Genetic Testing Updates for Surgeons

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Disclosures

• Ambry speaker
Outline

• “What the Breast Surgeon Needs to Know”
  - Plichta et al., Ann Surg Oncol 2019

• Genetic mutations and association with second breast cancers
What the Breast Surgeon Needs to Know

1. Identification of patients for cancer related genetic testing

2. Updated testing (pre-2013)

3. Re-testing + pre-test counseling

Plichta et al Ann Surg Oncol 2019
What the Breast Surgeon Needs to Know

4. Initial cancer genetic testing

5. Interpretation, post-test counseling and management

6. Cascade testing of family members
What the Breast Surgeon Needs to Know

7. Interpretation of other tests (i.e. DTC testing)

8. Somatic genetic tests

9. Management of variants of unknown significance

Plichta et al Ann Surg Oncol 2019
Initial Cancer Genetic Testing
Who is Allowed to Order Genetic Testing?

Any physician with expertise can order genetic testing

- ASBrS
- ASCO
- NAPBC
- AMA
- NCCN
- Insurance Companies

Plichta et al Ann Surg Oncol 2019
American Society of Breast Surgeons

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.

Adapted from ASBrS Consensus Guideline, February 2019
Who Orders Genetic Testing?

Survey of 907 ASBrS surgeons

- By me: 54%
- Genetics Counselor: 35%
- Medical Oncologist: 10%
- Someone else: 1%

Beitsch et al Ann Surg Oncol 2014; 21:4104
NAPBC Requirements for “Expertise”

- How to get “expertise”?
  - Providing cancer risk assessment on a regular basis
  - Employ a model that incorporates pre and post test counseling
  - 2 CME; one related to BRCA and one related to non-BRCA genes
  - Educational seminars
Types of Genetic Testing

- Single Syndrome Testing
- Multigene Panel Tests
- Polygenic Risk Score
- Direct-to-Consumer Tests
Multigene Testing to Consider for Hereditary Breast Cancer

**BRCAplus**
- 8 gene management guidelines panel
- Faster TAT (7-10 days)

**BreastNext**
- Comprehensive analysis of 17 genes for families with breast cancer

**CancerNext**
- Comprehensive test of 34 genes for families with breast and other types of cancer
Cancer Risk Assessment and Counseling

Pre-Test Counseling:
- Collect FHx out to third degree relatives
- Evaluate cancer risk
- Educate patient
- Prepare for possible outcomes
- On demand access to genetic counselors

NCCN guidelines, www.nccn.org
Cancer Risk Assessment and Counseling

Post-Test Counseling:

• Inform of results and impact to management
• Interpretation of results
• Inform and test at-risk family members
• Support Groups
• Research studies

NCCN guidelines, www.nccn.org
Who Should Get Genetic Testing?

Signs of Hereditary Cancer
(Adapted from Published Guidelines)

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple</td>
<td>2 or more primary cancers in the same person</td>
</tr>
<tr>
<td></td>
<td>3 or more breast or other cancers on the same side of the family</td>
</tr>
<tr>
<td>Young</td>
<td>BREAST CANCER DIAGNOSED ≤45Y, TRIPLE NEGATIVE BREAST CANCER ≤60Y</td>
</tr>
<tr>
<td>Rare</td>
<td>MALE BREAST CANCER, OVARIAN CANCER, PANCREATIC CANCER</td>
</tr>
<tr>
<td>Metastatic</td>
<td>METASTATIC PROSTATE CANCER AT ANY AGE</td>
</tr>
<tr>
<td>Ancestry</td>
<td>ASHKENAZI JEWISH</td>
</tr>
</tbody>
</table>
Who Should Get Genetic Testing?

Consensus Guideline on Genetic Testing for Hereditary Breast Cancer, ASBrS 2019

“Genetic testing should be made available to all patients with a personal history of breast cancer”
### Variant Prevalence in those not fulfilling NCCN Criteria

**Beitsch P et al: Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle?**

<table>
<thead>
<tr>
<th>NCCN criteria</th>
<th>% with P/LP Variant</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>49% met criteria</td>
<td>9.4%</td>
<td></td>
</tr>
<tr>
<td>50% did not meet criteria</td>
<td>7.9%</td>
<td>0.42</td>
</tr>
</tbody>
</table>

N= 959 Patients

Of 80 genes tested, 11 were breast related

BRCA genes:

<table>
<thead>
<tr>
<th>NCCN Criteria</th>
<th>% with P/LP Variant</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met criteria</td>
<td>2.5%</td>
<td>0.02</td>
</tr>
<tr>
<td>Did not meet criteria</td>
<td>0.6%</td>
<td></td>
</tr>
</tbody>
</table>
Genetic Testing Interpretation + Next Steps
What the Breast Surgeon Needs to Know

Interpretation+ Next Steps:

• Ask2Me.org for more information
• NCCN Management Guidelines
• Discuss with geneticist or GC or refer as needed
• Surgeon must understand the role of screening, chemoprevention, surgery, etc…

Plichta et al  Ann Surg Oncol 2019
Beitsch et al  Ann Surg Oncol 2014; 21:4104
Germline Variants and Associated Breast Cancer Risk

<table>
<thead>
<tr>
<th>Gene</th>
<th>Easton et al 2015 (RR)</th>
<th>Couch et al 2017 (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>11.4</td>
<td>---</td>
</tr>
<tr>
<td>BRCA2</td>
<td>11.7</td>
<td>---</td>
</tr>
<tr>
<td>PALB2</td>
<td>5.3</td>
<td>7.46</td>
</tr>
<tr>
<td>CDH1</td>
<td>6.6</td>
<td>---</td>
</tr>
<tr>
<td>TP53</td>
<td>105</td>
<td>---</td>
</tr>
<tr>
<td>ATM</td>
<td>2.8</td>
<td>2.78</td>
</tr>
<tr>
<td>CHEK2 truncating</td>
<td>3.0</td>
<td>2.31</td>
</tr>
<tr>
<td>NF1</td>
<td>2.6</td>
<td>Not significant</td>
</tr>
<tr>
<td>NBN</td>
<td>2.7</td>
<td>Not significant</td>
</tr>
<tr>
<td>BARD1</td>
<td>---</td>
<td>2.16</td>
</tr>
<tr>
<td>RAD51D</td>
<td>---</td>
<td>3.07</td>
</tr>
<tr>
<td>PTEN</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>STK11</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>CHEK2 missense</td>
<td>---</td>
<td>1.48</td>
</tr>
</tbody>
</table>
### Variants and NCCN Guideline Recommendations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Risk Reducing Mastectomy Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>Discuss option of RRM</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Discuss option of RRM</td>
</tr>
<tr>
<td>PTEN</td>
<td>Discuss option of RRM</td>
</tr>
<tr>
<td>TP53</td>
<td>Discuss option of RRM</td>
</tr>
<tr>
<td>ATM</td>
<td>Insuff evidence, manage based on family hx</td>
</tr>
<tr>
<td>CDH1</td>
<td>Insuff evidence, manage based on family hx</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Insuff evidence, manage based on family hx</td>
</tr>
<tr>
<td>NBN</td>
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<tr>
<td>STK11</td>
<td>Insuff evidence, manage based on family hx</td>
</tr>
<tr>
<td>BARD1</td>
<td>Insuff evidence, manage based on family hx</td>
</tr>
</tbody>
</table>

*“High penetrance”*

*“Moderate penetrance”*
Cancer risk estimates for a 47 year old female with a pathogenic ATM variant

ATM (Ataxia Telangiectasia Mutated) is a gene located on chromosome11 (11q22-q23). Pathogenic variants in ATM are responsible for Hereditary Breast Cancer Syndrome, which show(s) autosomal dominant inheritance. Pathogenic variants in ATM are significantly associated with the following cancers: breast (female), colorectal, gastric, pancreatic.

Risk Estimates as a Summary Graph
Finding a Genetic Counselor

NSGC.org Homepage

Telehealth GC Options
Impact on Medical Management – BRCA1/2

- Annual breast MRI beginning between ages 25-29, annual MRI and mammogram after age 30
- Consideration of risk-reducing mastectomy
- Recommendation of risk-reducing oophorectomy
- Male breast cancer and prostate cancer screening for male mutation carriers
- Consider screening for pancreatic cancer and melanoma in certain individuals
- Option of PARP inhibitor therapy for patients with advanced ovarian cancer
Direct-to-Consumer vs. Clinical Genetic Testing
MIT Review 2017, Antonia Regalaldo, “2017 was the year that consumer DNA testing blew up”

1 in 25 people has had DTC testing of some sort
### Direct-to-Consumer vs. Clinical Testing

<table>
<thead>
<tr>
<th>DTC Testing</th>
<th>Clinical Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic/Limited Technology: SNP Array</td>
<td>Technology: Full gene sequencing and deletion/duplication analysis</td>
</tr>
<tr>
<td>Not a comprehensive risk assessment</td>
<td>Comprehensive assessment for one or more diseases</td>
</tr>
<tr>
<td>Results <strong>not</strong> intended for medical use</td>
<td>Results are intended for medical use with guidance of a healthcare professional</td>
</tr>
</tbody>
</table>
DTC Tests – A Cautionary Tale

Risk of False Positives

- 49 cases of variants identified by DTC sent for clinical confirmation at Ambry
- Use caution when interpreting DTC tests
- Clinical confirmation should be considered

Tandy-Connor S. *et al*, Genetics in Medicine, 2018
DTC Tests – A Cautionary Tale
Risk of False Negatives

Study presented at ACMG - 100,000 pts

<table>
<thead>
<tr>
<th>N=5,000 pts with BRCA variants</th>
<th>Founder Mutations</th>
<th>Non-Founder mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jews</td>
<td>81%</td>
<td>19%</td>
</tr>
<tr>
<td>All others</td>
<td>6%</td>
<td>94%</td>
</tr>
</tbody>
</table>
World population

11 million people with Ashkenazi Jewish heritage candidate for 23andMe BRCA test

7.7 billion people without Ashkenazi Jewish heritage 23andMe BRCA test not useful

2% Positive result
Must confirm results

98% Negative result
Results do not r/o risk

Must get a clinical test

New York Times, Feb 1 2019, Editorial Board
What do I do with a DTC report?

- Proceed with Caution
  - Do not make medical management recommendations based on the information provided

- Refer to a Genetic Counselor
  - Find a Genetic Counselor on NSGC.org

- Consider Confirmatory Testing
  - Through an experienced clinical laboratory, when applicable

Ambry Genetics
A Konica Minolta Company
Management of VUS
Possible Classifications/Results

- Pathogenic
- Likely pathogenic
- Uncertain significance
- Likely benign
- Benign

"Positive"  "VUS"  "Negative"

ACMG Standards and Guidelines, Genet Med 2015
## Variants of Unknown Significance (VUS)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>%VUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tung et al</td>
<td>488</td>
<td>33.2%</td>
</tr>
<tr>
<td>PROMPT registry, Balmana et al</td>
<td>518</td>
<td>37.0%</td>
</tr>
<tr>
<td>Mersh et al</td>
<td>304,000</td>
<td>18.7%</td>
</tr>
</tbody>
</table>
VUS Rates - Ambry Panels

<table>
<thead>
<tr>
<th>Panel</th>
<th>Positive</th>
<th>VUS</th>
<th>Negative</th>
<th>MUTYH Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCAPlus</td>
<td>88.92%</td>
<td>5.30%</td>
<td>5.78%</td>
<td>6.55%</td>
</tr>
<tr>
<td>GYNplus</td>
<td>83.31%</td>
<td>10.14%</td>
<td>6.55%</td>
<td>6.55%</td>
</tr>
<tr>
<td>BreastNext</td>
<td>70.22%</td>
<td>19.71%</td>
<td>10.52%</td>
<td>8.76%</td>
</tr>
<tr>
<td>OvaNext</td>
<td>63.84%</td>
<td>14.44%</td>
<td>11.47%</td>
<td>11.08%</td>
</tr>
<tr>
<td>ColoNext</td>
<td>72.29%</td>
<td>14.44%</td>
<td>11.47%</td>
<td>11.08%</td>
</tr>
<tr>
<td>CancerNext</td>
<td>60.01%</td>
<td>27.35%</td>
<td>11.08%</td>
<td>13.27%</td>
</tr>
<tr>
<td>CancerNext-Expanded</td>
<td>49.16%</td>
<td>36.07%</td>
<td>11.08%</td>
<td>13.27%</td>
</tr>
</tbody>
</table>
Managing Patients with a VUS
Key Take Home Points

• Manage patients with a VUS based on family history and NOT based on the genetic test result
• Surgical decisions should NOT be made based on a VUS
• Testing for a VUS is NOT recommended for family members
Re-Characterization of Variants

Benign, likely benign
6.0% reclassified

- 99.9% likely benign to benign
- 0.1% upgraded to VUS

Pathogenic, likely pathogenic
3.1% reclassified

- 2.2% likely path to pathogenic
- 0.1% upgraded to VUS
- 97.3% remained same

VUS
7.7% reclassified

- 91.2% downgrade to benign/likely benign
- 8.7% upgrade to likely pathogenic/pathogenic

Mersch et al 2018;320:1266
Variants in Patients with Second Breast Cancers
## Contralateral Breast Cancer Risk

### BRCA Carriers

<table>
<thead>
<tr>
<th></th>
<th>CBC risk 5 yrs</th>
<th>CBC risk 10 yrs</th>
<th>CBC risk 15 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>15%</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>9%</td>
<td>19%</td>
<td>23%</td>
</tr>
<tr>
<td>BRCA -</td>
<td>3%</td>
<td>5%</td>
<td>--</td>
</tr>
</tbody>
</table>
**CBC Risk in BRCA Mutation Carriers**

**Prospective Study**

<table>
<thead>
<tr>
<th>Yrs Since First Breast Cancer</th>
<th>Cumulative Risk (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1:</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;20yrs</td>
<td>53%</td>
</tr>
<tr>
<td>First BC &lt;40yo</td>
<td>60%</td>
</tr>
<tr>
<td>First BC &gt;50yo</td>
<td>38%</td>
</tr>
<tr>
<td><strong>BRCA2:</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;20yrs</td>
<td>65%</td>
</tr>
<tr>
<td>First BC &lt;40yo</td>
<td>68%</td>
</tr>
<tr>
<td>First BC &gt;50yo</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Kuchenbaekeer et al JAMA 2017; 317:2402*
CBC risk for Non-BRCA Genes

ATM:

- Not associated with CBC risk
- Risk of breast cancer is increased in those undergoing radiation therapy
- Homozygous

Bernstein et al Int J Radiat Biol 2017; 93:1121
Bernstein et al JNCI 2010; 102:475
CBC risk for Non-BRCA Genes

CHEK2

- CBC risk mostly associated with c.1100delC variant
- Breast Cancer Association Consortium: 22 studies OR 2.77 for a second breast cancer OR 3.52 for a second breast cancer if the primary breast cancer was ER positive
- One WeCare study showed no association

Kriege et al Brit J Cancer 2014;111:1004
Mellemkjaer Br J Cancer 2008; 98:728
Weischer et al JCO 2012;30:4308
CBC risk for Non-BRCA Genes

**PALB2**

- WeCare study showed that deleterious truncating *PALB2* mutations were higher in CBC cohort
- Small numbers

*Tischkowitz et al Hum Mutat 2012;33:674*
• Genetic Mutation Data Removed to protect the integrity of unpublished data
Conclusions

• Surgeons will be ordering more genetic testing in the future
• Universal testing for all newly diagnosed breast cancer patients?
• Direct to consumer testing will continue to grow
• More VUS, surgeons need to be comfortable discussing
• Further refinement of who needs a bilateral mastectomy for non-BRCA gene carriers
Thank you
Appendix
Population Based Screening

- *Claire MK et al Proc Natl Acad Sci 2014; 111: 14205*
- Population based study of 8,000 males in Israel
- 50% of BRCA carriers had no close family history or breast of ovarian cancer
- Most studies in AJ population
Population Based Screening

- *JAMA 2017; 318:825*
  - Simultaneous sequencing of tumor and normal DNA and correlating with std clinical genetic testing
  - Of 1040 pts, 182 had positive results
  - 101 of these 182 pts would not have been tested using clinical guidelines
  - Prostate, breast, renal, colon cancers