DEMYSTIFYING THE RISK AND GENETICS OF BREAST CANCER

Erin Hofstatter MD
Associate Professor, Yale School of Medicine
Co-Director, Smilow Cancer Genetics & Prevention Program

March 27, 2019
Disclosures

• None
Objectives

• Describe recent updates to hereditary cancer genetic testing

• Review clinical management of patients with high or moderate penetrance gene mutations

• Understand implications for breast cancer treatment and prevention
Practical Clinical Considerations for Hereditary Breast Cancer

- *What genes should I be aware of? What are the risks?*

- *Which patients should be tested? (Or re-tested?)*

- *If a gene mutation is identified, what do I do?*
  - Unaffected healthy patients (“High-Risk” clinics/Primary Care)
  - Patients with breast cancer
Practical Clinical Considerations for Hereditary Breast Cancer

• What genes should I be aware of? What are the risks?

• Which patients should be tested? (Or re-tested?)

• If a gene mutation is identified, what do I do?
  – Unaffected healthy patients (“High-Risk” clinics/Primary Care)
  – Patients with breast cancer
How much of breast cancer is hereditary?

- BRCA 1/2 account for ~50% of hereditary breast cancers
- US: BRCA 1/2 in 1:190 persons; Ashkenazi Jews 1:40
How much of breast cancer is hereditary?

- BRCA 1/2 account for ~50% of hereditary breast cancers
- US: BRCA 1/2 in 1:190 persons; Ashkenazi Jews 1:40
- Assuming 250,000 new breast cancers per year, 5% of patients = 12,500 hereditary breast cancer cases per year
Breast Cancer Susceptibility Genes and Loci

Foulkes 2008
# BRCA1/2 Breast and Ovarian Ca Risks

<table>
<thead>
<tr>
<th></th>
<th>General Population</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Cancer</strong></td>
<td>12-13%</td>
<td>55-85%*</td>
<td>50-80%</td>
</tr>
<tr>
<td><strong>Second Primary Breast Cancer</strong></td>
<td>~10% in 20 yrs</td>
<td>Up to 40-65%</td>
<td>Up to 30-40%</td>
</tr>
<tr>
<td><strong>Ovarian Cancer</strong></td>
<td>1-2%</td>
<td>15-60%</td>
<td>15-40%</td>
</tr>
</tbody>
</table>

* >60% of BRCA1-breast cancers are Triple-Negative.
### BRCA1/2 Other Cancer Risks

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>General Population</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Breast Ca</td>
<td>0.1%</td>
<td>Increased (1-2%?)</td>
<td>5-10%</td>
</tr>
<tr>
<td>Prostate Ca</td>
<td>15-20%</td>
<td>Increased</td>
<td>~30%</td>
</tr>
<tr>
<td>Pancreatic Ca</td>
<td>0.5%</td>
<td>Increased (1-3%?)</td>
<td>4-8%</td>
</tr>
</tbody>
</table>

- Possible increased risk for melanoma (cutaneous and uveal - <5%) and gall bladder/bile duct with BRCA2
# Rare High Penetrance Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Location</th>
<th>Gene Function</th>
<th>Hereditary Syndrome; Associated Cancers</th>
<th>Associated Lifetime Risk for BC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>17p13.1</td>
<td>Tumor suppressor gene (cell growth regulator)</td>
<td>Li-Fraumeni syndrome; BC, adrenocortical carcinomas, brain cancer, leukemias, sarcomas</td>
<td>90</td>
</tr>
<tr>
<td>PTEN</td>
<td>10a23.3</td>
<td>Phosphatase tension homologue; specific function unclear; mutation associated with improper cell cycle arrest</td>
<td>Cowden disease; BC, disseminated benign and malignant hamartomas, endometrial and thyroid cancers</td>
<td>~ 50</td>
</tr>
<tr>
<td>SKT-11</td>
<td>19p13.3</td>
<td>Tumor suppressor gene; associated with apoptosis; also negative regulator of mTOR pathway</td>
<td>Peutz-Jeghers syndrome; BC, ovarian, pancreatic, gastric, small intestine, and colorectal cancers</td>
<td>~ 50</td>
</tr>
<tr>
<td>CDH1</td>
<td>16q22.1</td>
<td>Epithelial cell-cell adhesion molecule</td>
<td>Hereditary diffuse gastric cancer; BC</td>
<td>39</td>
</tr>
</tbody>
</table>
Moderate Penetrance Breast Cancer Genes

- PALB2
- ATM
- CHEK2
- NBN?
- NF1?
- BARD1?
- BRIP1?
- RAD51C?
- RAD51D?
- Others (Lynch)?

Mutation prevalence ~1-10% among patients having panel testing

Tung et al 2016
Breast Cancer DNA Repair Pathways: Potential Role for Moderate Penetrance Genes
PALB2

• Partner and localizer of BRCA2
• Fanconi anemia pathway; biallelic mutations cause FA
• Prevalence: 1-3% of women with BRCA-negative breast cancer
• Risk varies based on mutation, age and family history
  – May approach BRCA2-related breast ca risk in some cases
  – 14% lifetime risk by age 50; 35% by age 70
  – 33% by age 70 with no FH; 58% if 2 1st-deg relatives
• Breast cancer prognosis may be worse than non-carriers (48% vs 75% 10-year survival)
• Possible increased risk of pancreatic ca; risk of male breast, ovarian and prostate cancers unclear
Table 4. Risk of Breast Cancer for Female PALB2 Mutation Carriers, According to Family History of Breast Cancer.

| Age | Mean Estimate without Family History Taken into Account | Mother Unaffected at 50 Yr of Age, Maternal Grandmother Unaffected at 70 Yr of Age
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>percent</td>
<td></td>
</tr>
<tr>
<td>30 yr</td>
<td>0.4 (0.3–0.7)</td>
<td>0.3 (0.2–0.6)</td>
</tr>
<tr>
<td>35 yr</td>
<td>2 (1.0–2.4)</td>
<td>1 (0.9–2.2)</td>
</tr>
<tr>
<td>40 yr</td>
<td>4 (3–6)</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>45 yr</td>
<td>8 (5–12)</td>
<td>7 (5–11)</td>
</tr>
<tr>
<td>50 yr</td>
<td>14 (9–20)</td>
<td>13 (8–18)</td>
</tr>
<tr>
<td>55 yr</td>
<td>20 (14–28)</td>
<td>19 (13–26)</td>
</tr>
<tr>
<td>60 yr</td>
<td>26 (19–35)</td>
<td>24 (18–33)</td>
</tr>
<tr>
<td>65 yr</td>
<td>31 (23–42)</td>
<td>29 (22–39)</td>
</tr>
<tr>
<td>70 yr</td>
<td>35 (26–46)</td>
<td>33 (25–44)</td>
</tr>
<tr>
<td>75 yr</td>
<td>40 (30–51)</td>
<td>38 (28–48)</td>
</tr>
<tr>
<td>80 yr</td>
<td>44 (34–55)</td>
<td>41 (32–53)</td>
</tr>
</tbody>
</table>

Breast-Cancer Risk in Families with Mutations in PALB2

ATM

• Ataxia-telangiectasia mutated

• Biallelic mutations cause Ataxia-telangiectasia (AT)
  – Characterized by childhood onset progressive cerebellar neurodegeneration, ataxia, telangiectasia, immunodeficiency, sensitivity to ionizing radiation, predisposition to cancer (esp. lymphoma and leukemia)

• U.S. Population carrier frequency is ~3% among Caucasians
ATM: Cancer Risks

- Meta-analysis of three cohort studies of relatives with AT
  - RR 2.8 (90% CI 2.2-3.7, p<0.001)
- Cumulative lifetime breast cancer risk of about 30% (and 6% to age 49)
- Risk may vary by specific mutation: c.7271T>G missense mutation
  - 69% risk by age 70
  - HR 8.0 (95% CI 2.3-27.4, p<0.001)
- No definitive increased risk for contralateral breast cancer, ovarian, pancreatic or other cancers
- No definitive risk of XRT

Easton et al NEJM 2015
vanOs et al Clin Genet 2016
Goldgar et al Br Cancer Res 2011
CHEK2

- Cell cycle checkpoint kinase 2
- Associated with the DNA damage repair response Fanconi anemia (FA)-BRCA pathway
- Best characterized mutation is 1100delC, common in individuals of Northern and Eastern European ancestry (~0.7% carrier frequency)
  - Lifetime cumulative risk of breast cancer to age 49 = 6%; to age 80 = 32%
  - Possible increased risk of colon cancer (12% lifetime risk vs 6% gen pop)
- Missense variant I157T
  - Cumulative lifetime risk of breast cancer to age 49=3%; to age 80 = 18 percent
- Possible increased risk of male breast cancer, stomach, prostate, kidney, and thyroid cancer and sarcoma

Walsh et al JAMA 2006
Tung et al 2016
Moderate Penetrance Breast Cancer Genes

- PALB2
- ATM
- CHEK2
- NBN?
- NF1?
- BARD1?
- BRIP1?
- RAD51C?
- RAD51D?
- Others (Lynch)?

RR ~2-fold, if at all
Challenges in Interpreting Positive Results for a Moderate Penetrance Gene

• Specific germline finding may or may not explain the occurrence of breast cancer in a patient or family

• Classic familial phenotypes do not predict for all moderate penetrance genes

• Risk estimates continue to change
  – BARD1, RAD51C and D, BRIP1
Challenges in Interpreting Negative Results

• VUS not clinically useful; go back to FH for management

• Cascade testing of family members and “True Negatives”
  – “True negative”-population risk has still not been proven to be equal to “average risk” with most moderate penetrance genes ➔ go back to FH to determine management
  – BOTTOM LINE: Relatives who test negative for a moderate penetrance gene mutation may NOT be average risk (PALB2 as possible exception)
Cancer Genetic Counseling

• Complete 3-generation family history
• Best test to send
• Insurance navigation: Health, life insurance
• Test interpretation in context of pedigree
• Up to date with changing risk estimates and management recommendations
• Coordinates testing for family members
• VUS reclassification follow-up
**Metastatic breast cancer, considering PARP**

**Somatic tumor testing NOT a substitute for germline testing**
BRCA 1/2 Large deletion/duplications

- Accounts for ~10% of all BRCA 1/2 mutations
- Appears more common in Hispanic and Middle Eastern descent
- NOT detected by regular sequencing
- Not clinically available until ~2007
- NOT done in most cases between 2007 and 2013
- Listed on test results as “duplication/deletion” or “comprehensive large rearrangement” (called BART by Myriad Genetics)

- BOTTOM LINE: Patients who were tested prior to 2013 probably need updating
Gaps in Receipt of Clinically Indicated Genetic Counseling After Diagnosis of Breast Cancer

Steven J. Katz, Kevin C. Ward, Ann S. Hamilton, M. Chandler Mcleod, Lauren P. Wallner, Monica Morrow, Reshma Jagsi, Sarah T. Hawley, and Allison W. Kurian

Among 1,711 patients with *early stage breast cancer* who met NCCN BRCA testing guidelines only 53% were actually tested.
Consensus Guideline on Genetic Testing for Hereditary Breast Cancer

1. **Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing.** When the patient’s history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes.

2. **Genetic testing should be made available to all patients with a personal history of breast cancer.** Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies.
Practical Clinical Considerations for Hereditary Breast Cancer

• What genes should I be aware of? What are the risks?

• Which patients should be tested? (Or re-tested?)

• If a gene mutation is identified, what do I do?
  – Unaffected healthy patients (“High-Risk” clinics/Primary Care)
  – Patients with breast cancer
Risk Management Options for Hereditary Breast Cancer Syndromes

• Screening
• Risk Reduction
  – Risk Reducing Surgery
  – Chemoprevention
  – Lifestyle
Management Considerations: Key Points

• One size does NOT fit all!
• Management should be tailored to the patient
  – Age
  – Overall short and long term risks of breast cancer
  – Affected or unaffected with cancer
  – Other competing risks
• What are the risks/benefits of the options?
• What is the patient’s understanding of these risks/benefits (ie QOL vs quantity of life)? What are the patient’s goals?
• Patient goals and values may change over time

• There is no “right” answer in many/most cases!
# Breast and Ovarian Management Based on Genetic Test Results

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetration genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Increased risk of breast cancer</td>
<td>Potential increase in ovarian cancer risk, with insufficient evidence for recommendation of RRSO</td>
<td>Unknown or insufficient evidence for pancreas or prostate cancer</td>
</tr>
<tr>
<td>• Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• RRM: Evidence insufficient, manage based on family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>Increased risk of breast cancer</td>
<td>Increased risk of ovarian cancer</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>• See BRCA Pathogenic Variant-Positive Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>Increased risk of breast cancer</td>
<td>Increased risk of ovarian cancer</td>
<td>Pancreas, Prostate, Melanoma</td>
</tr>
<tr>
<td>• See BRCA Pathogenic Variant-Positive Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td>Unknown or insufficient evidence</td>
<td>Increased risk of ovarian cancer</td>
<td>N/A</td>
</tr>
<tr>
<td>• Consider RRSO at 45–50 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td>Increased risk of lobular breast cancer</td>
<td>No increased risk of ovarian cancer</td>
<td>Diffuse gastric cancer</td>
</tr>
<tr>
<td>• Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• RRM: Evidence insufficient, manage based on family history</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| RRM: Risk-reducing mastectomy |
| RRSO: Risk-reducing salpingo-oophorectomy |

**Footnotes on GENE-6**

**Continued**
BRCA Breast Cancer Screening Recommendations: NCCN

• Mammogram and Breast MRI
  – Each done annually; often alternated every 6 months
  – Screening usually starts at age 25, or individualized based on earliest age of onset in family
  – Age 25-29: Annual breast MRI with contrast
    • Due to concerns about possibility of diagnostic radiation exposure increasing breast ca risk in young women
  – Age 30-75: Annual mammogram and annual breast MRI
  – Age >75: Individualize management

• Clinical Breast Exam
  – Every 6-12 months starting at age 25
BRCA Ovarian Cancer Screening Recommendations: NCCN

• “Consider at clinician’s discretion”
• Pelvic ultrasound and CA 125 blood test
  – Every 6-12 months
  – Starting at age 30-35, or individualized based on earliest age of onset in family
• Uncertain benefit (i.e., not proven to catch disease early and save lives)
• NOT a substitute for surgery
• Risks: False positives vs false reassurance
• Some major institutions don’t recommend it at all
BRCA Other Cancer Screening Recommendations: NCCN

BRCA MUTATION-POSITIVE MANAGEMENT

MEN
- Breast self-exam training and education starting at age 36 y
- Clinical breast exam, every 12 mo, starting at age 35 y
- Starting at age 45 y: (See Guidelines for Prostate Early Detection)
  » Recommend prostate cancer screening for BRCA2 carriers
  » Consider prostate cancer screening for BRCA1 carriers

MEN AND WOMEN
- Education regarding signs and symptoms of cancer(s), especially those associated with BRCA gene mutations.
- No specific screening guidelines exist for pancreatic cancer and melanoma, but screening may be individualized based on cancers observed in the family.

- Risks of pancreatic cancer and melanoma are higher for BRCA2 than BRCA1
- Melanoma: Annual full-body Skin exam and eye exam
- Pancreatic cancer: CAPS-5 study (annual endoscopic ultrasound and abdominal MRI);
  Eligibility requires a FH pancreatic cancer
Risk Reducing Mastectomies (RRM)

NCCN: “Discuss option of RRM”
• Degree of protection, reconstruction options, and risks. Consider FH and residual breast cancer risk with age and life expectancy

• Pros
  – Most effective way to reduce the risk of developing a breast cancer → reduces risk by >90%
  – No screening imaging needed! (Silicone implants get checked by noncontrast MRI or us every 2-5 years)
  – Nipple sparing considered safe

• Cons
  – Big surgery! Recovery and time off work/childcare
  – Cosmetics sometimes an issue
    • Can take 6-12 months to get the “tweaking” done
  – Diminished/absent nipple and breast sensation
  – Body image/intimacy issues
BRCA and RRM

- What is the “right” thing to do?
  - There is no “magic age”…but probably not ideal for a 25 yo or a 75 yo
  - Absolute benefits diminish with age!
  - Patient understanding of goals needs to be made clear:
    - “I'll just wait until I get a breast cancer…”
    - “I have breast cancer, so I want to do as much as I can to survive.”
  - In my own practice, I lean more heavily on younger BRCA1 carriers for RRM→Data suggests survival benefit; morbidity of TNBC tmt

Chen and Parmigiani 2007
Risk Reducing Bilateral Salpingo-Oophorectomy (RRBSO) for BRCA Carriers

- Recommended by age 35-40, once childbearing is complete, or earlier based on age of onset of ovarian ca in relatives
- Recent guidelines suggest that BRCA2 carriers can reasonably wait until age 40-45
- Associated with ~80% reduction in risk of ovarian, fallopian tube, or peritoneal cancer

- Several studies suggest a breast cancer risk reduction by ~50% following BSO
  - Some academics are critical of statistical methods and cohort selection of prior studies; benefit may be overstated and depend on age and mutation
Other RRSO Considerations

• Salpingectomy alone
  – Under investigation; not yet a standard of care

• Hysterectomy in BRCA1
  – 1.1% risk of aggressive serous uterine carcinoma at 10 years in BRCA1 carriers; not yet a standard of care

• HRT after BSO
  – Generally considered safe up to the time of natural menopause; I recommend it
  – Risks (if any) appear higher with combined HRT vs E alone

PROSE Study Group 2011; Kotsopoulos et al, JAMA Oncology May 2018
BRCA Risk Reduction Options

• Chemoprevention
  – SERM or AI for Breast cancer Prevention
    • Data is limited for BRCA; can be offered
  – OCPs for Ovarian cancer prevention:
    • 5 years: 60% risk reduction; 10 years: 80% risk reduction
    • Data are conflicting over OCPs and breast cancer risk; generally felt that pros outweigh cons
    • Controversy: How much benefit from OCPs in women who opt for BSO at age 40 anyway?

• Lifestyle counseling
Other High Penetrance Genes

- CDH1
- PTEN (Cowden syndrome)
- STK11 (Peutz Jeghers syndrome)
- TP53 (Li Fraumeni syndrome)

Breast cancer screening and risk reduction approach generally similar to BRCA
  - TP53: Annual Breast MRI starts age 20

Specific NCCN (and other) guidelines exist for each syndrome
Moderate Penetrance Breast Cancer Genes

• PALB2
• ATM
• CHEK2

• NBN?
• NF1?
• BARD1?
• BRIP1?
• RAD51C?
• RAD51D?
• Others?
### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

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<tr>
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<th>Other Cancer Risks and Management</th>
</tr>
</thead>
</table>
| **ATM** | Increased risk of breast cancer  
- Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y f  
- RRM: Evidence insufficient, manage based on family history | Potential increase in ovarian cancer risk, with insufficient evidence for recommendation of RRSO | Unknown or insufficient evidence for pancreas or prostate cancer |
| **BARD1** | Potential increase in breast cancer risk, with insufficient evidence for management recommendations | Unknown or insufficient evidence for ovarian cancer risk | N/A |
| **BRCA1** | Increased risk of breast cancer  
- See BRCA Pathogenic Variant Positive, Management | Increased risk of ovarian cancer  
- See BRCA Pathogenic Variant Positive, Management | Prostate cancer  
- See BRCA Pathogenic Variant Positive, Management |
| **BRCA2** | Increased risk of breast cancer  
- See BRCA Pathogenic Variant Positive, Management | Increased risk of ovarian cancer  
- See BRCA Pathogenic Variant Positive, Management | Pancreas, Prostate, Melanoma  
- See BRCA Pathogenic Variant Positive, Management |
| **BRIP1** | Unknown or insufficient evidence | Increased risk of ovarian cancer  
- Consider RRSO at 45–50 y | N/A |
| **CDH1** | Increased risk of lobular breast cancer  
- Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y f  
- RRM: Evidence insufficient, manage based on family history | No increased risk of ovarian cancer | Diffuse gastric cancer  
- See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer |

**RRM:** Risk-reducing mastectomy  
**RRSO:** Risk-reducing salpingo-oophorectomy

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**Footnotes on GENE-6**

**Continued**
# NCCN Guidelines Version 2.2019
Genetic/Familial High-Risk Assessment: Breast and Ovarian

## BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

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</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td>Increased risk of breast cancer • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y+ • RRM: Evidence insufficient, manage based on family history</td>
<td>No increased risk of ovarian cancer</td>
<td>Colon: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td>MSH2, MLH1, MSH6, PMS2, EPCAM</td>
<td>Unknown or insufficient evidence for breast cancer risk • Manage based on family history</td>
<td>Increased risk of ovarian cancer • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
<td>Colon, Uterine, Others: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td>NF1</td>
<td>Increased risk of breast cancer • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 30 y+ • RRM: Evidence insufficient, manage based on family history</td>
<td>No increased risk of ovarian cancer</td>
<td>Colon, peripheral nerve sheath tumors, GI/GIST, others: Malignant peripheral nerve sheath tumors, GI/GIST: specialist for evaluation and management</td>
</tr>
<tr>
<td>Comments: All this time, there are no data to suggest an increased breast cancer risk after age 50 y+ Screening recommendations only apply to individuals with a clinical diagnosis of NF. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.</td>
<td></td>
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</tr>
</tbody>
</table>

**RRM: Risk-reducing mastectomy**

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**Footnotes on GENE-5**

**Continued**
BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS\(^{a,d}\)

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<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
</table>
| **PALB2** | Increased risk of breast cancer  
- Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y  
- RRMI: Evidence insufficient, manage based on family history | Unknown or insufficient evidence for ovarian cancer risk | Unknown or insufficient evidence |
| **Comments**: Counsel for risk of autosomal recessive condition in offspring. | | |
| **PTEN** | Increased risk of breast cancer  
- See Cowden Syndrome Management | No increased risk of ovarian cancer | See Cowden Syndrome Management |
| **RAD51C** | Unknown or insufficient evidence for breast cancer risk  
- Consider RRMI at 45-50 y | Increased risk of ovarian cancer | N/A |
| **Comments**: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in RAD51C appears to be sufficient to justify consideration of RRMI. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45-50 y or earlier based on a specific family history of an earlier onset ovarian cancer. | | |
| **RAD51D** | Unknown or insufficient evidence for breast cancer risk  
- Consider RRMI at 45-50 y | Increased risk of ovarian cancer | N/A |
| **Comments**: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in RAD51D appears to be sufficient to justify consideration of RRMI. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45-50 y or earlier based on a specific family history of an earlier onset ovarian cancer. | | |
| **STK11** | Increased risk of breast cancer  
- Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment, Colorectal  
- RRMI: Evidence insufficient, manage based on family history | Increased risk of non-epithelial ovarian cancer  
- See NCCN Guidelines for Genetic/Familial High-Risk Assessment, Colorectal | See NCCN Guidelines for Genetic/Familial High-Risk Assessment, Colorectal |
| **TP53** | Increased risk of breast cancer  
- See Li-Fraumeni Syndrome Management | No increased risk of ovarian cancer | See Li-Fraumeni Syndrome Management |

RRMI: Risk reducing mastectomy  
RRSO: Risk-reducing salpingo-oophorectomy

Footnotes on GENE-5

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Clinical Management of **AFFECTED** Patients with Hereditary Breast Cancer Syndromes
Surgical Considerations: Risk-reducing prophylactic mastectomies and BRCA 1/2-related breast cancer

• Patients with Breast cancer
  – Decision should be based on:
    1. Risk of cancer recurrence
       • Similar outcomes stage for stage for BRCA carriers vs non-carriers
       • No evidence to suggest increased risks from XRT for BRCA carriers**
    2. Future risk of contralateral new primary breast cancer
    3. Patient preference
       • Symmetry
       • Screening
       • Quality of life

**TP53: Mastectomies recommended due to possible increased risks with XRT
<table>
<thead>
<tr>
<th></th>
<th>General Population</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>12-13%</td>
<td>55-85%</td>
<td>50-80%</td>
</tr>
<tr>
<td>Second Primary</td>
<td>~10% in 20 yrs</td>
<td>Up to 40-65%</td>
<td>Up to 30-40%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>1-2%</td>
<td>15-60%</td>
<td>15-40%</td>
</tr>
</tbody>
</table>

BRCA1/2 Breast and Ovarian Ca Risks
BRCA Risks of 2\textsuperscript{nd} Breast Cancer

• Risk of CBC depends on patient age at time of 1\textsuperscript{st} diagnosis

• Graeser et al, JCO 2009
  – Risks of CBC diminish substantially if first breast cancer is diagnosed > age 50, esp for BRCA1
  – BRCA1 < age 40: 25 year risk of CBC = 62.9%
  – BRCA1 > age 50: 25 year risk of CBC = 19.6%

• Menes et al Br Ca Res Treat 2015
  – 10-year incidence of a second primary breast cancer in \textit{BRCA1} = 17%, even higher estimates in those first diagnosed < age 40 = 21%
  – Lower rates were found in BRCA2 mutation carriers = 7% CBC risk over 10 years
Surgical Considerations: Risk-reducing prophylactic mastectomies and BRCA 1/2-related breast cancer

- RRSO may lower CBC risk
- Use of Tamoxifen/AI may lower CBC risk
- No evidence to suggest RRM improves overall survival!
- RRM remains the best way to prevent a CBC
Surgical Considerations: Risk-reducing prophylactic mastectomies and Moderate Penetrance Genes

• Risk of recurrence
  – No data to suggest that moderate risk genes confer worse breast cancer outcomes
  – Specific discussion about goals of surgery should be made clear to patient prior to surgery: RRM is unlikely to confer survival benefit
Surgical Considerations: Risk-reducing prophylactic mastectomies and Moderate Penetrance Genes

• Future risk of contralateral disease
  – Data is lacking for moderate penetrance genes
  – Counsel about RRM similar to other patients with FH or LCIS
  – Those patients on endocrine therapy may already be reducing risk of new 2nd primary breast cancer by 50%
Synthetic Lethality = Complementary Lethality
Molecular defects that individually are not lethal, become lethal when they occur together

BRCA and Platinums

Bottom Line: Data is suggestive but not yet definitive

- Byrski et al JCO 2010:
  - Neoadjuvant cisplatin in BRCA1+ carriers → 83% pCR rate (10/12 patients) as compared with 11 of 51 (22 percent) of those treated with anthracycline-based regimens

- GeparSixto 2014 analysis/CALGB 40603 2014 analysis:
  - Higher pCR rates in TNBC randomized to receive platinum chemotherapy in addition to anthracycline-based therapy (versus anthracycline-based therapy alone)
  - The only consistent factor predicting benefit from platinum agents was BRCA status

- TNT Trial 2014:
  - Phase III trial randomly assigned 376 patients with metastatic breast cancer with either germline BRCA mutations or triple-negative breast in the first-line setting to treatment with either carboplatin or docetaxel.
  - Overall, no difference in outcome was found, but for the 43 patients with a BRCA mutation, the objective response rate with carboplatin was 68% as compared with only 30% with docetaxel.
Clinical trial results with PARP inhibitors in germline BRCA mutant breast cancers

• Phase III trial results
  – Olaparib
  – Talazoparib

• Other PARPi in clinical trials
  – Niraparib
  – Veliparib
  – Rucaparib
Primary endpoint
• Progression-free survival

Secondary endpoints
• Overall survival (OS)
• ORR by investigator
• Safety
• Quality of life (EORTC QLQ-C30)

Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

Metastatic HER2-negative breast cancer and a germline BRCA1 or BRCA2 mutation with up to 2 prior chemotherapies for MBC

Stratification factors:
• Prior chemo regimens (yes vs no)
• TNBC or hormone receptor positive (HR+)

Olaparib 300 mg PO BID

N=302 Randomized 2:1

Physician’s choice of: Vinorelbine Capecitabine Eribulin
OlympiAD Trial
Olaparib versus Chemotherapy of Physicians’ Choice in gBRCA-Associated Metastatic Breast Cancer
Progression-Free Survival

PFS: 7.0 s vs. 4.2 months

Objective Response rate:
60% vs. 29%

US FDA approved olaparib to treat germline BRCA mutant metastatic breast cancer on Jan 12, 2018
OlympiAD Trial

Overall Survival

Overall Survival over time, with a comparison between Olaparib (N=205) and Standard therapy (N=97). The hazard ratio is 0.90 (95% CI, 0.63–1.29) with a P-value of 0.57.

Robson et al, NEJM 2017
EMBRACA Trial
A phase 3 trial of talazoparib versus physician’s choice chemotherapy in germline \textit{BRCA}-mutated metastatic breast cancer

Locally advanced or metastatic HER2-negative breast cancer and a germline \textit{BRCA1} or \textit{BRCA2} mutation

Stratification factors:
- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

Primary endpoint
- Progression-free survival

Secondary endpoints
- Overall survival
- ORR by investigator
- Safety

Exploratory endpoints
- Duration of response
- Quality of life EORTC QLQ-C30, QLQ-BR23

Talazoparib
1 mg PO daily

Physician’s choice of:
- Vinorelbine
- Capecitabine
- Eribulin
- Gemcitabine

N=431
Randomized 2:1

Litton et al, SABCS 2017; GS6-07
EMBRACA
PFS by Blinded Central Review

<table>
<thead>
<tr>
<th></th>
<th>TALA (n = 287)</th>
<th>Overall PCT (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, no. (%)</td>
<td>186 (65%)</td>
<td>83 (58%)</td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>8.6 (7.2, 9.3)</td>
<td>5.6 (4.2, 6.7)</td>
</tr>
<tr>
<td>Hazard ratio, 95% CI</td>
<td>0.54, 0.71</td>
<td>0.41, 0.71</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .0001</td>
<td></td>
</tr>
</tbody>
</table>

Objective response rate: 63% vs 27%

Litton et al, SABCS 2017; GS6-07
Clinical summary

• Compared to chemotherapy, both olaparib and talazoparib significantly improved:
  – Progression free survival
  – Overall tumor response rate
  – Time to deterioration of quality of life
  – BUT, with higher rates of anemia, grade 1/2 nausea, thrombocytopenia

• Olaparib is currently FDA approved
• Talazoparib just FDA approved October 2018
• Remaining unanswered questions:
  – Do PARPi also work in germline BRCA normal or somatic BRCA mutant/BRCA-like metastatic breast cancers?
  – What are the best partners for combination therapy (e.g. Platinum? Immunotherapy?)
  – Impact on survival of MBC?
  – Will PARPi increase cure rates in early stage gBRCA mutant breast cancers?
PARP Inhibitors: Selected ongoing trials

BRAVO: Phase 3 Niraparib vs chemo gBRCA 1/2 metastatic breast cancer

NSABP B-55: OlympiA: Olaparib in adjuvant gBRCA setting

TBCRC 048: “Olaparib Expanded”
- Tests olaparib in metastatic patients with other germline mutations in DNA repair genes
- Tests olaparib in metastatic patients with somatic mutations in BRCA and other DNA repair genes

VIOLETTE: olaparib +/- ATR or WEE-1 inhibitors
- Tests olaparib combinations in patients with gBRCA or other germline/somatic mutations in DNA repair genes in metastatic TNBC

SWOG1416: Cisplatin +/- veliparib
- Tests cisplatin with or without veliparib in metastatic triple negative breast cancer either (i) germline BRCA positive or (ii) somatic “BRCA-like” cancers

PARP + Immuno Oncology Combinations
- Niraparib + pembrolizumab
- Olaparib + durvalumab
Practical Clinical Considerations for Hereditary Breast Cancer

• *What genes should I be aware of? What are the risks?*

• *Which patients should be tested? (Or re-tested?)*

• *If a gene mutation is identified, what do I do?*
  – Unaffected healthy patients (“High-Risk” clinics/Primary Care)
  – Patients with breast cancer
Summary: Tailor your Recommendations to Your Patient!

• One size does NOT fit all!
• NCCN is an excellent resource, updated frequently given ever-changing risk data
• Have a low threshold to refer for genetic counseling, including especially metastatic breast cancer patients (Two PARPi now FDA-approved!)
• Management should be tailored to the patient
  – Age
  – Overall short and long term risks of breast cancer
  – Affected or unaffected with cancer
  – Other competing risks
• What is the patient’s understanding of these risks/benefits (ie QOL vs quantity of life)? What are the patient’s goals?
• Usually no “right” answer in most cases…
Questions & Comments

• Thank you!

• Contact: erin.hofstatter@yale.edu