UNDERSTANDING CANCER RISKS IN FAMILIES

Dee Lewis, MA, MS, LCGC
July 16, 2019
Disclosure Slide

• None
Objectives

• Genetic counseling and testing
• Overview of common genetic cancer syndromes
• Hereditary Breast/Ovarian Cancer syndromes (HBOC)
• Hereditary Non-Polyposis Colorectal Cancer syndromes (HNPCC or Lynch syndrome)
• New topics in genetic testing
Patient: Jane

Jane is 72F diagnosed with stage I ER+ breast cancer. She wonders if she should be tested for a genetic risk for breast cancer.

- Mother had **breast cancer** at 75
- Maternal grandmother had **uterine cancer** at 84
- Father had **lung cancer** at 75
- Paternal uncle had **colon cancer** at 70
Patient: Mary

Mary is 45F diagnosed with stage I ER+ breast cancer. She wonders if she should be tested for a genetic risk for breast cancer

- Mother had breast cancer at 55
- Maternal grandmother had ovarian cancer at 50
- Father had lung cancer at 75
- Paternal uncle had colon cancer at 70
What are genes?

• **Genome**: the entire set of the genetic material (instructions) containing information to build and maintain a life form
  – 23 chromosome pairs (46 total)
  – 3.2 billion base pairs in human genome

• Variation is normal
  – Makes us unique
  – Genetic variants of genes (e.g. hemoglobin)
Genes are inherited
Why test for genetic risk?

• Information for patient
  – Understand own risk for cancer(s)
  – Impacts screening recommendations
  – Prevention
  – Can alter treatment of cancer

• Information for family
  – Who else to test in the family
  – When to offer testing
Genetic cancer syndromes

- Hereditary Breast/Ovarian Cancer syndromes (HBOC)—BRCA-1/2
- Hereditary Non-Polyposis Colon Cancer (HNPCC) or Lynch syndrome—MMR mutations
- Li-Fraumeni Syndrome—P53
- Cowden syndrome—PTEN
- Familial Adenomatous Polyposis (FAP)
- Many others
Triggers for genetic referrals

- Early onset of cancer: under 45 for breast, 50 for colon
- More than 1 primary cancer in the same patient
- Cancer in multiple generations on same side of family
- Constellations of cancer: breast/ovarian cancer, colon/endometrial cancer, pancreatic and melanoma
- Unusual cancers: male breast cancer, ocular melanoma
- Uncommon histology: medullary thyroid cancer
- Geographic/ethnic considerations: Ashkenazi-Jewish heritage
Since 2003, the Capital Health Cancer Genetics Program has evaluated 1200+ patients.
Now: 200+ patients evaluated/year
15% mutations rate
Why genetic counseling is “Not Just a Simple Blood Test”

• Perform modeling and risk assessment
• Full assessment of other hereditary cancer syndromes
• Aware of new tests and testing; select the right one!
• Follow-up
• Access to research trials
• Provide full summary letters
• Time spent per patient = 1-1½ hours minimum
Patient: “Eve”

• Eve is a 50F diagnosed with breast cancer
  – Screening MMG: 1.4 cm asymmetry in LUOQ, confirmed by Dx imaging
  – Bx: Invasive ductal cancer, gr 2, ER/PR+, H2-
  – Considering breast conservation vs. mastectomy.

• Family history notable for cancer
Eve’s Family History

- Father with colorectal cancer, early stage, at 62
- Paternal grandmother with stomach cancer, at 49
- Maternal aunt with ovarian cancer, at 79
- Maternal uncle with prostate cancer, at 68
- Maternal aunt with bilateral breast cancer, at 50, 55
- Maternal grandfather with pancreatic cancer, at 75
Eve has a deleterious mutation in BRCA-2
Breast cancer predisposition

- Inherited: 10%
- Familial: 10%
- Sporadic: 80%
Hereditary Breast Ovarian Cancer Syndrome

BRCA1

BRCA2

BREAST

OVARY

PROSTATE

PANCREAS

MELANOMA
BRCA1-Associated Breast and Ovarian Cancers: Risk to Patients Age 70 Years

Breast cancer - mean age 43 (50%-65%)

Contralateral breast cancer (20%-83%; 27% within 5 years)

Ovarian cancer - mean age 52 (40%-59%)

Male breast cancer (1%-3%)

Prostate cancer RR ~3x

Dr. Lindor

Cancer Genetics Program

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capitalhealth.org/cancer
BRCA2-Associated Breast and Ovarian Cancers: Risk to Patients Age 70 Years

Breast cancer - mean age 47 (49%-55%*)
Contralateral breast cancer (20%-62%; 12% within 5 years)
Ovarian cancer - mean age 62 (16%-18%)

Male breast cancer (5%-10%)
Prostate cancer RR ~5-9x

*28% in Jewish populations with BRCA2 6174delT
## Female cancer risks in BCRA-1/2

### LIFETIME BRCA1 AND BRCA2 CANCER RISKS FOR WOMEN

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>BRCA 1</th>
<th>BRCA 2</th>
<th>Population Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>60-80%</td>
<td>50-55%</td>
<td>12%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>40-60%</td>
<td>15-20%</td>
<td>1%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2-3%</td>
<td>2-7%</td>
<td>1%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>-</td>
<td>3-5%</td>
<td>1-2%</td>
</tr>
</tbody>
</table>
### LIFETIME BRCA1 AND BRCA2 CANCER RISKS FOR MEN

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>BRCA 1</th>
<th>BRCA 2</th>
<th>Population Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1-5%</td>
<td>5-9%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Prostate</td>
<td>1-3x</td>
<td>5-9x (33%)</td>
<td>16%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2-3%</td>
<td>2-7%</td>
<td>1%</td>
</tr>
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## Management options for HBOC

<table>
<thead>
<tr>
<th></th>
<th><strong>Breast cancer</strong></th>
<th><strong>Ovarian cancer</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td>Self-breast exam monthly</td>
<td>No good screening</td>
</tr>
<tr>
<td></td>
<td>Clinical breast exams: 6-12 months</td>
<td>CA125 annually</td>
</tr>
<tr>
<td></td>
<td>Mammograms: 25 or 30</td>
<td>Pelvic U/S</td>
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<tr>
<td></td>
<td>MRI screening: 25</td>
<td></td>
</tr>
<tr>
<td><strong>Chemoprophylaxis</strong></td>
<td>Tamoxifen: 50% reduction</td>
<td>Birth control pills</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>Bilateral mastectomies</td>
<td>BSO after child-bearing</td>
</tr>
<tr>
<td></td>
<td>Oophorectomy: 50%</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Platinum and PARP inhibitors</td>
<td>PARP inhibitors</td>
</tr>
</tbody>
</table>
Who to refer for HBOC genetic counseling

- Early onset breast cancer
- Breast, ovarian and/or pancreatic cancer in family history
- Bilateral Breast Cancer, Multiple Breast Cancers
- Male breast cancer
- Ashkenazi-Jewish heritage with breast/ovarian cancer
- Breast and ovarian cancers in same individual
- Triple negative breast cancer
Eve’s decisions

• Decides to do bilateral mastectomies

• Considering BSO after decisions about breast cancer treatment
Case 2: “Adam”

- Adam and Eve want to know about risks to their children
- We explore Adam’s history
  - Adam had a colonoscopy with 5 polyps
  - He has a family history notable for:
    - Mother with **ovarian cancer**, age 50
    - Brother with **colon cancer**, age 52
    - Maternal aunt with **uterine cancer**, age 48
    - Maternal grandfather with **kidney cancer**, age 70
Adam has a mutation in MSH2
Clinical Features of Lynch Syndrome

- Early but variable age at CRC diagnosis (~45 years)
- Multiple primary cancers
- Accelerated carcinogenesis
- Tumor site in proximal colon predominates
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors
Genetic syndromes in CRC

- Sporadic: 75%
- Lynch: 3%
- FAP: 1%
- Familial sx: 1%
- Other rare CRC: 1%
Adam’s decisions

• Follows up with colonoscopy as planned

• Will discuss endoscopy and urinalysis with Primary Care Physician (PCP)
Newer issues in genetic testing

- Panel testing
- Understanding VUS results
- Direct-to-Consumer testing
- Paired inherited and tumor testing
Recent Developments

   - More labs involved
   - Lower costs for testing
   - Improved technology

2. Over 50 genes now identified with cancer

3. Panel Testing – High and Moderate Genes
Panel Testing

- Tests multiple genes at the same time
- Same cost as previous testing for one gene
- Indicated for those that have tested negative in the past.
- Indicated for those with overlapping hereditary cancer syndromes
## Panel Testing

<table>
<thead>
<tr>
<th>Ambry Panel</th>
<th>Number of Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BreastNext</td>
<td>18 genes</td>
</tr>
<tr>
<td>ColoNext</td>
<td>17 genes</td>
</tr>
<tr>
<td>OvaNext</td>
<td>25 genes</td>
</tr>
<tr>
<td>PancNext</td>
<td>13 genes</td>
</tr>
<tr>
<td>RenalNext</td>
<td>19 genes</td>
</tr>
<tr>
<td>CancerNext</td>
<td>34 or 67 genes</td>
</tr>
</tbody>
</table>
Take Away Message #1

If tested before 2013, contact a Cancer Genetics Program for re-evaluation
Take Away Message #2

Use a licensed genetic counselor

“LCGC” • “LGC” • “CGC” credentials
Patient: Lynn Update

• 44F diagnosed with Stage I triple negative breast cancer
• Family history: adopted
• Did 23&me testing and found to have Ashkenazi-Jewish heritage
• Panel testing revealed: CHEK2 mutation and VUS in RAD51C (likely pathogenic)
Understanding Possible Risks

Positive

Increased Cancer Risk

Negative

Has a mutation been found in the family?

Yes

No

Uncertain Variant

Cancer Risk Not Altered – based on family history

No Increased Cancer Risk
Patient: Diane

• 28F whose father died of pancreatic cancer
• Did direct-to-consumer genetics testing
• Found to have a BRCA2 mutation
Direct-to-Consumer Testing

Q: Will Color Genomics Be Able To Bypass FDA?

$99 Per Test vs. $250 Per Test
Direct-to-Consumer Testing

- Limited genetic counseling
- May not be right test
- Reliability of test results
- Counseling regarding implications of a positive result
Paired Inherited and Tumor Tests

- Compares germline (inherited) and tumor (acquired)
- Should identify targets that are drivers of the cancer
- Potential treatment implications
Summary

- Understanding genetic risks in families is important
  - Allows for appropriate screening and prevention strategies
  - Increasingly impacting treatment decisions, i.e. olaparib in breast/ovarian cancer or surgical decisions

- Value of genetic counseling
  - Right test, right time
  - Information for family
Cancer Genetics Program at Capital Health

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• Mercer Bucks Hematology Oncology

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