Genetic counseling and testing

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ESMO Breast Cancer Preceptorship – June 2019
Disclosures

Roche: Speakers bureau, honoraria, consultancy
Astra Zeneca: Speakers bureau, honoraria, consultancy
Novartis: Speakers bureau, honoraria, consultancy
Pfizer: Speakers bureau, honoraria, consultancy
Nanostring: Speakers bureau, honoraria
Teva: Speakers bureau, honoraria
Cancer Arises From Gene Mutations

Germline mutations

- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Somatic mutations

- Occur in nongermline tissues
- Are nonheritable

Mutation in egg or sperm

All cells affected in offspring

Somatic mutation (e.g., lung)
Cancer can cluster in families because of shared environmental exposures (diet, lifestyle, "environment", work related exposures).

Those 15-20% referred to as “familial”, may be caused by the interaction of low-penetrance genes, gene-environment interaction, or both.
Hereditary cancers

- Multiple affected family members
- Early onset
- Bilateral BC or multiple primaries
- Clustering in family of diseases suggestive of a hereditary cancer syndrome
- Extensive family history

Risk for cancer is HIGH

Familial Cancer

- Occurring in or affecting more members of family than would be expected by chance
- Generally, two or more family members with the same type of cancer, age appropriate

Risk for cancer is MODERATE

Sporadic cancers

- Age appropriate
- Common cancers

Risk for cancer is AVERAGE
BRCA1/2 Mutations
BRCA1 and BRCA2

• Cloned in families with multiple cases of breast and/or ovarian cancer

BRCA1- cloned 1994  
BRCA2- cloned 1995
Prevalence

In unselected populations - 1/300-1/800.

Founder mutations:

Iceland - BRCA2 999del5 - 0.6% (~1/170)

Ashkenazi Jews -

BRCA1 - 185del AG 1%

5382insC  0.1%

BRCA2 - 6174delT 1.4%

2.5% (1/40)
## The prevalence of BRCA1/BRCA2 mutations: Contribution to cancer

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Non-selected population</th>
<th>Ashkenazi Jewish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>2.5-5%</td>
<td>~11%</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>10-15%</td>
<td>~40%</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>?</td>
<td>~8%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>?</td>
<td>~5%</td>
</tr>
</tbody>
</table>
Cancer susceptibility genes other than \( BRCA1/2 \)

<table>
<thead>
<tr>
<th>Cancer Susceptibility Gene</th>
<th>Breast Cancer RR (90% CI when available) or Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast ATM</td>
<td>2.8 (2.2 to 3.7)(^{35})</td>
</tr>
<tr>
<td>Breast BARD1</td>
<td>Breast cancer association reported; RR not yet determined(^{17,46,47})</td>
</tr>
<tr>
<td>BRIP1</td>
<td>2.0 (1.3 to 3.0)(^{48}), ovarian cancer RR 11.2(^{9})</td>
</tr>
<tr>
<td>CDH1</td>
<td>6.6 (2.2 to 19.9)(^{49})</td>
</tr>
<tr>
<td>CHEK2</td>
<td>3.0 (2.6 to 3.5)(^{35}); most data for 1100delC</td>
</tr>
<tr>
<td>NBN</td>
<td>2.7 (1.9 to 3.7)(^{35})</td>
</tr>
<tr>
<td>PALB2</td>
<td>5.3 (3.0 to 9.4)(^{35})</td>
</tr>
<tr>
<td>PTEN</td>
<td>RR 2.0-5.0(^{50,51})</td>
</tr>
<tr>
<td>STK11</td>
<td>RR 2.0-4.0(^{52,53})</td>
</tr>
<tr>
<td>TP53</td>
<td>105 (62 to 165)(^{35})</td>
</tr>
</tbody>
</table>

Tung et al JCO 2016
Prevalence of BRCA1/2 mutation amongst Breast Cancer patients

### Table 4. Frequency of Deleterious Mutations by Age at Breast Cancer Diagnosis

<table>
<thead>
<tr>
<th>Genes</th>
<th>Patients ≤ 45 Years of Age</th>
<th>Patients 46-60 Years of Age</th>
<th>Patients &gt; 60 Years of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
<td>No.</td>
</tr>
<tr>
<td><strong>Any deleterious mutation</strong></td>
<td>30</td>
<td>16.7 (11.5 to 22.9)</td>
<td>15</td>
</tr>
<tr>
<td>Genes related to breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>BRCA1 or BRCA2</em></td>
<td>29</td>
<td>16.1 (11.1 to 22.3)</td>
<td>14</td>
</tr>
<tr>
<td><em>BRCA1</em></td>
<td>22</td>
<td>12.2 (7.8 to 17.9)</td>
<td>6</td>
</tr>
<tr>
<td><em>BRCA2</em></td>
<td>15</td>
<td>8.3 (4.7 to 13.4)</td>
<td>2</td>
</tr>
<tr>
<td><em>CHEK2</em></td>
<td>7</td>
<td>3.9 (1.6 to 7.9)</td>
<td>4</td>
</tr>
<tr>
<td>Other genes related to breast cancer</td>
<td>8</td>
<td>4.4 (1.9 to 8.6)</td>
<td>8</td>
</tr>
<tr>
<td><em>ATM</em></td>
<td>3</td>
<td>1.7 (0.4 to 4.8)</td>
<td>1</td>
</tr>
<tr>
<td><em>BRIPT</em></td>
<td>1</td>
<td>0.6 (0.01 to 3.1)</td>
<td>2</td>
</tr>
<tr>
<td><em>CHEK2</em></td>
<td>4</td>
<td>2.2 (0.6 to 5.6)</td>
<td>3</td>
</tr>
<tr>
<td><em>NBN</em></td>
<td>0</td>
<td>0.0 (0.0 to 2.0)</td>
<td>1</td>
</tr>
<tr>
<td><em>PALB2</em></td>
<td>1</td>
<td>0.6 (0.01 to 3.1)</td>
<td>0</td>
</tr>
<tr>
<td><em>PTEN</em></td>
<td>0</td>
<td>0.0 (0.0 to 2.0)</td>
<td>1</td>
</tr>
<tr>
<td>Genes not clearly related to breast cancer</td>
<td>2</td>
<td>1.1 (0.1 to 4.0)</td>
<td>1</td>
</tr>
<tr>
<td><em>MSH6</em></td>
<td>0</td>
<td>0.0 (0.0 to 2.0)</td>
<td>1</td>
</tr>
<tr>
<td><em>PMS2</em></td>
<td>1</td>
<td>0.6 (0.01 to 3.1)</td>
<td>0</td>
</tr>
<tr>
<td><em>RAD51C</em></td>
<td>0</td>
<td>0.0 (0.0 to 2.0)</td>
<td>0</td>
</tr>
<tr>
<td><em>RAD51D</em></td>
<td>1</td>
<td>0.6 (0.01 to 3.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Tung et al JCO 2016
When to refer for onco-genetic counseling & testing?
Germline Genetic Testing for Breast Cancer Patients

• Why test?
• Who to test?
• What should we test?
• How to test?
• What are the results and yield of testing?
Why perform genetic testing?

**Affected women (breast or ovarian cancer)**

- Prevent additional cancers (ovarian, contralateral breast)
- Enable testing in relatives

**Therapeutic implications** – chemotherapy, radiotherapy, targeted therapy (incl. clinical trials), extent of surgery

**Therapeutic implications are a game changer:**
Timeline; Scope of testing: patients & genes

**Unaffected women**

- Prevent breast & ovarian cancer (in carriers)
- Avoid unnecessary prevention/surveillance measures (in non-carriers)
- Enable testing in relatives
Who should we test for gBRCA mutations?

• From classical genetics to genetically-driven precision medicine...

• **Current guidelines** (historical target: 10% tested positive; use family history, male cancer, ovarian cancer, TNBC < 50 or 60, age < 40, askenazi descent) identify only part of the carriers

• **Risk-benefit** of testing to be re-estimated provided targeted therapeutic benefit is relevant

What is risk?? VUS, cost...

Courtesy of Karen Gelmon
NCCN Guidelines Version 2.2019
Breast and/or Ovarian Cancer Genetic Assessment

CRITERIA FOR FURTHER GENETIC RISK EVALUATION

- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene within the family, including such variants found on research testing.
- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene found on tumor testing. (See BR/OV-A 3 of 3)
- An individual diagnosed at any age with any of the following:
  - Ovarian cancer
  - Pancreatic cancer
  - Metastatic prostate cancer
  - Breast cancer or high-grade (Gleason score ≥7) prostate cancer and of Ashkenazi Jewish ancestry
- An individual with a breast cancer diagnosis meeting any of the following:
  - Breast cancer diagnosed age ≤50 y
  - Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed age ≤60 y
  - Two breast cancer primaries
  - Breast cancer at any age, and:
    - ≥1 close blood relative with:
      - breast cancer age ≤50 y; or
      - invasive ovarian cancer; or
      - male breast cancer; or
      - pancreatic cancer; or
      - high-grade (Gleason score ≥7) or metastatic prostate cancer
    - ≥2 close blood relatives with breast cancer at any age

The criteria for further risk evaluation and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

Irrespective of degree of relatedness.

Includes fallopian tube and primary peritoneal cancers. BRCA-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome. (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence.

Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.

Close blood relatives include first-, second-, and third-degree relatives. (See BR/OV-E).

When possible, genetic testing should be performed first on an affected family member.

For dermatologc manifestations, see COVID-1.

For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

Consider referral to cancer genetics professional. See Assessment (BR/OV-2).

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.
BRCA1/2 TESTING CRITERIA

- **BRCA1/2 pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis**

- Regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment.

- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood relative meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

For further details regarding the nuances of genetic counseling and testing, see BRCA1/2.

Irrespective of degree of relatedness.

For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.

Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BRCA1/2).

Secondary tumor including non-mammary tumors. The specific types of non-epithelial ovarian tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with atypical adenomatous hyperplasia and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.
NICE Guidelines (UK) June 2013

• Carrier probability at which genetic testing should be offered

• **Breast/ovarian cancer cases** with combined *BRCA1/BRCA2 mutation carrier probability of >10% (based on acceptable methods)*

• NICE 2013 guidelines indicate that research is needed on the benefits and harms of RGCT (Rapid Genetic Counseling and Testing)
Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle?

Peter D. Beitsch, MD1; Pat W. Whitworth, MD2; Kevin Hughes, MD3; Rakesh Patel, MD4; Barry Rosen, MD5; Gia Compagnoni, MD5; Paul Baron, MD6; Rache Simmons, MD7; Linda Ann Smith, MD8; Ian Grady, MD9; Michael Kinney, MD10; Cynara Coomer, MD11; Karen Barbosa, DO12; Dennis R. Holmes, MD13; Eric Brown, MD14; Linsey Gold, MD14; Patricia Clark, MD15; Lee Riley, MD, PhD16; Samuel Lyons, MD17; Antonio Ruiz, MD18; Sadia Kahn, DO19; Heather MacDonald, MD19; Lisa Curcio, MD20; Mary Kay Hardwick,21; Shan Yang, PhD22; Ed D. Esplin, MD, PhD22; and Robert L. Nussbaum, MD22

J Clin Oncol 37:453-460. © 2018

PURPOSE An estimated 10% of breast and ovarian cancers result from hereditary causes. Current testing guidelines for germ line susceptibility genes in patients with breast carcinoma were developed to identify carriers of BRCA1/2 variants and have evolved in the panel-testing era. We evaluated the capability of the National Comprehensive Cancer Network (NCCN) guidelines to identify patients with breast cancer with pathogenic variants in expanded panel testing.

METHODS An institutional review board–approved multicenter prospective registry was initiated with 20 community and academic sites experienced in cancer genetic testing and counseling. Eligibility criteria included patients with a previously or newly diagnosed breast cancer who had not undergone either single- or multigene testing. Consecutive patients 18 to 90 years of age were consented and underwent an 80-gene panel test. Health Insurance Portability and Accountability Act–compliant electronic case report forms collected information on patient demographics, diagnoses, phenotypes, and test results.

RESULTS More than 1,000 patients were enrolled, and data records for 959 patients were analyzed; 49.95% met NCCN criteria, and 50.05% did not. Overall, 8.65% of patients had a pathogenic/likely pathogenic (P/LP) variant. Of patients who met NCCN guidelines with test results, 9.39% had a P/LP variant. Of patients who did not meet guidelines, 7.9% had a P/LP variant. The difference in positive results between these groups was not statistically significant (Fisher’s exact test \[ P = .4241 \]).

CONCLUSION Our results indicate that nearly half of patients with breast cancer with a P/LP variant with clinically actionable and/or management guidelines in development are missed by current testing guidelines. We recommend that all patients with a diagnosis of breast cancer undergo expanded panel testing.
Consider genetic counseling & testing for BRCA1/2 when:

- Bilateral breast cancer
- Early onset breast cancer (≤40-45)
- Histo-pathologic features including: triple negative subtype (Medullary carcinoma, lymphocytic infiltration)
- Personal or family history of – breast (incl. male breast cancer), ovarian, pancreatic or prostate cancer
- Certain ethnic groups (eg Ashkenazi Jewish ancestry)
- When there’s therapeutic implication – in all ABC?
Genetic counseling
- what, how, when?
Genetic counseling for inherited cancer predisposition

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease*

*Journal of Genetic Counseling, Vol. 15, April 2006.*
Who *can* give genetic counseling?

- **USA** – Physicians and genetic counselors *(relatively new profession, MSc to PhD; ABGC)*

- **Europe** – also “genetic nurses”

- **Israel** – *Genetic Information Law (2001):* Physicians within their specialty and genetic counselors.
Genetic counseling for inherited cancer predisposition

Affected vs. Healthy

Common issues:
• Risk assessment for specific cancers.
• Cancer surveillance and prevention.
• Familial implications: mode of inheritance, relatives at risk, reproduction.
• Genetic testing: sensitivity, clinical utility, method, result interpretation.

Issues for affected women:
• Therapeutic implications – Surgical & Medical.
• Recently diagnosed – time pressure & information overload
• Reproductive
 Genetic counseling for inherited cancer predisposition

The traditional model:

- Pretest counseling (30-45 min, and more)
  - Drawing a family pedigree
  - Discussion – inheritance, risk assessment, etc.
  - Reaching an informed decision about testing.

- Genetic testing

- Post-test counseling (variable length)
  - Discussion of results
  - Recommendations for patient and relatives
Genetic Counseling - Issues

• Different national requirements and institutional policies
• Could be a bottleneck to timely testing
• New studies suggesting that written information or post-testing counseling as acceptable alternative
BRCA1/ BRCA2 testing at breast cancer diagnosis:

Potential concerns

• Information overload
• Psychological distress
• Delay in treatment initiation — if testing takes too long.
<table>
<thead>
<tr>
<th></th>
<th>Traditional</th>
<th></th>
<th>Rapid</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uptake</td>
<td>70% (1058/1520)</td>
<td></td>
<td>100% (110/110)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BRCA1/BRC2A positive</td>
<td>20% (209/1058)</td>
<td></td>
<td>33% (36/110)</td>
<td>.003</td>
</tr>
<tr>
<td>RRM in BRCA positive</td>
<td>4.7% (10/209)</td>
<td></td>
<td>42% (15/36)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Contralateral disease</td>
<td>20% (2/10)</td>
<td></td>
<td>27% (4/15)</td>
<td>NS</td>
</tr>
<tr>
<td>by pathology @ RRM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological support usage</td>
<td>50% (5/10)</td>
<td></td>
<td>53% (8/15)</td>
<td>NS</td>
</tr>
<tr>
<td>post RRM (voluntary)</td>
<td>Age: 38y (SD =7y)</td>
<td></td>
<td>Age: 37y (SD =6y)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions – Modena Cancer Clinic Study

Rapid genetic testing:
• Increased uptake of testing
• Identification of more carriers (higher rate)
• Increased uptake of contralateral RRM
• No increased use of psychological support services
How BRCA testing has evolved with the introduction of BRCA targeting therapies?

- More patients referred for testing
- Quicker results needed
- Testing will take place earlier - at diagnosis or during early treatment phase
- Role\timing of counselling will need to change
Hereditary breast cancer syndrome & multi-gene panel testing
How to test?

• Specific mutations
• Specific genes
• Gene panels
Other HBOC Syndromes

- Li Fraumeni Syndrome
- \(p53\) mutation
- \(PTEN/\)Cowden Syndrome
- \(ATM\) mutation
- Lynch Syndrome
- \(MLH1, MSH2, MSH6, EPCAM\) and \(PMS2\) mutations
- \(RAD51\) mutation
- \(BRIP1\) mutation
- \(PALB2\) mutation
- \(CHEK2\) mutation
- \(STK11\) mutation
- (Peutz-Jeghers Syndrome)
- \(CDH1\) mutation

Clinical implications for prevention and screening not well understood for all these mutations…..
DNA repair genes in hereditary cancer

Kobayashi H et al, Oncol Rep, 2013
Not all genes (and mutations) are created equal

• **High risk** (penetrance) *vs.* **moderate/low risk** genes

• **Specific variants** can be associated with specific risks (e.g. polymorphic stop p.K3326X in BRCA2 CHEK2 p.I157T – low risk?)

• **Genes with vs. without evidence-based risks (guidelines)**
What is the risk (penetrance)?
BRCA1/2-associated cancers: lifetime risk
Significant variability in penetrance

Breast cancer: 50%-70%
Second primary breast cancer: 40%-50%
Ovarian cancer: 15-45%  BRCA1>BRCA2

Increased risk of other cancers:
Male breast cancer       BRCA2>BRCA1
Pancreatic cancer       BRCA2
Prostate cancer         BRCA2
Melanoma                BRCA2

Different definitions of “lifetime” yield different outcomes
“Remaining lifetime risk” higher for younger patients
Breast Cancer Risk

<table>
<thead>
<tr>
<th>Age During Follow-up, y</th>
<th>No. of Women Contributing in Age Category</th>
<th>No. of Person-Years</th>
<th>No. of Events</th>
<th>Incidence per 1000 Person-Years (95% CI)</th>
<th>Cumulative Risk, % (95% CI)</th>
<th>Standardized Incidence Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brca1 Mutation Carriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>53</td>
<td>74.0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>604</td>
<td>2222.5</td>
<td>13</td>
<td>5.9 (3.4-10.1)</td>
<td>4 (2-7)</td>
<td>73.7 (42.9-126.8)</td>
</tr>
<tr>
<td>31-40</td>
<td>1048</td>
<td>3831.6</td>
<td>90</td>
<td>23.5 (19.1-28.9)</td>
<td>24 (21-29)</td>
<td>46.2 (37.3-57.1)</td>
</tr>
<tr>
<td>41-50</td>
<td>870</td>
<td>3317.8</td>
<td>94</td>
<td>28.3 (23.1-34.7)</td>
<td>43 (39-48)</td>
<td>17.2 (14.0-21.2)</td>
</tr>
<tr>
<td>51-60</td>
<td>479</td>
<td>1905.9</td>
<td>49</td>
<td>25.7 (19.4-34.0)</td>
<td>56 (51-61)</td>
<td>9.7 (7.2-12.9)</td>
</tr>
<tr>
<td>61-70</td>
<td>201</td>
<td>761.3</td>
<td>19</td>
<td>25.0 (15.9-39.1)</td>
<td>66 (61-72)</td>
<td>7.0 (4.5-11.0)</td>
</tr>
<tr>
<td>71-80</td>
<td>55</td>
<td>243.0</td>
<td>4</td>
<td>16.5 (6.2-43.9)</td>
<td>72 (65-79)</td>
<td>4.8 (1.8-12.8)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2276</td>
<td>12356.1</td>
<td>269</td>
<td>21.8 (19.3-24.5)</td>
<td>72 (65-79)</td>
<td>15.6 (14.7-18.7)</td>
</tr>
<tr>
<td><strong>Brca2 Mutation Carriers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>30</td>
<td>44.0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>329</td>
<td>1046.0</td>
<td>5</td>
<td>4.8 (2.0-11.5)</td>
<td>4 (2-9)</td>
<td>60.8 (25.5-144.9)</td>
</tr>
<tr>
<td>31-40</td>
<td>625</td>
<td>2136.1</td>
<td>23</td>
<td>10.6 (7.2-16.2)</td>
<td>13 (9-19)</td>
<td>20.3 (13.5-30.5)</td>
</tr>
<tr>
<td>41-50</td>
<td>669</td>
<td>2365.0</td>
<td>65</td>
<td>27.5 (21.6-35.1)</td>
<td>35 (29-41)</td>
<td>16.4 (12.9-20.9)</td>
</tr>
<tr>
<td>51-60</td>
<td>384</td>
<td>1437.2</td>
<td>44</td>
<td>30.6 (22.8-41.1)</td>
<td>53 (46-59)</td>
<td>11.4 (8.4-15.5)</td>
</tr>
<tr>
<td>61-70</td>
<td>174</td>
<td>610.2</td>
<td>14</td>
<td>22.9 (13.6-38.7)</td>
<td>61 (55-68)</td>
<td>5.4 (3.8-10.7)</td>
</tr>
<tr>
<td>71-80</td>
<td>68</td>
<td>274.6</td>
<td>6</td>
<td>21.9 (9.8-48.6)</td>
<td>69 (61-77)</td>
<td>6.6 (3.0-14.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1610</td>
<td>7913.1</td>
<td>157</td>
<td>19.8 (17.0-23.2)</td>
<td>12.9 (11.1-15.1)</td>
<td></td>
</tr>
</tbody>
</table>

Kuchenbacker, JAMA 2017
Cumulative Risks of Breast and Ovarian Cancer in BRCA1\2 Carriers

Figure 2. Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers

A) Cumulative risk of first breast cancer among BRCA1 and BRCA2 mutation carriers

B) Cumulative risk of ovarian cancer among BRCA1 and BRCA2 mutation carriers

Kuchenbacker, JAMA 2017
## Lifetime risk of breast cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Estimated lifetime risk of breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>55-65%\textsuperscript{10}</td>
</tr>
<tr>
<td>BRCA2</td>
<td>45-47%\textsuperscript{13}</td>
</tr>
<tr>
<td>TP53</td>
<td>49-60%\textsuperscript{36}</td>
</tr>
<tr>
<td>PTEN</td>
<td>25-50%\textsuperscript{61,62}</td>
</tr>
<tr>
<td>PALB2</td>
<td>33-58%\textsuperscript{56}</td>
</tr>
<tr>
<td>STK11</td>
<td>30-50%\textsuperscript{58,63,64}</td>
</tr>
<tr>
<td>CDH1</td>
<td>39-52%\textsuperscript{65,66}</td>
</tr>
<tr>
<td>ATM</td>
<td>15-52%\textsuperscript{67-70}</td>
</tr>
<tr>
<td>CHEK2</td>
<td>20-44%\textsuperscript{71-74}</td>
</tr>
</tbody>
</table>
Average estimated cumulative 5-year and lifetime breast cancer risks

<table>
<thead>
<tr>
<th>Population</th>
<th>ATM/NBN (RR 2.7-2.8)*</th>
<th>CHEK2 (1100delC)(RR 3.0)‡</th>
<th>CHEK2 (I157T)(RR 1.58)</th>
<th>PALB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5 year risk</td>
<td>Cumulative</td>
<td>5 year</td>
<td>Cumulative</td>
</tr>
<tr>
<td>25-29</td>
<td>0.04%</td>
<td>0.1%</td>
<td>0.12%</td>
<td>0.1%</td>
</tr>
<tr>
<td>30-34</td>
<td>0.14%</td>
<td>0.2%</td>
<td>0.38%</td>
<td>0.5%</td>
</tr>
<tr>
<td>35-39</td>
<td>0.30%</td>
<td>0.5%</td>
<td>0.84%</td>
<td>1.4%</td>
</tr>
<tr>
<td>40-44</td>
<td>0.61%</td>
<td>1.1%</td>
<td>1.70%</td>
<td>3.0%</td>
</tr>
<tr>
<td>45-49</td>
<td>0.94%</td>
<td>2.0%</td>
<td>2.64%</td>
<td>5.6%</td>
</tr>
<tr>
<td>50-54</td>
<td>1.12%</td>
<td>3.1%</td>
<td>3.14%</td>
<td>8.5%</td>
</tr>
<tr>
<td>55-59</td>
<td>1.33%</td>
<td>4.4%</td>
<td>3.71%</td>
<td>11.8%</td>
</tr>
<tr>
<td>60-64</td>
<td>1.72%</td>
<td>6.0%</td>
<td>4.81%</td>
<td>16.0%</td>
</tr>
<tr>
<td>65-69</td>
<td>2.11%</td>
<td>8.0%</td>
<td>5.92%</td>
<td>20.8%</td>
</tr>
<tr>
<td>70-75</td>
<td>2.20%</td>
<td>10.0%</td>
<td>6.17%</td>
<td>25.5%</td>
</tr>
<tr>
<td>CLTR (80)</td>
<td>2.24%</td>
<td>12.0%</td>
<td>30.0%</td>
<td>31.8%</td>
</tr>
</tbody>
</table>

TUNG, NATURE REVIEWS CLINICAL ONCOLOGY, 2016
Considerations in the healthy BRCA carrier
Risk reduction & screening

- Risk reducing surgery
  - Bilateral RRM
  - RRSO
- Chemoprevention
- Lifestyle intervention
- Screening for early detection:
  ✓ Breast & Ovarian cancer
  ?? Pancreatic cancer, prostate cancer
REPRODUCTIVE ISSUES
Reproductive issues

• Timing of RRSO (risk reducing oophorectomy)
  - For BRCA1 – between 35-40
  - For BRCA2 – 40-45
• Fertility preservation
• Understanding the clinical significance of reduced ovarian reserve in \textit{BRCA} carriers
• PGD – pre-implantation genetic diagnosis
• Premature menopause – impact on sexual health, bone health, quality of life
• Understanding the hormonal axis & breast cancer in \textit{BRCA} carriers:
  - Role of oophorectomy in ↓ BC risk & mortality
  - HRT in healthy & affected \textit{BRCA} carriers
Management of Mutation Carriers

Consider...

- **Psychosocial support to assist with:**
  - Adjusting to new information
    - most adjust within 3-6 months
    - subset remain psychologically distressed (16-25% anxiety and/or depression)
  - Making decisions regarding management
    "to inflict surgery is a hard decision to make... when I don’t have the disease and feel healthy"
  - Addressing family issues, self concept, body image
  - Dealing with future concerns i.e. child bearing, surgical menopause after oophorectomy

- **Referral to support groups**
Precision medicine in risk reduction

Risk Reduction measures

• Prevention studies: BRCA-P

• Salpingectomy - 1st step risk-reducing procedure?? Under study!

• Fine tuning timing of RRSO (*tailored to family history):
  - For BRCA1 – between 35-40
  - For BRCA2 – 40-45

Risk assessment tools

• Clinical utility/validity of genetic modifiers → tailoring risk and risk-reducing measures

RRSO= risk reducing salpingoophorectomy
In summary:
Unique challenges in BRCA1/2 associated BC

• Multitude of therapeutic & reproductive decisions
• Knowledge of BRCA1/2 status may arrive at a time of great distress
• Risk reducing measures are often an assault on self-image, “womanhood”
• Far reaching implications for family planning and for the extended family
• Multiple psychosocial issues - support is imperative
• Multi-disciplinary care – is a MUST
Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening

S. Paluch-Shimon, F. Cardoso, C. Sessa, J. Balmana, M. J. Cardoso, F. Gilbert & E. Senkus, on behalf of the ESMO Guidelines Committee

1Division of Oncology and the Dr Pinchas Borenstein Talpiot Medical Leadership Program, Sheba Medical Center, Ramat Gan, Israel; 2Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal; 3Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland; 4Vall d’Hebron University Hospital Institut d’Oncologia, Barcelona, Spain; 5School of Clinical Medicine, University of Cambridge, Cambridge, UK; 6Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland
THANK YOU

Advanced Breast Cancer

Fifth ESO-ESMO International Consensus Conference

14-16 November 2019 | Lisbon, Portugal
Coordinating Chair: F. Cardoso, PT
Co-Chairs: G. Curigliano, IT - S.A. Mertz, US
Scientific Committee Members: K. Gelmon, CA - F. Penault-Llorca, FR - E. Senkus, PL
C. Thomssen, DE

The ABC5 guidelines will be developed by ESO and ESMO
The ABC5 conference and guidelines are endorsed by
The ABC5 conference is held under the auspices of with official representatives of and is endorsed by

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“I already diagnosed myself on the Internet. I’m only here for a second opinion.”