
Presenter: Emily Kuchinsky, MS, CGC
Experiences with Genetic Testing

• “I am BRCA1/2 negative, so I can never get breast cancer.”
• Result misinterpreted and patient was diagnosed with cancer
• No genetic counseling or testing offered
Outline

• Risk Assessment
  – Risk Models
  – Genetic Testing

• Role of Expanded Genetic Testing
  – Most common mutations beyond BRCA1/2
  – Benefits and Limitations
Hereditary cancer syndromes are uncommon

- 90 – 95% of all cancers are sporadic
- Only 5 – 10% of all cancers are hereditary
- Some cancers show familial clustering
Red Flags for Referring Patients for Genetic Counseling

Features in the family history which may suggest HBOC:
- Relative with a \textit{BRCA1} or \textit{BRCA2} mutation
- Breast cancer diagnosed at an early age (i.e. less than age 45 or 60 or under with TNBC)
- Ovarian cancer diagnosed at any age
- Several women in multiple generations with breast cancer and/or ovarian cancer on same side of family
- Multiple primary cancers in the same individual
- Male breast cancer
- Ashkenazi Jewish ancestry
Testing Affected Relative First

• Test relative with highest chance of positive result FIRST

• If BRCA1/2 positive
  – unaffected patient with negative results → Reassurance

• If negative
  – unaffected patient → no testing warranted
  – continue to manage based on family hx (i.e. breast MRI)
ACS Guidelines for Breast Screening with MRI as an Adjunct to Mammography

• **Recommend Annual MRI Screening (Based on Evidence*)**
  - BRCA mutation
  - First-degree relative of *BRCA* carrier, but untested
  - Lifetime risk ∼20–25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history

• **Recommend Annual MRI Screening (Based on Expert Consensus Opinion†)**
  - Radiation to chest between age 10 and 30 years
  - Li-Fraumeni syndrome and first-degree relatives
  - Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives
ACS Guidelines for Breast Screening with MRI as an Adjunct to Mammography

• **Insufficient Evidence to Recommend for or Against MRI Screening**
  – Lifetime risk 15–20%, as defined by BRCAPRO or other models that are largely dependent on family history
  – Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)
  – Atypical ductal hyperplasia (ADH)
  – Heterogeneously or extremely dense breast on mammography
  – Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)

- **Recommend Against MRI Screening (Based on Expert Consensus Opinion)**
  - Women at <15% lifetime risk
T-C Lifetime risk: 25.3%

LEGEND
- Red: Bilateral breast cancer
- Gray: Breast cancer
- Green: Lung cancer
Next Steps???
Genetic Testing Considerations

- Motivations for testing?
- Implications on Health and Life Insurance?
- Insurance require genetic counseling prior to genetic testing?
- Cost?
What about expanded testing?

Timothy J. R. Harris & Frank McCormick. The molecular pathology of cancer
Nature Reviews Clinical Oncology 7, 251-265 (May 2010)

- Two cohorts
  - Cohort 1: 1781 individuals (no previous BRCA1/2 testing), all phx breast cancer
  - Cohort 2: 377 (previous negative BRCA1/2 testing, 7 since found to have BRCA mutation excluded), all phx breast ca
- 25 gene panel, performed del/dup studies
<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Additional Characteristics</th>
<th>Cohort 2</th>
<th>Additional Characteristics</th>
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</thead>
<tbody>
<tr>
<td>BRCA positive</td>
<td>9.3%</td>
<td>3 had BRCA mutation and 1 other gene</td>
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<tr>
<td>Other HBOC gene</td>
<td>3.9%</td>
<td>CHEK2 most common (33%), then PALB2 (15%) and ATM (15%)</td>
<td>2.9%</td>
<td>None were AJ (P=.026)</td>
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<tr>
<td>Incidental Finding</td>
<td>0.3%</td>
<td>5/6 had Lynch syn genes</td>
<td>0.8%</td>
<td></td>
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<tr>
<td>(ex. Lynch Syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gene)</td>
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<tr>
<td>Total</td>
<td>13.5%</td>
<td></td>
<td>3.7%</td>
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<tr>
<td>Total, excluding</td>
<td>4.3%</td>
<td></td>
<td>3.7%</td>
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<tr>
<td>BRCA1/2</td>
<td></td>
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<tr>
<td>VUS Rate</td>
<td>41.7%</td>
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<td>41.6%</td>
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PALB2 Breast Cancer Risk

- Breast cancer risk previously reported as 2.3 fold increase (Rahman et al. 2007), or 20-40% lifetime risk
- Antoniou et al. 2014, NEJM
  - 175 families with at least one member who had breast cancer and a germline loss-of-function mutation in PALB2
  - 311 woman (229 with breast cancer) and 51 men (7 with breast cancer) with PALB2 mutations
  - Relative breast cancer risk 8-9 times higher up to 40 years of age, 6-8 times higher between 40 and 60, and ~5 at 60 and older
  - 2.3 relative risk for ovarian cancer
  - 8.3 relative risk for male breast cancer
**CHEK2 Clinical Significance: Breast Cancer**

*Fig 4.* Comparison of breast cancer risk. Estimates of relative risk and cumulative risk of breast cancer at 70 years of age is shown for white women in the general population, for white women with *CHEK2*1100delC heterozygotes in studies of familial breast cancer, and for women with *BRCA1* and *BRCA2* mutation heterozygotes in family studies of breast cancer risk. Data adapted (Chen et al).
ATM

- Homozygous have ataxia-telegiectasia
  - Cerebellar ataxia
  - Immune disease
  - Increased risk for malignancy (30% leukemias and lymphomas)
- Heterzygous (1% of the population)
  - Increased risk breast ca (2-4 fold, 17-52%)
    - Age of onset, may be dependent on family history
  - Increased risk pancreas ca (?magnitude)
  - Possible increased risks for other cancers (prostate, colon)
  - Sensitive to radiation

Benefits and Limitations of Panel Testing

**Benefits**
- Cost
- One sample submission
- Higher likelihood of receiving positive result
- Possible Change in Medical Management
- Incidental Findings

**Limitations**
- Lack of data on risk-benefit ratio for moderate penetrance genes
- Higher likelihood of receiving VUS
- Longer TAT
ACMG Classification of Variants

- Benign
- Likely benign
- Unknown significance
- Likely pathogenic
- Pathogenic
True Negatives? In Moderate Penetrance Genes

- CHEK2 and ATM moderate penetrance genes (2 to 3-fold increase risk for breast ca)
- Cannot generalize management from high penetrance genes
- CHEK2 and other mod genes often do not track with breast in the family ➔ cautious about reassurance to mutation negative family members
NCCN Guidelines

• Available For:
  - BRCA1/2
  - TP53
  - PTEN
  - STK11
  - PALB2
  - ATM
  - CHEK2
Change to Genetic Counseling Paradigm

- Less focus on description of individual genes → Binning
- Pull out examples of genes
  - Higher Penetrance
  - Moderate Penetrance
  - Incidental Findings
Change to Genetic Counseling Pardigm

- More time on types of results possible, especially VUS
  - “The car is gray.”
  - “The car is grey.”
- More time on testing options
  - BRCA1/2
  - High Risk Breast Panel (BRCA1/2 Plus 5 High Penetrant Genes (TP53, CDH1, STK11, PTEN, PALB2))
  - Clinically Actionable Breast Panel (High Risk Panel Plus ATM and CHEK2)
  - Breast Panel (High Risk and Moderate Penetrant Genes)
  - Pan-cancer panel (25, 42 and beyond gene panels associated with breast, colon, ovarian and uterine cancers)
Phase Two: Interpretation

I think I found a corner piece.
Phone a Friend

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https://encrypted-tbn2.gstatic.com/images?q=tbn:ANd9GcT-J2B9XUQ_iLAphipavHj1k1_ZAgC2Jbdcltv1rA1msIgTJsquog