Genetic Testing for Breast Cancer

Outline

• The hereditary basis of breast cancer
  – BRCA1/2
  – Additional high- and moderate-risk genes

• Current approach to clinical genetic testing
  – Single-gene vs. multi-gene panels

• Case vignettes

Breast Cancer Etiology

- Sporadic: 10%
- Familial: 20%
- Hereditary: 70%
Flags 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

Breast Cancer Etiology

- Sporadic: 10%
- Familial: 20%
- Hereditary: 70%
- BRCA1 and BRCA2: 50%
- ~15 other genes known in 2015
- Unknown: 20%

BRCA1 and BRCA2

Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1

HBOC >20 years later...

- BRCA1/2 are tumor suppressor genes whose mutations are highly penetrant.
- Well-defined, increased lifetimes risks for breast, ovarian, prostate, pancreatic cancer are associated with BRCA mutations.
- Younger ages at cancer diagnosis and increased risks for second primary cancers are common in HBOC.
- There are well-defined cancer risk management strategies.
- Founder mutations in specific populations have been reported.
- Genotype-phenotype correlations have started emerging.

HBOC Lifetime Cancer Risks

- Breast Cancer
- Ovarian Cancer
- Male Breast Cancer
- Prostate Cancer
- Pancreatic Cancer

WOMEN

- Breast Cancer Management: Breast awareness starting at 18, clinical breast exam every 6-12 months and breast MRI annually, starting at age 25, annual breast MRI and mammogram at age 30-35, optional risk-reducing mastectomy, discuss chemoprevention options.
- Ovarian Cancer Management: Risk-reducing bilateral salpingo-oophorectomy before age 35-40, or after completion of childbearing. Consider transvaginal ultrasound and CA-125 every 6 months, beginning at age 30 or 5-10 years before earliest ovarian cancer in family, discuss chemoprevention options.

MEN

- Breast Cancer Management: Breast self-exam training and education, starting at age 25, clinical breast exam every 6-12 months, starting at age 35, consider mammogram at age 40, annual mammogram if indicated based on baseline study findings.
- Prostate Cancer Management: Consider prostate screening starting at age 40 with digital rectal exam and PSA.

NCCN, v2.2015

www.ambrygen.com
• Carrier rate among Ashkenazi Jews = 1/40 (2.5%)
• Carrier rate among Ashkenazi Jewish women with breast cancer at any age = 1/10 (10%)

Ashkenazi Jews
(3 founder mutations, particularly BRCA1, 185delAG)

• Carrier rate among Bahamians = 1/35 (2.8%)
• Carrier rate among Bahamian women with breast cancer at any age = 1/20 (20%)

Bahamians
(7 founder mutations, particularly BRCA1, IVS13+1G>A)

HBOC More Recent Data


Genetic testing for BRCA1/2 genes is common practice among general practitioners, breast/GYN specialists, and cancer genetics centers.
When to offer BRCA testing? (NCCN v2, 2015) (1/2)

- Breast cancer diagnosis and any of the following:
  - Age at diagnosis ≤ 45
  - Age at diagnosis ≤ 50 AND any of the following:
    - An additional breast ca primary
    - ≥ 1 close relative with BC at any age, pancreatic or prostate ca (Gleason score ≥ 7)
    - Limited family history
  - Any age at diagnosis AND any of the following:
    - ≥ 2 individuals with BC, pancreatic or prostate ca in the same side of the family
    - ≥ 1 close relative with BC diagnosed ≤ 50 or ovarian ca at any age
    - Ashkenazi Jewish ancestry
    - Prior history of ovarian/fallopian tube cancer
    - Triple negative histopathology diagnosed at ≤ age 60
    - Male breast ca

When to offer BRCA testing? (NCCN v2, 2015) (2/2)

- Prostate cancer diagnosis (Gleason score ≥ 7) AND ≥ 1 close blood relative with any of the following:
  - Breast cancer ≤ age 50
  - Invasive ovarian cancer
  - Pancreatic cancer
  - Prostate cancer (Gleason score ≥ 7)

- Pancreatic cancer diagnosis AND any of the following:
  - Ashkenazi Jewish ancestry
  - ≥ 1 close blood relative with any of the following:
    - Breast cancer ≤ age 50
    - Invasive ovarian cancer
    - Pancreatic cancer

Breast Cancer Etiology

- Sporadic
- Familial
- Hereditary
- BRCA1 and BRCA2
- ~15 other genes known in 2015
Hereditary Breast Cancer Genes

<table>
<thead>
<tr>
<th>Type</th>
<th>Increased Risks</th>
<th>Lifetime Breast Cancer Risk (%)</th>
<th>Established Testing and Risk Management Guidelines</th>
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</thead>
<tbody>
<tr>
<td>High-risk</td>
<td>Well-defined for ≥ 1 type of cancer</td>
<td>~60-80%</td>
<td>Yes</td>
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<tr>
<td></td>
<td>BRCA1, BRCA2, TP53, PTEN, CDH1, PALB2(*)</td>
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<td></td>
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<tr>
<td>Moderate-risk</td>
<td>Less-defined for mostly one type of cancer</td>
<td>~20-40%</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>CHEK2, ATM, STK11, PALB2(*)†, RAD50, RAD51C, RAD51D, BARD1, BRIP1, MRE11A, NBN, NF1</td>
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</table>

How does the expanded genetic landscape of hereditary breast cancer reflect into current clinical practice?
Single-gene Testing

- **Scope:** One or a number of genes associated with a single hereditary cancer syndrome.
- **Technology:** Sanger sequencing and MLPA

Multi-gene Panel Testing

- **Scope:** Multiple genes associated with more than one hereditary cancer syndrome (simultaneous analysis).
- **Technology:** Next-Generation Sequencing/Targeted Microarray

**Benefits**
- Increased diagnostic yield
  - BRCA1/2 only: ~5% vs. Multi-gene panel: ~8-12% (ASCO, 2015)
- Minimized testing fatigue
- Cost effectiveness (*)

**Challenges**
- Increased likelihood of variants of unknown significance
- Limited clinical information for moderate-risk genes
- Panel variation among testing laboratories

**Professional Statements (Multi-gene Panel Testing)**

**NCCN, v2. 2015:**
"Multi-gene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling"

**ASCO, August 31 2015:**
"ASCO asserts that providers with particular expertise in cancer risk assessment should be involved in ordering and interpreting multi-gene panels that include genes of uncertain clinical utility and genes not suggested by the patient’s personal and/or family history. Further, ASCO encourages research to delineate the optimal use of panel-based testing, development of evidence-based practice guidelines as data emerges, and education of providers on the challenges of using these tests."
Clinical Case Vignette #1

- 54 yo woman with a past history of bilateral breast ca diagnosed at 48 (invasive ductal; ER/PR positive, Her2 negative)

- Treatment consisted of bilateral mastectomy followed by adjuvant chemotherapy. She was on Tamoxifen for 5 years. Doing well.

- She has no history of colon polyps. Ovaries are in place.

- **BRCA1/2** sequencing and deletion/duplication analysis in 2009 revealed two variants of unknown significance in the BRCA1 gene (P1614L, V1234L). Variants continued to be unclassified by the testing company in 2015.

Topics of discussion during pre-test counseling session:

- Availability of multi-gene panel testing
- Differences between high- and moderate-risk gene mutations
- Potential impact of positive test results depending on gene involved
- Inheritance patterns
- Previously identified BRCA1 variants of unknown significance and differences in VUS interpretation among testing laboratories

Test of choice:

- 17-gene hereditary breast cancer panel

Results?
Clinical Case Vignette #2...

Topics of discussion during post-test counseling session:
- CHEK2 associated cancers risks
- Potential implications for medical management
- Risk assessment for family members
- Reproductive risks for CHEK2 carriers (Fanconi anemia)
- Contact information for non-local genetics professionals to share with family members
- Need of additional family history details to review surveillance recommendations
- PROMPT

Clinical Case Vignette #2

• 38 yo Ashkenazi Jewish male with a family history of breast/ovarian cancer
• Mother identified as BRCA1+ through a research protocol overseas

Clinical Case Vignette #2...

Topics of discussion during pre-test counseling session:
- 50% risk for positive results
- BRCA lifetime cancer risks for men
- Risk management strategies for men who are BRCA positive
- GINA (benefits and limitations)
- Appropriateness of genetic testing after age 18 for at-risk family members
• Test of choice:
  - BRCA1/2 Ashkenazi Jewish founder mutation panel
• Results?
Clinical Case Vignette #2

- 38 yo Ashkenazi Jewish male with a family history of breast/ovarian cancer
- Mother identified as BRCA1+ through a research protocol overseas
- Personal history of adenomatous colon polyps since age 25 (>20)
- No family history of colorectal cancer or polyps

Is there room for additional genetic testing?

Test of choice:
- 14 gene panel associated with colorectal cancer

Result:
- Variant of unknown significance in APC (APC, p.Ser130Gly)
  - Reported in population databases
  - Reported in individuals with colon cancer and one individual with FAP (pathogenic mutation)
  - In-silico tools predict that this variant may affect mRNA splicing
  - Located in a part of the gene that resembles the patient’s clinical presentation
  - APC codons 1-177

Current and Future Challenges

- Multi-gene panel testing for cancer-free individuals
  - Potential of false reassurance by negative results
- Limited availability of clinicians with expertise in genetics
- Increasingly complex genetic testing technologies may eventually become mainstream in cancer genetics
  - Whole-exome sequencing
  - Whole-genome sequencing
Thank you!

References


