Updates in Breast Cancer Genetics

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This Workshop will Address the following:

Many young women diagnosed with breast cancer make the decision to undergo genetic testing. In this session, you will hear about the genetics of breast cancer in young women and what information testing can provide. Also, our expert will discuss how and when genetic counseling can be useful— a first step toward understanding your individual and family risk including heredity and genetics.
Learning Objectives

The presentation will enable the participant to:

1. Risk Factors and Genetic Testing
2. Risk Estimation Models and Counseling
   a. Implications for you and your family
3. Screening Recommendations
4. Standard Risk Reduction Approaches
Who is at high risk for cancer?
Assessing Risk
### Major and Minor Risk Factors

<table>
<thead>
<tr>
<th>Major Risk Factors</th>
<th>Minor Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2-fold increase in risk</td>
<td>&gt;1 but &lt;2-fold increase in risk</td>
</tr>
<tr>
<td>Known germline mutation (ie. BRCA1 or BRCA2 mutation)</td>
<td>Early menarch (&lt;12)</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; degree relative (younger &lt;50)</td>
<td>Nullparity/Late age of 1&lt;sup&gt;st&lt;/sup&gt; live birth</td>
</tr>
<tr>
<td>Chest radiation (&lt;30y/o)</td>
<td>Late menopause</td>
</tr>
<tr>
<td>Prior DCIS, LCIS, Atypia</td>
<td>Family history: multiple relatives including 2&lt;sup&gt;nd&lt;/sup&gt; &amp; 3&lt;sup&gt;rd&lt;/sup&gt; degree</td>
</tr>
<tr>
<td>Prior breast or ovarian cancer</td>
<td>Combined estrogen &amp; progestin</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>Serum hormones: sex hormones, SHGB, insulin/growth factors</td>
</tr>
<tr>
<td></td>
<td>Obesity/Inactivity</td>
</tr>
<tr>
<td></td>
<td>Alcohol consumption</td>
</tr>
</tbody>
</table>
## Major Risk Factors: Risk Per Year

<table>
<thead>
<tr>
<th>Major Risk Factor</th>
<th>Absolute Risk</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA 1 or BRCA2</td>
<td>1-2%</td>
<td>10-20X</td>
</tr>
<tr>
<td>Chest XRT &lt;30</td>
<td>1-2%</td>
<td>10-20X</td>
</tr>
<tr>
<td>DCIS (lump + XRT)</td>
<td>1%</td>
<td>10X</td>
</tr>
<tr>
<td>LCIS</td>
<td>1%</td>
<td>10X</td>
</tr>
<tr>
<td>Atypia &amp; Family Hx</td>
<td>1%</td>
<td>8-10X</td>
</tr>
<tr>
<td>Atypia</td>
<td>0.5%</td>
<td>4-5X</td>
</tr>
<tr>
<td>Prior Invasive BrCa</td>
<td>0.75%</td>
<td>5-8X</td>
</tr>
<tr>
<td>Age &gt;60 (vs. age 30)</td>
<td>0.33%</td>
<td>10X</td>
</tr>
</tbody>
</table>
Breast Cancer Risk Factors

Relative Risk

- BRCA1 or 2
- In-situ
- AH + FH
- AH
- HRT
- Early Menarche
- 1st Birth
- Obesity
BRCA1/2 Mutations Responsible for a majority of “Hereditary Breast Cancers”
Total Hereditary Breast Cancer

BRCA1 or BRCA2 (>50-85%)

Next Generation (15-30%)

Unknown
CRITERIA FOR FURTHER GENETIC RISK EVALUATION

An affected individual with one or more of the following:
- A known mutation in a breast cancer susceptibility gene within the family
- Early-age-onset breast cancer
- Triple negative (ER-, PR-, HER2-) breast cancer
- 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 epithelial ovarian
  - Cancer at any age, or
  - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age
  - From a population at increased risk
- ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score ≥7); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of GI tract, diffuse gastric cancer
- Ovarian cancer
- Male breast cancer

An unaffected individual with a family history of one or more of the following:
- A known mutation in a breast cancer susceptibility gene within the family
- ≥2 breast primaries in single individual
- ≥2 individuals with breast primaries on the same side of family (maternal or paternal)
- ≥1 ovarian cancer primary from the same side of family (maternal or paternal)
- First- or second-degree relative with breast cancer ≤45 y
- ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score ≥7); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of GI tract, diffuse gastric cancer
- Male breast cancer

For populations at increased risk, requirements for inclusion may be modified (eg, women of Ashkenazi Jewish descent with breast or ovarian or pancreatic cancer at any age).

For dermatologic manifestations, see COWD-1.

For hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, STK11 testing should be considered. See NCCN Guidelines for Colorectal Cancer Screening: Peutz-Jeghers syndrome.

For lobular breast cancer with a family history of diffuse gastric cancer, CDH1 gene testing should be considered.

Genetic counseling is highly recommended when genetic testing is offered and after results are disclosed. 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 counseling patients who potentially meet criteria for an inherited syndrome.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Hereditary vs Familial vs Sporadic

**Hereditary**

- Ov, 52
- Br, 32
- Br, 45

2 Breast cancers under 50 and ovarian cancer, Multiple generations, 50% women affected

**Familial Clustering**

- Br, 67
- Br, 71
- Br, 58

**Sporadic**

- Br, 63
- Br, 71
Autosomal Dominant Pattern of Inheritance

50/50 Chance of inheriting Genetic mutation
Newly Diagnosed Capture Rate: 34%

Leads to Survivor Patient Population AT RISK

<table>
<thead>
<tr>
<th>Appropriate Patients</th>
<th>Breast Cancer</th>
<th>Ovarian Cancer</th>
<th>CRC/Endo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly Diagnosed Patients¹</td>
<td>289,534</td>
<td>22,240</td>
<td>192,480</td>
<td>504,254</td>
</tr>
<tr>
<td>Newly Diagnosed Patients Meeting NCCN²³⁴</td>
<td>116,976</td>
<td>20,016</td>
<td>48,095</td>
<td>185,087</td>
</tr>
<tr>
<td>Patients Tested⁵</td>
<td>53,041</td>
<td>4,827</td>
<td>4,376</td>
<td>62,244</td>
</tr>
<tr>
<td>% Captured</td>
<td>44.5%</td>
<td>24.1%</td>
<td>9.1%</td>
<td>34.0%</td>
</tr>
</tbody>
</table>

Every year, more patients are missed than tested

Large Survivor Patient Population

5. Internal Myriad data
National Capture Rate of Total At-Risk Patients = 20%

National At-Risk Capture Rate by Patient Status and Disease

- Newly Diagnosed: 45%
- Survivor Patients: 34%
- All Patients: 28%

- Breast Ca
- OV Ca
- CRC/Endo
- Total
BRCA Mutations Increase Risk of 2nd Primary Cancers
BRCA1-Associated Cancers: Risk by age 70

- Breast cancer: 50-85% (often early age at onset)
- Second primary breast cancer: 20%-60%
- Ovarian cancer: 15-45%

Possible increased risk of other cancers

JCO 2004;22: 735-42; NCI 2005
BRCA2-Associated Cancers: Risk by age 70

Breast cancer (50-85%)
Second primary breast cancer (20-60%)
Ovarian cancer (10-27%)

Breast cancer (6%)

Prostate (20%)

Increased risk of pancreatic cancer and melanoma

JCO 2004;22: 735-42; NCI 2005
Next Generation/Multi-Gene Cancer Panels

1. Many patients with suggestive family histories test negative on standard testing
   a. Need for additional/expanded screening

2. Patients do not meet classic guidelines for hereditary cancer syndromes
   a. Variable expressivity and reduced penetrance

3. Many genes implicated in cancer
   a. Testing multiple genes simultaneously can be more time and cost effective

4. Overlapping phenotypes of different hereditary cancer syndromes
Next Generation/Multi-Gene Testing

- Currently moving from research to clinical
  - Research: limited eligibility
  - Clinical: turn around time (pre-certification & testing)
  - If positive: Lack of formal risk and surveillance recommendations
    - More likely to identify moderate-low penetrance genes
    - High number of variants of uncertain significance (VUS)
  - Free, accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence
    - Sharing Clinical Reports Project (SCRP): http://sharingclinicalreports.org/index.html
    - Patient or Provider submission + reimbursement

- LATER
  - Whole genome sequencing
    - Analysis of entire genetic makeup of an individual
  - Whole exome sequencing
    - Analysis of all coding regions of genetic material
NextGen Testing: Who to test??

Cast the net widely, test nearly anyone
  • Pro
    — No sure approach for excluding anyone
    — Find more mutation carriers
  • Con
    — Difficult to interpret and develop management recommendations

Test Selectively
  • Pro
    — Higher penetrance families
    — Easier to interpret and recommend management
  • Con
    — Missed mutations

Always test the relative with the highest mutation probability in the family
Reduce non-informative negative results
Testing Process

• Pre-test Counseling/Informed Consent
  — Possible results
    — Discuss VSB/VUS
  — Cancer risks
  — Clinical management
  — Costs/Pre-certification/Financial assistance

• Post-test Counseling
  — Disclose/Discuss
  — Management plan
  — Implication for the family

• Maintain contact files
  • Notify patients with variants are reclassified
Rare changes in other genes associated with breast cancer.

<table>
<thead>
<tr>
<th>GENE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN</td>
<td>Helps regulate cell growth. Causes Cowden syndrome leading to higher risk of both benign and cancerous tumors in the breast, digestive tract, thyroid, uterus, and ovaries.</td>
</tr>
<tr>
<td>TP53</td>
<td>Provides instructions for making a protein to stop tumor growth. Causes Li-Fraumeni syndrome and increases soft tissue cancer at young ages and higher risk of BrCa, leukemia, brain tumors, and sarcomas.</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Provides instructions for making a protein to stop tumor growth. Causes Li-Fraumeni syndrome and can double breast cancer risk.</td>
</tr>
<tr>
<td>CHD1</td>
<td>Supports protein growth that helps cell adherence and tissue formation. Increased risk of lobular BrCa and rare, early onset stomach cancer.</td>
</tr>
<tr>
<td>PALB2</td>
<td>Supports protein growth that works with the BRCA2 protein to repair damaged DNA and stop tumor growth. Doubles BrCa Risk. Inheriting 2 abnormal PALB2 genes causes Fanconi anemia, higher risk of cancer, including kidney cancer and brain cancer.</td>
</tr>
<tr>
<td>ATM</td>
<td>Helps repair damaged DNA. Linked to increased risk of BrCa.</td>
</tr>
</tbody>
</table>
Li-Fraumeni Syndrome

**NCCN Guidelines Version 3.2013**

**Li-Fraumeni Syndrome**

**LI-FRAUMENI SYNDROME TESTING CRITERIA**

- Individual from a family with a known **TP53** mutation
- Classic Li-Fraumeni syndrome (LFS) criteria:
  - Combination of an individual diagnosed age <45 y with a sarcoma
  - AND
  - A first-degree relative diagnosed age <45 y with cancer
  - AND
  - An additional first- or second-degree relative in the same lineage with cancer diagnosed age <45 y, or a sarcoma at any age
- Chompret criteria:
  - Individual with a tumor from LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age
  - OR
  - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years
  - OR
  - Individual with adrenocortical carcinoma or choroid plexus carcinoma at any age of onset, regardless of the family history
- Early-onset breast cancer:
  - Individual with breast cancer <35 y with a negative **BRCA1/BRCA2** test

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**FOLLOW-UP**

- LFS testing criteria met
  - See Follow-up (LIFR-2)
- LFS testing criteria not met
  - Individualized recommendations according to personal and family history

**Cancers associated with LFS include but are not limited to:**
- Premenopausal breast cancer
- Bone and soft tissue sarcomas
- Acute leukemia
- Brain tumor
- Adrenocortical carcinoma
- Choroid plexus carcinoma
- Colon cancer
- Early onset of other adenosarcomas or other childhood cancers

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Cowden Syndrome

COWDEN SYNDROME TESTING CRITERIA

- Individual from a family with a known PTEN mutation
- Individual meeting clinical diagnostic criteria for CS
- Individual with a personal history of:
  - Bannayan-Riley-Ruvalcaba syndrome (BRRS) or
  - Adult Lhermitte-Duclos disease (cerebellar tumors) or
  - Autism spectrum disorder and macrocephaly or
  - Two or more biopsy-proven trichilemmomas or
  - Two or more major criteria (one must be macrocephaly) or
  - Three major criteria, without macrocephaly or
  - One major and ≥ three minor criteria or
  - Four minor criteria

FOLLOW-UP

- At-risk individual with a relative with a clinical diagnosis of CS or BRRS for whom testing has not been performed
- The at-risk individual must have the following:
  - Any one major criterion or
  - Two minor criteria

CS testing criteria met → See Follow-up (COWD-2)

CS testing criteria not met → Individualized recommendations according to personal and family history

Major criteria:
- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas
- Macrocephaly (megalocephaly) (ie, ≥97%, 56 cm in adult women, 60 cm in adult men)
- Macular pigmentation of glans penis
- Nodular cutaneous lesions
  - One biopsy proven trichilemmoma
  - Multiple palmpoplantar keratoses
  - Multiple cutaneous facial papules (often verrucous)

Minor criteria:
- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthosis (≥3)
- Lipomas
- Mental retardation (ie, IQ ≤75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (eg, adenoma, nodule(s), goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
<table>
<thead>
<tr>
<th>Lab</th>
<th>Tests Offered</th>
<th>Kits Available</th>
<th>Price</th>
<th>Insurance Pre-verification</th>
<th>Result Turn-Around Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambry Genetics</strong></td>
<td>BRCA 1/2</td>
<td>Yes</td>
<td>$2,200</td>
<td>Yes-3-4 Days to Weeks Usually requires a Letter of Medical Necessity</td>
<td>3-4 weeks</td>
</tr>
<tr>
<td></td>
<td>• gene sequencing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• deletion/duplication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BRCAplus</td>
<td></td>
<td>$3,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BRCA1, BRCA2, CDH1, PTEN, TP53, STK11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BRCA 1/2 Del-Dup</td>
<td></td>
<td>$500</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• large rearrangement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BRCA 1/2 Site</td>
<td></td>
<td>$400</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BreastNext</td>
<td></td>
<td>$4,120</td>
<td>Tests priced under $400 will not be pre-authorized</td>
<td>12-16 weeks</td>
</tr>
<tr>
<td></td>
<td>16 genes including BRCA1, BRCA2, TP53, PTEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>City of Hope</strong></td>
<td>• PTEN</td>
<td>Yes</td>
<td>$930</td>
<td>Yes</td>
<td>4-8 weeks</td>
</tr>
<tr>
<td></td>
<td>• TP53</td>
<td></td>
<td>$578</td>
<td>Pre-authorization 7-10 business days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast Cancer Sequencing</td>
<td></td>
<td>$3,328</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CHEK2, PALB2, ATM, CDH1, PTEN, TP53, STK11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DNA Traits by Gene to Gene</strong></td>
<td>BRCA1, BRCA2</td>
<td>Yes</td>
<td>$475</td>
<td>No, payment due with order</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td><strong>GeneDx</strong></td>
<td>OncoGeneDx</td>
<td>No</td>
<td>$4,530</td>
<td>Yes, some insurance Usually 80%</td>
<td>6-8 weeks</td>
</tr>
<tr>
<td></td>
<td>35 gene panel including BRCA1/2</td>
<td></td>
<td>$600</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Myriad Genetics</strong></td>
<td>BRCA Analysis</td>
<td>Yes</td>
<td>$4,040</td>
<td>Yes</td>
<td>&lt;14 days</td>
</tr>
<tr>
<td></td>
<td>BRCA1, BRCA2, BART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Site Specific</td>
<td></td>
<td>$475</td>
<td>(call if over $375)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multi-Site</td>
<td></td>
<td>$600</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>myRisk Hereditary Cancer (launch 2014)</td>
<td></td>
<td>$4000-4500</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 gene panel including BRCA1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quest</strong></td>
<td>BRCAdvantage</td>
<td>Yes</td>
<td>$2500</td>
<td>Yes</td>
<td>2-4 weeks</td>
</tr>
<tr>
<td><strong>University of Washington Lab</strong></td>
<td>BROCA Panel</td>
<td>No</td>
<td>$3,350</td>
<td></td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>40 genes including BRCA1, BRCA2, MLH1, MLH2, MSH6, PTEN, TP53, PALB2, CDKN2A, STK11</td>
<td></td>
<td></td>
<td>No Charge, must meet criteria &gt;3 affected living &amp; willing</td>
<td></td>
</tr>
<tr>
<td><strong>Do not directly bill Medicare, institutional billing only</strong></td>
<td>Current Clinical Trials: Genomic Analysis of Breast and Ovarian Cancer in Families (&gt;4 cases on the same side of the family)</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk Counseling & Testing
(For BRCA1/2 Mutations)
Triple Negative Breast Cancer (TNBC)

207 patients with stage I-IV triple negative BrCa underwent Comp BRCA1/2 testing

- Deleterious germline mutation in BRCA1 in 11.1% (23/207) and BRCA2 in 4.3% (9/207) of the patients, respectively, giving an overall prevalence rate of 15.4% (32/207).

- Mutation rates in patients with or without SFH was 32.5% and 6.1%, respectively. When examined by age at diagnosis, the mutation rates were: 27.6% <50), 11.4% (51-60), and 4.9% (>61). If SFH or age <50, were the only criteria used 25% and 34% of mutations would have been missed.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years) at diagnosis (range)</td>
<td>55 (25-85)</td>
</tr>
<tr>
<td>Accrual site</td>
<td></td>
</tr>
<tr>
<td>Academic Community</td>
<td>121 (58%)</td>
</tr>
<tr>
<td>Community</td>
<td>86 (42%)</td>
</tr>
<tr>
<td>Menopausal status at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Pre/perimenopausal</td>
<td>85 (41%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>122 (59%)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>168 (80%)</td>
</tr>
<tr>
<td>African American</td>
<td>30 (15%)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Indian American</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>Ashkenazi Ancestry</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (2.4%)</td>
</tr>
<tr>
<td>LN status</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>140 (69%)</td>
</tr>
<tr>
<td>Positive</td>
<td>64 (31%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>71 (34%)</td>
</tr>
<tr>
<td>II</td>
<td>105 (51%)</td>
</tr>
<tr>
<td>III</td>
<td>24 (12%)</td>
</tr>
<tr>
<td>IV</td>
<td>7 (3.3%)</td>
</tr>
<tr>
<td>ER and PR 0%</td>
<td>189 (91%)</td>
</tr>
<tr>
<td>1-5%</td>
<td>18 (9%)</td>
</tr>
<tr>
<td>Any family history of breast/ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>128 (62%)</td>
</tr>
<tr>
<td>No</td>
<td>79 (38%)</td>
</tr>
<tr>
<td>Significant family history of breast/ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76 (37%)</td>
</tr>
<tr>
<td>No</td>
<td>131 (63%)</td>
</tr>
<tr>
<td>Limited Family structure*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (16%)</td>
</tr>
<tr>
<td>No</td>
<td>158 (86%)</td>
</tr>
</tbody>
</table>

### Table 2. Mutation prevalence and Clinical and Demographic characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>Patients with Deleterious Mutations</th>
<th>Deleterious Mutation Prevalence % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at TNBC Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>76 (37%)</td>
<td>21</td>
<td>27.6% (18%-38%)</td>
<td>0.0007</td>
</tr>
<tr>
<td>51-60</td>
<td>70 (34%)</td>
<td>8</td>
<td>11.4% (4%-19%)</td>
<td></td>
</tr>
<tr>
<td>&gt;61</td>
<td>61 (29%)</td>
<td>3</td>
<td>4.9% (&lt;1%-10%)</td>
<td></td>
</tr>
<tr>
<td><strong>Any Family History of BC/OC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>128 (62%)</td>
<td>27</td>
<td>21.1% (14%-28%)</td>
<td>0.0043</td>
</tr>
<tr>
<td>No</td>
<td>79 (38%)</td>
<td>5</td>
<td>6.3% (1%-12%)</td>
<td></td>
</tr>
<tr>
<td><strong>Significant Family History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76 (37%)</td>
<td>24</td>
<td>31.6% (21%-42%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>131 (63%)</td>
<td>8</td>
<td>6.1% (2%-10%)</td>
<td></td>
</tr>
<tr>
<td><strong>Accrual location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>121 (58%)</td>
<td>23</td>
<td>19.0% (12%-26%)</td>
<td>0.0938</td>
</tr>
<tr>
<td>Community</td>
<td>86 (42%)</td>
<td>9</td>
<td>10.5% (4%-17%)</td>
<td></td>
</tr>
<tr>
<td><strong>ER and PR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>189 (91%)</td>
<td>28</td>
<td>14.8% (10%-20%)</td>
<td>0.4909</td>
</tr>
<tr>
<td>1-5%</td>
<td>18 (9%)</td>
<td>4</td>
<td>22.2% (3%-41%)</td>
<td></td>
</tr>
<tr>
<td><strong>Met NCCN Guidelines for HBOC Testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>175 (85%)</td>
<td>32</td>
<td>18.3% (13% 24%)</td>
<td>0.0059</td>
</tr>
<tr>
<td>No</td>
<td>32 (15%)</td>
<td>0</td>
<td>0 (---)</td>
<td></td>
</tr>
</tbody>
</table>

Results

- Deleterious BRCA1 mutation
- Deleterious BRCA2 mutation
- Variants of uncertain significance
- No mutation

81.2% Deleterious BRCA1 and BRCA2 mutations
11.1% Variants of uncertain significance
4.3% No mutation
3.4% Other mutations
TNBC and Hereditary BrCa

- 77 TNBC from MD Anderson
  - Unselected for age and family history

- 18.2% had deleterious germline mutations in BRCA1 or BRCA2

- Mutation carriers had better 5-year recurrence free survival ($p = 0.016$)
199 TNBC from community network
  – Unselected for age and family history

10.6% found to have a deleterious mutation in BRCA1 or BRCA2

Higher prevalence of BRCA2, not BRCA1 (unlike previous report)
## Comparison - NCCN Guidelines

### Results of Gonzalez-Angulo and Hartman Papers

<table>
<thead>
<tr>
<th></th>
<th>Gonzalez-Angulo</th>
<th>Hartman</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>77</td>
<td>199</td>
</tr>
<tr>
<td>Staining threshold for TNBC</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Germline BRCA1/2 Mutations Detected</td>
<td>14 (18.2%)</td>
<td>21 (10.6%)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>BRCA2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Patients missed by pre-2011 NCCN Guidelines</td>
<td>6 (43%)</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Patients missed by 2011 NCCN Guidelines</td>
<td>0</td>
<td>2 (10%)*</td>
</tr>
</tbody>
</table>

*Would have been captured if NCCN Guidelines were expanded to include TNBC under 65
What About DCIS?

- Ductal carcinoma in situ (DCIS; also known as *intraductal carcinoma*) is the most common type of non-invasive breast cancer
- About 1 in 5 new breast cancer cases will be DCIS
- NCCN and Medicare criteria
  - Both include DCIS as an equal cancer to invasive breast cancer when considering who should get testing for *BRCA1* or *BRCA2*
Cancer Risk Counseling and Genetic Testing

“Who, When Why, and What?”
Who to Test For BRCA1/2

- **Have Breast Cancer and**
  - Onset < age 45
  - Ovarian Cancer
  - Onset < 50 and another affected relative < 50 or ovarian cancer
  - Male
  - Triple-negative < 60
  - Ashkenazi Heritage
  - Pancreatic + BrCa in family

- **No Breast Cancer but**
  - Known mutation in family
  - First or second-degree blood relative meeting NCCN criteria
  - Family history suggests hereditary pattern but no affected relative alive or willing to test
When to Test For BRCA1/2

- **Have Breast Cancer**
  - Anytime after dx but preferably prior to definitive breast surgery or radiation
  - Takes about 1-2 weeks after insurance approval
  - Perform during neo-adjuvant tx.
  - Survivorship: changes in family history/guidelines

- **No Breast Cancer**
  - > Age 18 (usually between 21-25 or older)
  - Health insurance is not a concern (GINA)
  - Life insurance procured
## Why Test For BRCA1/2

<table>
<thead>
<tr>
<th>Have Breast Cancer</th>
<th>No breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>– May affect choice of surgery and reconstruction</td>
<td>– Breast screening starts at 25, insurance pays for MRI</td>
</tr>
<tr>
<td>– <strong>Prophylactic TLH/BSO</strong></td>
<td>– Ovarian screening at 30-35 with TV US</td>
</tr>
<tr>
<td>– Additional cancer risk/screening options</td>
<td>– <strong>Prophylactic TLH/BSO</strong> after childbearing complete or 35</td>
</tr>
<tr>
<td>– Implications for relatives</td>
<td></td>
</tr>
</tbody>
</table>
NCCN Recommended Management Reduces Cancer Risk

- Oral Contraceptive: As much as 60%
- Tamoxifen: As much as 53%
- Mastectomy: At least 90%
- Oophorectomy: As much as 96%
Assists with surgical management decisions

- **Surgery:**
  - Breast
    - Lumpectomy vs. Mastectomy
    - +/- Prophylactic mastectomy
      - ↓ risk by up to 90-95%
  - Ovaries
    - Risk Reducing Salpingo-oophorectomy + fallopian tubes
      - +/- uterus (↓ risk by ≥95%)
      - ↓ risk of breast cancer by 50-70%
      - ↓ risk of ovarian cancer by > 95%
      - 15% Survival Advantage Probable for BRCA1/2 Carriers
      - Cost Effective
Assists with screening and treatment decisions

- Long-term screening
  - More intensive

- Chemotherapy (under investigation)
  - Triple-negative BrCa (response to treatment)
  - Use of PARP inhibitor
What to Do With Equivocal or Non-Informative Results

<table>
<thead>
<tr>
<th>Breast Cancer and BRCA Mutation</th>
<th>No Breast Cancer and No or uncertain mutation. Affected Carriers not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertain significance in patient and other affected relatives</td>
<td>– Unclear</td>
</tr>
<tr>
<td>– Screening and prophylaxis as dictated by clinical picture</td>
<td>– Screening and prophylaxis as dictated by clinical picture</td>
</tr>
</tbody>
</table>
Screening for High Risk Women
## Breast Screening Recommendations

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Average Risk</th>
<th>High Risk</th>
<th>BRCA 1/2 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Mammography</td>
<td>Beginning by age 40</td>
<td>5 -10 years prior to age of onset youngest relative</td>
<td>Age 25</td>
</tr>
<tr>
<td>Clinical Breast Examination</td>
<td>Annual</td>
<td>Annual or as clinically indicated</td>
<td>Semi-Annual</td>
</tr>
<tr>
<td>Add Breast MRI</td>
<td>No</td>
<td>Yes if familial risk. &gt; 20%</td>
<td>Yearly</td>
</tr>
<tr>
<td>Add ultrasound</td>
<td>As clinically indicated</td>
<td>As clinically indicated</td>
<td>Yes — if MRI not covered by Insurance</td>
</tr>
</tbody>
</table>
## Ovarian Cancer Screening Recommendations

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Average Risk</th>
<th>High Risk</th>
<th>BRCA 1/2 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic Ultrasound with doppler probe</td>
<td>Not indicated</td>
<td>No</td>
<td>Annual or semi-annual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Yes, if familial cancer risk and + family history)</td>
<td></td>
</tr>
<tr>
<td>CA-125 blood test</td>
<td>Not indicated</td>
<td>No</td>
<td>Annual or semi-annual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Yes, if familial cancer risk and + family history)</td>
<td></td>
</tr>
<tr>
<td>Pelvic Examination</td>
<td>Annual</td>
<td>Annual</td>
<td>Annual or semi-annual</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>
## Additional Recommendations

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Average Risk</th>
<th>High Risk</th>
<th>BRCA 1/2 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoprevention</td>
<td>Not indicated</td>
<td>Consider Tamoxifen or Raloxifene or Aromasin or Clinical Trials</td>
<td>Consider Tamoxifen or Raloxifene or Aromasin or Clinical Trials</td>
</tr>
<tr>
<td>Prophylactic Surgery</td>
<td>Not indicated</td>
<td>Possibly, but not common</td>
<td>Consider, significant risk reduction + survival benefit</td>
</tr>
<tr>
<td>Weight Control</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Increase Physical Activity</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Limit EtOH intake</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>
Case Study: Beth

Beth is a 38 year old woman recently diagnosed with triple negative breast cancer and is trying to determine her course of treatment. She has two young children (5 & 3 y/o), but also two female siblings. Beth reports the following family history:

- Maternal family history is negative for cancer
- Paternal family history is significant for:
  - Her father has one brother & one sister
    - Limited Family Structure
  - Paternal grandmother diagnosed with breast cancer age 52, but she thinks she was premenopausal
Case Study: Triple Negative BrCa

German

Dx 72
64
Dx 48
BRCA1/2 Neg

62
Beth Dx 38
Triple Neg

32
5
3

Dx 52

88

English/Irish

60

Key
- Breast CA
- Ovarian CA
- Prostate CA
- Pancreatic CA
Case Study: BRCA1/2 Risks

- **Rational for Testing:**
  - Testing will assist with informed treatment decision making (ASCO Guidelines)
  - Early age of Onset and Triple negative BrCa (NCCN guidelines)
- Limited family structure
- Paternal Aunt tested Negative for BRCA1/2 Genetic counseling & testing prior to definitive surgery and for treatment planning.
Case Study: Updated Pedigree

Key:
- Breast CA
- Ovarian CA
- Prostate CA
- Pancreatic CA

German

- Breast CA
- Ovarian CA
- Prostate CA
- Pancreatic CA

English/Irish

- Breast CA

- Prostate CA

- Pancreatic CA
Case Study: Impact of results – medical management

- Beth
  - BARD1+: Moderate BrCa risk
  - Discuss surgical management including:
    - Breast conservation
    - Therapeutic and Preventive Mastectomy
  - Discuss whether she has completed child-bearing
    - Options for fertility preservation
  - Risks for other cancers
Case Study: Impact of results – medical management

- Beth’s 1st degree relatives: sisters & father
  - Discuss results (duty to warn) and encourage genetic counseling and testing
  - If negative, General population risk for breast cancer – follow standard screening (ACS) guidelines
    - Cannot pass this on to their children
  - If positive, elevated risk for breast cancer – follow NCCN guidelines
- Beth’s children:
  - Genetic counseling and testing at the appropriate time/age
Case Study: Take Home Messages

- Risk assessment and genetic testing gives information to patient AND family members
  - Some family members may want this information and some may not

- Genetic testing, when informative, can help individuals make decisions about early detection and risk-reduction

- Can also relieve anxiety about cancer risk (if negative)

- Informed decision-making imperative

- Additional follow-up support and/or counseling sometimes necessary
Alternative Cancer Risk Assessment Tests
Entice the purchase and use of tests directly to consumers through advertising
- 960,000 specific single-nucleotide polymorphism (SNPs)
- Reports on 240+ health conditions and traits
- Testing for 40+ inherited conditions
- Discover your ancestry composition
- Updates on your DNA as science advances
- Eventual goal: whole genome sequencing

http://www.23andme.com
ConnectMyDNA
Learn About Yourself with a DNA Self-Discovery Kit

$29
buy now!

details
Discover more about your identity with this cutting-edge deal from ConnectMyDNA, which uses genetic fingerprinting to display your DNA pattern in a uniquely designed emblem:

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• Get your unique DNA signature
• Use the Gene Ring to visually compare your DNA profile to friends and family
• Compare your DNA to regions and countries from around the world to discover

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Buy first, then share a special link. If three friends buy, yours is free!

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QUESTIONS?