Objeclves

• Review genetic testing criteria for Breast cancer.
• Discuss single gene vs. multi-gene panel approaches.
• Discuss Variants of Uncertain Significance (VUS)
• Recognize the importance of taking a thorough family history.
• Review new information regarding cancer risks in BRCA carriers.

Fags for Hereditary Breast Cancer

• Early-onset breast cancer diagnosis (≤ 50)
• Bilateral presentation or multiple primary cancers
• Male breast cancer
• Families with 3 or more cases of breast cancer over 2 or more generations
• Triple negative histopathology (≤ 60)
• Ashkenazi Jewish ancestry
• A history of breast and ovarian cancer in the same individual
• Specific associations of different primary cancers in the same side of the family
  • Breast, ovarian, prostate, pancreatic
  • Breast, endometrial, thyroid
  • Lobular breast, and stomach

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John M. Cassel Memorial Breast Cancer Symposium 2017
Hereditary Breast Cancer Syndromes Update

Disclosures

• No commercial relationship relevant to this presentation
The case for multigene panels

Changing Landscape of Genetic Testing

- Cancer genetic testing is currently offered by >30 laboratories in the United States
- Genetic testing options consist of:
  - Syndrome-driven testing
  - Multi-gene panels
- Indications for multi-gene panels:
  - Personal and/or family history is strongly suggestive of a hereditary component
  - Personal and/or family history could be explained by 2 or more hereditary cancer syndromes
- Multi-gene panels are rapidly gaining popularity in clinical practice

Multi-gene Panel Testing

Benefits
- Increased diagnostic yield
- Minimized testing fatigue
- Identification of unforeseen opportunities for prevention
- Cost effectiveness
  - Evidence-based research testing

Challenges
- Increased likelihood of identifying variants of unknown significance (VUS)
- Limited clinical utility for moderate-risk and newer genes
- Incidental results may be accompanied by anxiety
- Wide variation among testing laboratories
  - Techniques and interpretation

Breast Cancer and Multigene Germline Sequencing in ~2,700 Women with Breast Cancer

Figure 1. Distribution of pathogenic variants in women with breast cancer (n=2700)

- BRCA1 and BRCA2
- Other genes associated with breast cancer risk
- Lynch syndrome genes
- Other genealogical and germline sequences

10% of all BC patients had at least one germline mutation.

- BRCA1 (or 46%), BRCA2 (25%), non-BRCA1/2 (39%).
• 35 y/o female of AJ descent diagnosed with right DCIS Stage 0
• Evaluated in an Outside Hospital
• Genetic testing was offered by treating MD

Recommended testing in outside facility for DCIS

• 2014 - Multisite 3 Ashkenazi Jewish – Negative
• 2015 - Breast Cancer panel; BRCA1, BRCA2, PALB2, PTEN and TP53- Negative

Treatment: Right nipple sparing mastectomy
Tamoxifen, reportedly not offered

At age 37

• Patient had a uterine evaluation as part of the fertility evaluation
• Stage 4 uterine adenocarcinoma high grade with metastases bladder and mesentery
• S/P Total abdominal hysterectomy, BSO, partial bladder resection and lymph nodes dissection
Testing history

- 2017-34 gene panel;

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>Pathogenic Mutation: c.3943delCAHG</th>
</tr>
</thead>
</table>

**SUMMARY**

POSITIVE: Pathogenic Mutation Detected

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Treatment plan

- Chemotherapy: Carboplatin and Taxol with Neulasta
- Radiation oncology-evaluated but treatment not recommended at this time
- Colonoscopy pending—to be done after chemotherapy

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Lynch Syndrome

- Approximately 3-5% of colorectal cancers (CRC) are due to Lynch Syndrome.
- Lynch Syndrome is caused by autosomal dominantly inherited mutations in the mismatch repair (MMR) genes MLH1, MSH2 (EPCAM*), MSH6 and PMS2 and EPCAM.
- Individuals with Lynch Syndrome have a substantial increased risk of developing colorectal cancer.

*EPCAM deletions that disrupt the 3' end lead to inactivation of the adjacent MSH2 gene through methylation induction of its promoter.*
Lynch Syndrome

Colon cancer: 

Multigene Panel Testing Provides a New Perspective on Lynch Syndrome

Results
• Reviewed of 34,981 patients who had multigene panel testing from March 2012 and June 2015.
• 528 were found to carry a pathogenic variant in the mismatched repair (MMR) genes.
• 63 patient (11.9%) had breast cancer only
• 144 (27.3%) had colorectal cancer only
• For those with breast cancer only MSH6 and PMS2 were more frequent

Canadian study
• An increased risk of breast cancer in MSH2 mutation carriers was demonstrated in a Canadian familial cancer registry. Women with breast cancer often had a personal and family history of multiple LS-related malignancies. These results suggest a potential role for intensified breast cancer surveillance among women with LS (J Med Genetics, 2017)
• Prospective cohort study 1997-2011 female carriers;  
  - BRCA1-6,036  
  - BRCA2-3,820  
  5,046 unaffected and 4,810 affected  
  • From large national studies: UK, Netherlands and France

### Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers

**Risks BRCA1/2**

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime breast cancer risk to age 80</td>
<td>72%</td>
<td>69%</td>
</tr>
<tr>
<td>Incidence (per y)</td>
<td>30-40y</td>
<td>40-50y</td>
</tr>
<tr>
<td>Contralateral breast cancer (risk for 20y)</td>
<td>40% (2.5 per year)</td>
<td>26% (1.3% per year)</td>
</tr>
<tr>
<td>Ovarian Cancer risk</td>
<td>44%</td>
<td>17%</td>
</tr>
</tbody>
</table>

### Direct to Consumer Genetic testing

Recently available recently for BRCA1 and BRCA2  
$99 with genetic counseling  
• Laboratory do not report variant of uncertain significance  
  (~ 10% are reclassified as positive)  
• Genetic counselor only if requested by consumer.  
• This test is consider incomplete in 2017 given the availability of additional genes.  
• Probability of false sense of security  
• Genomic Health literacy is an issue —since this is order by non genetic providers

American College of Genetic and Genomics statement Direct-to-consumer genetic testing: a revised position statement of the American College of Medical Genetics and Genomics:  
- Recommends certified medical genetics or genetic counselor-to interpret test results in light of personal and family history  
- The consumer should be fully informed regarding what the test can and cannot say about his or her health.  
- The consumer implications of genetic test results for family members.  
- The scientific evidence base describing the validity and utility of a genetic test should be clearly stated  
The general public and the health care provider community need to be aware of the potential utility and limitations of such tests.
### High-Risk Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk</th>
<th>Age</th>
<th>Other Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2</td>
<td>Up to 83%</td>
<td>25-29</td>
<td>Colon, pancreatic, ovarian, prostate, melanoma</td>
</tr>
<tr>
<td>CDH1</td>
<td>39-52%</td>
<td>30</td>
<td>Consider based on family history</td>
</tr>
<tr>
<td>PTEN</td>
<td>Up to 80%</td>
<td>30-35</td>
<td>Recommend</td>
</tr>
<tr>
<td>STK11</td>
<td>45-50%</td>
<td>25</td>
<td>Lobular</td>
</tr>
<tr>
<td>TP53</td>
<td>Up to 79%</td>
<td>20-29</td>
<td>Recommend</td>
</tr>
</tbody>
</table>

### Moderate-Risk Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk</th>
<th>Age</th>
<th>Other Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>24-48%*</td>
<td>40</td>
<td>Consider based on family history</td>
</tr>
<tr>
<td>CHEK2</td>
<td>30%*</td>
<td>40</td>
<td>Recommend</td>
</tr>
<tr>
<td>NBN</td>
<td>Up to 30%</td>
<td>40</td>
<td>Recommend</td>
</tr>
<tr>
<td>NF1</td>
<td>Elevated</td>
<td>30-50</td>
<td>Recommend</td>
</tr>
<tr>
<td>PALB2</td>
<td>33%*</td>
<td>30</td>
<td>Endometrial, thyroid, renal, colorectal, melanoma</td>
</tr>
<tr>
<td>BARD1</td>
<td>Elevated</td>
<td>IE</td>
<td></td>
</tr>
<tr>
<td>MRE11A</td>
<td>Elevated</td>
<td>IE</td>
<td></td>
</tr>
</tbody>
</table>

* IE: Insufficient Evidence

### DCG Genetics Evaluation Process

1. **Referral to DCG**
2. **Triaging**
3. **Pre-test Consultation/Testing**
4. **Follow-up and counseling**
5. **Post-test consultation/testing**
6. **Follow-up if necessary**

### The Gene Team

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- Jeff Boyd, PhD

**Miami Cancer Institute**

**DCG Genetics Evaluation Process**

**High-Risk Genes**

- ATM: 24-48%
- CHEK2: 30%
- NBN: Up to 30%
- NF1: Elevated
- PALB2: 33%
- BARD1: Elevated
- MRE11A: Elevated

**Moderate-Risk Genes**

- ATM: 24-48%
- CHEK2: 30%
- NBN: Up to 30%
- NF1: Elevated
- PALB2: 33%
- BARD1: Elevated
- MRE11A: Elevated

**IE: Insufficient Evidence**
References

- Genet Med advance online publication 17 December 2015
- NCCN guidelines 2017
- ACMG website: American College of Genetic and Genomics statement Direct-to-consumer genetic testing