.

• There is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility.

• Multi-gene testing are ideally offered in the context of professional genetic expertise for pre- and post- test counseling.
Challenges with Panel Testing

• Can be hard to determine actual cancer risk if mutation found in a gene causing a cancer syndrome that is not suggested by pedigree (e.g. mutation in hereditary colon cancer gene in breast cancer family).

• Not all genes included on available multi-gene tests are necessarily clinically actionable.

• It is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions.

• In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.

• “Variant of Uncertain Significance” (VUS): the more genes you analyze, the higher the rate of VUS
DNA Variants

Possible consequences
1. No change in amino acid encoded-**polymorphism**
2. Change in amino acid but no impact on protein function-polymorphism
3. Results in major disruption of protein function-**mutation** (causes disease)
<table>
<thead>
<tr>
<th>Type of Variant</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Directly contributes to the development of disease. Additional evidence is not expected to alter the classification of this variant. [Note: Not all pathogenic variants are fully penetrant.]</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Very likely to contribute to the development of disease, but scientific evidence is currently insufficient to prove this conclusively.</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Not expected to have a major effect on disease, but the scientific evidence is currently insufficient to prove this conclusively.</td>
</tr>
<tr>
<td>Benign</td>
<td>Does not cause disease. Additional evidence is not expected to alter classification of this variant.</td>
</tr>
</tbody>
</table>

Adapted from Richards et al.[6]

Variant of Uncertain Significance (VUS)

- Not rare (4-5% of BRCA testing)
- The more genes tested, the higher the chance of a VUS
- Most are actually benign polymorphisms
- Do NOT base clinical management on the presence of a VUS
- Do NOT test other family members for a VUS, unless that will help clarify pathogenicity
- Sometimes re-classified at a later date as more information becomes available
Management of BRCA Mutation Carriers

Women
- Age 18: breast self-awareness
- Age 25: begin annual breast MRI & clinical breast exam every 6-12 months
- Age 30: begin annual mammogram
- Discuss risk-reducing mastectomy
- Risk-reducing BSO (RRSO) age 35-40 after completion of child-bearing. Can consider waiting until age 40-45 in BRCA2 carriers
- “For those individuals who have not elected RRSO, transvaginal US and serum CA-125 level for ovarian cancer screening has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician’s discretion starting at age 30-35.”

Men
- Breast self exam training and annual CBE starting at age 35
- Start annual Prostate cancer screening at age 45

Both
- No specific screening guidelines exist for pancreatic cancer and melanoma, but screening may be individualized based on cancers in the family
Pancreatic Cancer Screening Guidelines

• Primary goal of screening= detect pre-invasive neoplasms that can be removed (Intraductal mucinous papillary neoplasms and pancreatic intraepithelial neoplasia)

• Recommendations for screening are primarily based on evidence of increased risk, rather than a proven efficacy of screening

• Expert opinion emphasizes the importance of performing PC surveillance in the setting of active peer-reviewed research protocols by experienced centers utilizing a multidisciplinary team approach

American College of Gastroenterology

• Screen BRCA1/2 mutation carriers with a first- or second-degree relative affected with PC (conditional recommendation; very low quality of evidence).

• Endoscopic ultrasound and/ or MRI of the pancreas annually starting at age 50 years, or 10 years younger than the earliest age of PC in the family


International Cancer of Pancreas Screening (CAPS) Consortium

• BRCA2 mutation carriers with ≥1 affected FDR or 2 affected family members.

• No consensus on age to start screening

• Initial screening should include endoscopic ultrasonography (EUS) and/or MRI/magnetic resonance cholangiopancreatography

• Disagreement on optimal intervals for follow-up imaging.

# NCCN Guidelines Version 1.2017

## Genetic/Familial High-Risk Assessment: Breast and Ovarian

### Breast and Ovarian Management Based on Genetic Test Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Screening</th>
<th>Risk-Reducing Mastectomy</th>
<th>Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATM</strong></td>
<td>Mammo age 40, <strong>consider MRI</strong></td>
<td>Consider based on family history</td>
<td>No increased risk</td>
</tr>
<tr>
<td><strong>BRIP1</strong></td>
<td>No increased risk</td>
<td>No increased risk</td>
<td><strong>Consider BSO age 45-50</strong></td>
</tr>
<tr>
<td><strong>CHEK2</strong></td>
<td>Mammo age 40, <strong>consider MRI</strong></td>
<td>Evidence insufficient, manage based on family history</td>
<td>No increased risk</td>
</tr>
<tr>
<td><strong>PALB2</strong></td>
<td>Mammo age 30, <strong>consider MRI</strong></td>
<td>Consider based on family history</td>
<td>Unknown risk</td>
</tr>
<tr>
<td><strong>RAD51C/D</strong></td>
<td>Unknown br ca risk</td>
<td>Unknown br ca risk</td>
<td><strong>Consider BSO age 45-50</strong></td>
</tr>
</tbody>
</table>
WHAT ABOUT WOMEN WITH FAMILIAL RISK BUT NEGATIVE DNA TESTING?

Quantify breast cancer risk with “empiric risk prediction models”

Management based on quantitative risk estimate
FAMILY HISTORY & BREAST CANCER RISK

Low risk cohort

Population average

Reproductive risk factors
- Atypical hyperplasia
- 1 relative breast cancer

2 relatives breast cancer

Hereditary Breast Cancer Syndrome

Lifetime risk
Management of Increased Breast Cancer Risk

<table>
<thead>
<tr>
<th>Gen Pop Risk</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>SERMs</td>
</tr>
<tr>
<td>Screening</td>
<td>Enhanced screening (e.g. MRI)</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>Genetic counseling/DNA testing</td>
</tr>
<tr>
<td></td>
<td>Prophylactic surgery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lifetime Breast Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
</tr>
<tr>
<td>10%</td>
</tr>
<tr>
<td>20%</td>
</tr>
<tr>
<td>30%</td>
</tr>
<tr>
<td>40%</td>
</tr>
<tr>
<td>50%</td>
</tr>
<tr>
<td>60%</td>
</tr>
<tr>
<td>70%</td>
</tr>
<tr>
<td>80%</td>
</tr>
</tbody>
</table>
What about families that have negative genetic testing?

Empiric Risk Models
Age of person is 47 years.
Age at menarche was 12 years.
Age at first birth was 24 years.
Person is premenopausal.

Risk after 10 years is 6.64%.
10 year population risk is 2.389%.
Lifetime risk is 20.82%.
Lifetime population risk is 8.826%.
Probability of a BRCA1 gene is 4.468%.
Probability of a BRCA2 gene is 2.041%.

Software download available at: http://www.ems-trials.org/riskevaluator/
Gail Model

- Risk factors: current age, age at menarche, age first live birth, number of first degree relatives with breast cancer, number of breast biopsies, presence of atypical hyperplasia

- Breast cancer rates specific for different ethnic/racial populations

- Predicts 5-year and lifetime risk of invasive breast cancer

- FDA criteria for chemoprevention with tamoxifen and raloxifene based on Gail score

- Available online: NCI Breast Cancer Risk Assessment Tool
Assessing Breast Cancer Risk

- BRCA mutation probability = 5%-15%
- Breast cancer risk for BRCA carrier = 50-80%

Sister: meets NCCN criteria for DNA testing >> panel testing negative

Empiric Risk Models

<table>
<thead>
<tr>
<th>Gail model</th>
<th>Claus model</th>
<th>IBIS model</th>
</tr>
</thead>
<tbody>
<tr>
<td>31%</td>
<td>32%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Age menarche = 12  G2P2
FLB = age 25  # breast biopsies = 0
Increased Risk:

Prior history of breast cancer

Women ≥35 y with 5-year Gail model risk of invasive breast cancer ≥1.7%[^d]

OR

**SCREENING OR SYMPTOM CATEGORY**  **SCREENING/FOLLOW-UP**

See NCCN Guidelines for Breast Cancer - Surveillance Section

- Clinical encounter[^a,^i] every 6–12 mo
  - to begin at the age identified as being at increased risk by Gail model
- Annual screening mammogram[^i]
  - to begin at the age identified as being at increased risk by Gail model
- Consider tomosynthesis[^a]
- Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness[^h]
Thank You!!
**BRCA testing**

- Negative sequencing
- Deletion of exon 17 on large rearrangement testing
DNA VARIANTS

Individual 1

Chr 2
copy1  ...CGATATTTCCGTATCGAATGTC...

Chr 2
copy2  ...GCTATAAGGATAGCTTACAG...

Individual 2

Chr 2
copy1  ...CGATATTTCCCATCGAATGTC...

Chr 2
copy2  ...GCTATAAGGATAGCTTACAG...

Individual 3

Chr 2
copy1  ...CGATATTTCCGTATCGAATGTC...

Chr 2
copy2  ...GCTATAAGGATAGCTTACAG...
DNA Testing of *BRCA* Genes

- **Benefits of testing:**
  - identifies women at high risk for breast and ovarian cancer,
  - informs management of women with br ca and ovarian cancer diagnosis
  - identifies women **not** at increased risk for breast/ovarian cancer

- **Limitations of testing:**
  - can only test living individuals
  - Many other breast cancer susceptibility genes exist

- **Importance of genetic counseling**
Crucial first step in evaluating family history of cancer