GENETICALLY ALTERED CELL

HYPERPLASIA

DYSPLASIA

IN SITU CANCER

INVASIVE CANCER

Causes of Hereditary Susceptibility to Breast Cancer

Sporadic (unknown cause)

Hereditary (~10%)

BRCA1 (~70%)

BRCA2 (~20%)

Other genes (~8%)
What Is Cancer?

Cells make up our organs.

In cancer...
- Cells reproducing uncontrollably
- Cells irregularly shaped
- Cells don’t function normally
- Cells lose communication with neighboring cells
- Cells can separate from neighbor cells and move

Adapted from *Understanding Gene Testing*, NIH, 1995
All cancers are the result of genetic mutations

Adapted from *Understanding Gene Testing*, NIH, 1995
Chromosomes, DNA, and Genes

Adapted from Understanding Gene Testing, NIH, 1995
Disease-Associated Mutations Alter Protein Function

Adapted from *Understanding Gene Testing*, NIH, 1995
Inherited Mutation

Egg 🍳 Sperm

Fertilized Egg

Reproductive 🤱️ Bone 🏛️ Breast 🇺🇸 Brain 🧠

Adapted from Understanding Gene Testing, NIH, 1995
Hereditary cancers are also the result of genetic mutations.
Different Genes - Different Functions

Bone Cell

Pancreas Cell

Brain Cell

Adapted from Understanding Gene Testing, NIH, 1995
When and How are New Cells Made?

Accelerators - called Oncogenes

Brakes - called Tumor Suppressor Genes
BRCA1

- Tumor suppressor gene on chromosome 17
- Important function in breast and ovary

![Diagram showing BRCA1 with annotations for Nonsense, Missense, and Splice-site variations]
**BRCA1-Linked Hereditary Breast and Ovarian Cancer**

- **Noncarrier**
- **BRCA1-mutation carrier**
- **Affected with cancer**

- Breast, dx 45 d. 89
- Ovary, dx 59 d. 62
- Breast, dx 59
- Breast, dx 36

- 92
- 86
- 73
- 68
- 71
- 59
- 36

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**ASCO**
BRCA1-Associated Cancers: Lifetime Risk

Breast cancer 45%–65% (34%-86% )(early age)
Second primary breast cancer 40%–60%
Ovarian cancer 15%–45% (42%-67%)

Possible increased risk of other cancers
(e.g., more aggressive prostate cancer)
BRCA2

- Tumor suppressor gene on chromosome 13
- Important function in breast and ovary

Breast Cancer Information Core
**BRCA2-Associated Cancers: Lifetime Risk**

- Breast cancer: (45%–65%) (24%-83%)
- Male breast cancer: (6%)
- Ovarian cancer: (10%–20%) (16%-51%)

Increased risk of melanoma, prostate, pancreatic cancers, possibly children with recessive Fanconi anemia.
**BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population**

An estimated 1 in 40 Ashkenazi Jews carries a *BRCA1* or *BRCA2* mutation.

- **BRCA1**
  - 185delAG
    - Prevalence = ~1%
  - 5382insC
    - Prevalence = ~0.15%

- **BRCA2**
  - 6174delT
    - Prevalence = ~1.5%

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Features That Indicate Increased Likelihood of BRCA Mutation

- Multiple cases of breast cancer
- Premenopausal breast cancer
- Ovarian cancer (fallopian tube, primary peritoneal)
- Breast and ovarian cancer on one side of family
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer
- Triple negative breast cancer (ER-/PR-/Her2-)
- Pancreatic cancer
- Aggressive prostate cancer (Gleason score ≥7)
1. The Prevalence of Deleterious Mutations in BRCA1 and BRCA2 (Excludes Individuals of Ashkenazi Ancestry)

<table>
<thead>
<tr>
<th>Family History (Includes at least one first- or second-degree relative)</th>
<th>No breast cancer &lt;50 or ovarian cancer in any relative</th>
<th>Breast cancer &lt;50 in one relative, no ovarian cancer in any relative</th>
<th>Breast cancer &lt;50 in more than one relative; no ovarian cancer in any relative</th>
<th>Ovarian cancer at any age in one relative; no breast cancer &lt;50 in any relative</th>
<th>Ovarian cancer at any age in more than one relative; no breast cancer &lt;50 in any relative</th>
<th>Breast cancer &lt;50 and ovarian cancer at any age$t^{11}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient's History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No breast cancer or ovarian cancer at any age</td>
<td>1.5%</td>
<td>2.6%</td>
<td>5.6%</td>
<td>3.0%</td>
<td>5.3%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Breast cancer ≥50</td>
<td>2.2%</td>
<td>3.9%</td>
<td>8.0%</td>
<td>4.9%</td>
<td>9.5%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Breast cancer &lt;50</td>
<td>4.7%</td>
<td>10.4%</td>
<td>21.2%</td>
<td>10.3%</td>
<td>21.9%</td>
<td>26.6%</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>6.9%</td>
<td>17.4%</td>
<td>36.6%</td>
<td>15.9%</td>
<td>*33.3%</td>
<td>28.3%</td>
</tr>
<tr>
<td>Ovarian cancer at any age, no breast cancer</td>
<td>7.7%</td>
<td>14.3%</td>
<td>27.4%</td>
<td>14.7%</td>
<td>22.7%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Breast cancer ≥50 and ovarian cancer at any age</td>
<td>12.1%</td>
<td>23.6%</td>
<td>50.0%</td>
<td>23.6%</td>
<td>44.2%</td>
<td>39.4%</td>
</tr>
<tr>
<td>Breast cancer &lt;50 and ovarian cancer at any age</td>
<td>26.3%</td>
<td>40.0%</td>
<td>64.5%</td>
<td>41.2%</td>
<td>45.5%</td>
<td>57.4%</td>
</tr>
</tbody>
</table>

$t^{11}$May include families with breast cancer ≥50 (in women or men)
$t^{11}$Includes family members with either or both diagnoses
$t^{10}$N=35
In situ data is now included in the “affected” categories

Number of observations in Table 1 is 182,914

2. The Prevalence of Deleterious Mutations in BRCA1 and BRCA2 in Individuals of Ashkenazi Ancestry

<table>
<thead>
<tr>
<th>Family History (Includes at least one first- or second-degree relative)</th>
<th>No breast cancer &lt;50 or ovarian cancer, in any relative</th>
<th>Breast cancer &lt;50 in one relative, no ovarian cancer in any relative</th>
<th>Breast cancer &lt;50 in more than one relative; no ovarian cancer in any relative</th>
<th>Ovarian cancer at any age in one relative; no breast cancer &lt;50 in any relative</th>
<th>Ovarian cancer at any age in more than one relative; no breast cancer &lt;50 in any relative</th>
<th>Breast cancer &lt;50 and ovarian cancer at any age$t^{11}$</th>
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</thead>
<tbody>
<tr>
<td>Patient's History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No breast cancer</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>
Cowden syndrome – PTEN

- Breast cancer – 25 to 50% risk
- May occur at younger age
- Some male breast cancer
- Thyroid cancer – 10%
- Endometrial (uterine) cancer – 5 – 10%
- Kidney cancer – unknown risk level
- Colon cancer – unknown risk level
- Skin cancer – unknown risk level
Other features of PTEN

- Fibrocystic breast disease
- Uterine fibroids
- Thyroid – goiter, thyroiditis
- Lipomas
- Hemangiomas
- GI polyps

50% chance to pass down the mutation to each child
<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast MRI</th>
<th>Consider RRM</th>
<th>Consider RRSO</th>
<th>Other Cancers</th>
<th>Risk to Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>BRIP1</td>
<td>No</td>
<td>No</td>
<td>45-50</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>CDH1</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>Diffuse Gastric</td>
<td></td>
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<tr>
<td>CHEK2</td>
<td>+</td>
<td>?</td>
<td>No</td>
<td>Colorectal</td>
<td></td>
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<tr>
<td>Lynch</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>Endometrial, Colon</td>
<td>Yes</td>
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<tr>
<td>NBN</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>NF1</td>
<td>+</td>
<td>?</td>
<td>No</td>
<td>MPNST, GIST</td>
<td>Yes</td>
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<tr>
<td>PALB2</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
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<tr>
<td>PTEN</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>Endometrial, thyroid, kidney</td>
<td>Yes</td>
</tr>
<tr>
<td>Rad51C</td>
<td>?</td>
<td>?</td>
<td>45-50</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rad51D</td>
<td>?</td>
<td>?</td>
<td>45-50</td>
<td>No</td>
<td>?</td>
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<tr>
<td>STK11</td>
<td>+</td>
<td>?</td>
<td>Nonepithelial</td>
<td>Uterus, Colon, Lung</td>
<td>Yes</td>
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<tr>
<td>TP53</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>Sarcoma, Other</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Panel Tests

- Multiple genes included
- Different labs offer different panels with different genes
- Some genes are known to be associated with HBOC
- Some genes are known to be associated with cancer
- Some genes might be associated with cancer
- Some panels cover lots of genes for different health conditions besides cancer
Genetic counseling – personal consultation with a genetics specialist in person or by phone

- Personalized review of the cancer pattern in the family and likelihood that genetic testing may find cause
- Discussion of genetic testing benefits and limitations and what cancer risks might be involved
- Finding the right test and best person in the family to test first to get the most information for the family
- Assistance with insurance coverage of testing
- Personal discussion of results and what the results mean for you and your family – what are your options?
- Information and resources - follow-up care, referral to experts, available research protocols