The Genetics of Breast Cancer - Beyond BRCA

SUE DEMSEY, MS, LCGC
RACHEL PERALTA, MS, LCGC

The Genetics of Breast Cancer

1. Family history primer
2. Genetic testing in 2017
3. Genetics at Kaiser Permanente
4. Case Examples
Our Goals:

- Enhance the care of patients you follow
- Update you on current genetics practices/guidelines
- Help you to understand the experience of a Genetics visit from the patient’s point of view
- Finding families that have hereditary cancer syndromes

Hereditary Breast Cancer Basics

THE TOOLS YOU NEED
Hereditary Breast Cancer 101

At what point should you be concerned?

...How do you know?

Red Flags... And Red Herrings

- Red Flags:
  - Also known as the rule of Two/Too:
    - Rare – ovarian, male breast cancer, triple negative breast cancer
    - Young – diagnosed <50yrs
    - Multiple – Breast, Ovarian, Prostate, Pancreatic, Uterine, Colon, Melanoma
      - Multiple cancers in the same individual
      - Multiple cancers on the same side of the family
    - Ashkenazi Jewish Ancestry (specifically for BRCA1/2)
- Red Herrings:
  - “Female cancer” – possibly ovarian or endometrial, possibly cervical
  - Ovarian cysts or other benign tumors of the ovaries – germ cell tumors
  - Atypical breast findings (Atypical ductal hyperplasia, dense breasts, etc.)
An individual with no personal history of cancer persisting to:
- A close relative with any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Two breast cancer primaries in a single individual
  - Two individuals with breast cancer primaries on the same side of the family with at least one diagnosed ≥50 y
  - Ovarian cancer
  - Male breast cancer
  - First- or second-degree relative with breast cancer ≥45 y
  - Family history of three or more of the following (especially if early onset and can include multiple primary cancers in some individuals): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, colorectal cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and lymphoma
- Hamartomatous polyps of the GI tract

**NCCN Guidelines Version 2.2017**

**Breast and Ovarian Cancer Genetic Assessment**

**Criterions for Further Genetic Risk Evaluation**
- An individual with an ovarian cancer
- An individual with a breast cancer diagnosis meeting any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Two breast cancer primaries in a single individual
  - Two breast cancer primaries in a single individual
  - Two close blood relatives with breast cancer ≥50 y, or
  - One close blood relative with invasive breast cancer
  - Two close blood relatives with breast cancer and pancreas cancer at any age, or
  - Pancreatic cancer at any age, or
  - From a population at increased risk
- Male breast cancer
- An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer
- An individual with a personal and family history of three or more of the following (especially if early onset and can include multiple primary cancers in some individuals): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, colorectal cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and lymphoma
- Hamartomatous polyps of the GI tract

**Consider Referral to Cancer Genetics Professional**

**Risk Assessment (BRCA2)**

**Note:** All recommendations are category 3a unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
5-Minute Family History

Do you have a family history of cancer?

Yes
- Who was it? Age of diagnosis?
- Type of cancer?
- History fits the rule of too/two?
  - Too early (<50)
  - Too many (multiple people)
  - Two types of cancer
  - Two cancers (recurrent)
  - Send Referral or Dr. Advice

No
- Routine, age-appropriate screening is recommended based on personal history
- All at older ages (>50’s)
  - Common cancers
  - Isolated
  - Distant relative

5-Minute Family History

- Remember the Rule of Two/Too
- Avoid Red Herrings:
  - How was the cancer diagnosed?
  - What treatment did they have?
Genetics in 2017
BEYOND BRCA

Using large, multi-case families, linkage studies were used to figure out the chromosomal location of “Breast Cancer Gene 1” better known as BRCA1.

The chromosomal region was delineated, and the race to sequence and clone the gene began.

- Was first successful by University of Utah and Myriad Genetics in 1994.
- “Breast Cancer Gene 2” or BRCA2 was cloned in 1995.
- Patents of the genes by Myriad Genetics existed until 2015.
  - Myriad had sequencing exclusivity in North America and Europe since 1994.
- Those with a BRCA mutation have Hereditary Breast and Ovarian Cancer syndrome (HBOC).

BRCA History

How do we find families that have hereditary cancer syndromes?

- Using large, multi-case families, linkage studies were used to figure out the chromosomal location of “Breast Cancer Gene 1” better known as BRCA1.
- The chromosomal region was delineated, and the race to sequence and clone the gene began.
  - Was first successful by University of Utah and Myriad Genetics in 1994.
- “Breast Cancer Gene 2” or BRCA2 was cloned in 1995.
- Patents of the genes by Myriad Genetics existed until 2015.
  - Myriad had sequencing exclusivity in North America and Europe since 1994.
- Those with a BRCA mutation have Hereditary Breast and Ovarian Cancer syndrome (HBOC).

1. Easton et. al “Linkage analysis in Familial Breast and Ovarian Cancer: Results from 214 Families” 1993
2. Miki et al “A strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1” 1994
3. Emory & Rimoin Genetics
BRCA History

Beyond BRCA
# High Risk Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer</th>
<th>Ovarian Cancer</th>
<th>Other Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>57-87%</td>
<td>24-54%</td>
<td>Melanoma ^</td>
</tr>
<tr>
<td>BRCA2</td>
<td>41-84%</td>
<td>11-27%</td>
<td>Pancreatic 5-7%</td>
</tr>
<tr>
<td>PALB2</td>
<td>25-58%</td>
<td>--</td>
<td>Pancreatic ^</td>
</tr>
<tr>
<td>TP53</td>
<td>54%</td>
<td>^</td>
<td>Virtually 100% lifetime risk for cancer</td>
</tr>
</tbody>
</table>

# Moderate Risk Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer</th>
<th>Ovarian Cancer</th>
<th>Other Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>STK11</td>
<td>8-45%</td>
<td>--</td>
<td>GI cancers ^</td>
</tr>
<tr>
<td>CDH1</td>
<td>39-52%</td>
<td>--</td>
<td>Diffuse gastric Cancer ^</td>
</tr>
<tr>
<td>PTEN</td>
<td>25-50%</td>
<td>--</td>
<td>Thyroid 3-10%</td>
</tr>
<tr>
<td>ATM</td>
<td>38%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CHEK2</td>
<td>28-37%</td>
<td>--</td>
<td>Colon ^</td>
</tr>
</tbody>
</table>
Kaiser 23 Gene Panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>BREAST</th>
<th>OVARIAN</th>
<th>COLON</th>
<th>UTERINE</th>
<th>MELANOMA</th>
<th>PANCREATIC</th>
<th>GASTRIC</th>
<th>PROSTATE</th>
<th>THYROID</th>
<th>RENAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51D</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMN1</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHK1</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHK2</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMP15A</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA4</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53AM</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOTH</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKN2A</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YK1</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Genetic Testing – Important Dates

- Those who had genetic testing prior to 2013 likely had only BRCA1/BRCA2 testing
  - They could have a mutation in a “newer” gene
- Kaiser began offering panel testing in 2013
  - 2013 - 12 genes “Comprehensive Cancer Panel”
  - 2014 - 20 genes “High/Moderate Risk Panel”
  - 2016 – 23 genes “High/Moderate Risk Panel”
- Moderate risk genes were added to keep up with NCCN guidelines
- Our panel will likely continue to grow as we learn more about cancer susceptibility genes
Does more genes = more knowledge?

- Possible test results:
  - Positive
    - We found a variant that is consistent with hereditary cancer
  - Negative
    - We found no variants (or only benign variants)
  - Variant of Uncertain Significance
    - We found a variant, but we don’t know how to classify it

Variant Classification

Adapted from Ambry Genetics – Clinical Tools (ambrygen.com)
Genetic Services at Kaiser Permanente
A CONSULTATIVE SERVICE FOR MEMBERS AND PROVIDERS

Genetics Department Website
For patients

https://thrive.kaiserpermanente.org/care-near-you/southern-california/genetics/

Our excellent genetic services contribute to the total health of our members
We offer a full range of genetic services to help you determine the chance that you or your children may have a genetic disorder.
Genetics Department Website
For patients

https://thrive.kaiserpermanente.org/care-near-you/southern-california/genetics/cancer/

Genetics Department Website
For patients

https://thrive.kaiserpermanente.org/care-near-you/southern-california/genetics/cancer/family-history/
The Genetic Counseling Visit

WHAT DOES THE PATIENT EXPERIENCE?

Roles of the Genetic Counselor

Case Manager

Patient Support

Genetic Education

Detective

Patient Advocate
Genetic Counseling for Cancer

- The counselor will ask for personal medical history and cancer screening history.
- The counselor will draw the family tree and include at least three generations, documenting which family members have had cancer, what type of cancer they had, and their age at diagnosis.
- Using guidelines, experience, and sometimes computerized risk tools, the counselor will assess the possibility of an inherited cancer risk.
- Review the science of how testing is accomplished at the lab.
- Discussion of the benefits and limitations of genetic testing for patient and patient’s family.
- The counselor will arrange appropriate follow up appointments and referrals.

Genetic Counseling Visit

- Contracting
- Family Pedigree
- Education
- Calling Sister for details
- Cancer
- Genetics
- Patient Questions
- Mutations
- Review chart and pathology
- Paper work
- Follow up planning
Genetic Counseling Visit

Who is the best person to test? Why?

- Living
- Youngest affected person
- Most rare cancer type

- Or, the person most closely related to the affected individual (when the best person is unavailable or deceased)
Case Examples from Clinic

Clinic Examples

- Breast Ca at 38
- Ovary CA at 50
- Your patient age 32
Clinic Examples

Breast Ca at 38
Ovary CA at 50

Your patient age 32

Clinic Examples

Breast Ca at 38
BRCA1 mutation Pos result

Your patient age 32
Cascade Testing

Cascade Testing or Screening

- TESTING OR SCREENING is targeted at the relatives of previously identified carriers.
- The carrier risk of close relatives of known carriers is higher than the population risk
- Cascade screening is more efficient than population screening
Your Patient age 49 yrs.

Colon CA

Breast CA Prostate CA

Breast CA
Clinic Examples

- Case 1: "38 year old female, weak family history of breast cancer (maternal grandmother) with new diagnosis of triple negative left infiltrating ductal carcinoma"
Results Summary: POSITIVE

Gene  | Results     | Classification | Zygosity        |
------|-------------|----------------|-----------------|
PALB2 | c.1767_1768insAT | PATHOGENIC     | HETEROZYGOUS    |

No additional reportable variants were detected by sequencing or deletion/duplication analysis of any of the genes on this panel.

Clinical Summary

This individual is heterozygous for a pathogenic variant in PALB2, consistent with an increased risk for breast cancer in women (25%-50%) and pancreatic cancer in women and men. See interpretation for detailed clinical summary.

Ethnicity: Mexico ϕAJ

Results Summary: POSITIVE

Gene  | Results     | Classification | Zygosity        |
------|-------------|----------------|-----------------|
PALB2 |             |                |                 |

No additional reportable variants were detected by sequencing or deletion/duplication analysis of any of the genes on this panel.

Clinical Summary

This individual is heterozygous for a pathogenic variant in PALB2, consistent with an increased risk for breast cancer in women (25%-50%) and pancreatic cancer in women and men. See interpretation for detailed clinical summary.

Ethnicity: Mexico ϕAJ

Results Summary: POSITIVE

Gene  | Results     | Classification | Zygosity        |
------|-------------|----------------|-----------------|
PALB2 |             |                |                 |

No additional reportable variants were detected by sequencing or deletion/duplication analysis of any of the genes on this panel.

Clinical Summary

This individual is heterozygous for a pathogenic variant in PALB2, consistent with an increased risk for breast cancer in women (25%-50%) and pancreatic cancer in women and men. See interpretation for detailed clinical summary.
Clinic Examples

- Case 2: “34 y/o lady with family h/o breast cancer in mother at age 48 and ovarian cancer in maternal aunt at age 58, both are deceased.”
Results Summary: VARIANT OF UNCERTAIN SIGNIFICANCE

<table>
<thead>
<tr>
<th>Gene</th>
<th>Results</th>
<th>Classification</th>
<th>Zygosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>c.3805delC (p.Asn1268Thr)</td>
<td>UNCERTAIN SIGNIFICANCE</td>
<td>HETEROZYGOUS</td>
</tr>
</tbody>
</table>

No additional reportable variants were detected by sequencing or deletion/duplication analysis of any of the genes on this panel.
Regional Statistics
DATA FROM KP SOUTH REGIONAL GENETICS SERVICES

Members we have identified

<table>
<thead>
<tr>
<th>Description</th>
<th>Seen by Genetics in 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td># Cases diagnosed with hereditary cancer</td>
<td>555</td>
</tr>
<tr>
<td># Cases diagnosed with personal history of cancer</td>
<td>318  (57%)</td>
</tr>
<tr>
<td># Cases with family history only</td>
<td>221</td>
</tr>
<tr>
<td>Unknown ascertainment</td>
<td>16</td>
</tr>
</tbody>
</table>
Regional

<table>
<thead>
<tr>
<th># Expected cases diagnosed in Region</th>
<th>BRCA1 or BRCA2</th>
<th>Lynch Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 400 or 10,500 members</td>
<td>1 in 370 or 11,351 members</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># Cases actually diagnosed in 20 years of Regional Genetic experience</th>
<th>1 in 1,800 members</th>
<th>1 in 415 members</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Filling the CARE GAP

“YOUNG AGE OF ONSET” OUTREACH PROGRAM

- 454 female patients with breast cancer under 45 were sent invitation letters.
  - Of these, 142 patients were seen by a genetic counselor
  - 122 patients were tested.
  - 6 mutation carriers (5%) and 6 VUS (5%) were detected.
Chart Review
WHERE TO FIND GENETIC RESULTS

Where to find Genetic information
Where to find Genetic information

Chart Review (Last refreshed: 5:43:15 PM)

<table>
<thead>
<tr>
<th>Scan Date/Time</th>
<th>Document Type</th>
<th>Description</th>
<th>Erct Date</th>
<th>File Attached to</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/19/2016 13:34</td>
<td>Laboratory Result</td>
<td>IP REFERENCE LAB</td>
<td>11/18/2016</td>
<td>LAB PROCEDURE SCANNED REPORT [981227289] on 11/18/2016</td>
</tr>
<tr>
<td>12/19/2016 13:27</td>
<td>Consent Form</td>
<td>CONSENT</td>
<td>11/18/2016</td>
<td>Allied Health/Nurse Visit on 11/18/2016 with Demsey, Susan A</td>
</tr>
<tr>
<td>12/19/2016 13:05</td>
<td>Progress Note</td>
<td>GENETIC HISTORY</td>
<td>11/18/2016</td>
<td>Allied Health/Nurse Visit on 11/18/2016 with Demsey, Susan A</td>
</tr>
<tr>
<td>11/7/2016 14:11</td>
<td>Colonoscopy and</td>
<td></td>
<td>11/7/2016</td>
<td>Procedure Only on 11/7/2016 with Lever, Eric L (M.D.), M.D.</td>
</tr>
<tr>
<td>9/19/2016 09:28</td>
<td>Consent Form</td>
<td>CONSENT</td>
<td>09/29/2016</td>
<td>Office Visit on 9/30/2016 with Chung, Joseph S (D.O.), D.O.</td>
</tr>
</tbody>
</table>
Where to find Genetic information

Support Groups and Resources
Support groups and organizations

In 2015, KPSC hosted a “Support and Education Conference”

Over 200 members who are BRCA1 and BRCA2 carriers and their families attended!
Thank you!

Genetics at Downey
562-657-4842