Hereditary Breast and Ovarian Cancer and Genetic Cancer Risk Assessment (GCRA)

UPR CCC 04/12/13

Jeffrey N. Weitzel, M.D.
Risks Related to Breast Cancer

- Advanced Age
- Genetics
- Alcohol
- Lack of Exercise
- Hormone Replacement Therapy
- Overweight
- Gender
- Late Menopause
- Close Relative Age at First Birth
- Early Menarche
- Education & Income
- Radiation
- Chemicals (Work, Home, Garden, Recreation)
- Benign Breast Disease
- ???
Timeline of Important Events in DNA Patenting (Top) and the Discovery and Use of Genes Conferring Susceptibility to Breast and Ovarian Cancer (Bottom)

1953
Watson and Crick publish *Nature* article describing DNA double helix

1950
International Breast Cancer Linkage Consortium founded

1960

1970

1980
Diamond v. Chakrabarty

1982
First gene patent issued (to Regents of University of California)

1988
Human Genome Project initiated

1989
International Breast Cancer Linkage Consortium founded

1990
Mary-Claire King and colleagues report in *Science* that gene linked to breast cancer (BRCA1) lies on chromosome 17

1991
Myriad Genetics founded

1994
BRCA1 sequence reported

1995
BRCA2 sequence reported

1998
BRCA1 and BRCA2 patents issued in United States

1998
BRCA1 and BRCA2 patents issued in United States

1999
BRCA1 Analysis test launched

2000
Complete draft sequence of human genome announced by Human Genome Project and Celera Genomics

2001
New USPTO guidelines make EST patents less likely

2004
Myriad’s patent rights severely limited by court in European Union

2006
Myriad launches follow-on test for rare, large rearrangements of BRCA1 and BRCA2 DNA

2009
Myriad lawsuit filed in Southern District of New York

2010

**BRCA1 and BRCA2**

- On chromosomes 17 and 13, respectively
- Autosomal dominant transmission
- Proteins have a role in genomic stability
- >2,000 different mutations, polymorphisms, and variants distributed over both genes

**Breast Cancer Information Core**

- Nonsense
- Missense
- Splice-site

Breast Cancer Information Core
BRCA1- and BRCA2-Associated Cancers: Lifetime Risk

Breast cancer 50%-85% (often early age at onset)

Second primary breast cancer 40%-60%

Ovarian cancer 15%-45%

Absolute risk likely to be higher than 10%
- Prostate cancer

Absolute risk 10% or lower
- Male breast cancer
- Fallopian tube cancer
- Pancreatic cancer
How Much Breast and Ovarian Cancer Is Hereditary? Is it different in different populations?

- Breast Cancer:
  - Sporadic: ~5%
  - Family clusters: 15% - 20%
  - Hereditary: >15%

- Ovarian Cancer:
  - Sporadic: ~5%
  - Family clusters: 15% - 20%
  - Hereditary: >15%
Access to care influences knowledge of genetic epidemiology
North American commercial vendor *BRCA* sequence analyses for 46,276 women: Summary 1996 to 2006

Deleterious mutations were identified in 12.5% of women

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>No.</th>
<th><em>BRCA1</em></th>
<th><em>BRCA2</em></th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western European</td>
<td>36,235</td>
<td>2501 (6.9)</td>
<td>1899 (5.2)</td>
<td>4400 (12.1)</td>
</tr>
<tr>
<td>Central European</td>
<td>4066</td>
<td>336 (8.3)</td>
<td>214 (5.3)</td>
<td>550 (13.5)</td>
</tr>
<tr>
<td>Latin American</td>
<td>1936</td>
<td>185 (9.6)</td>
<td>105 (5.4)</td>
<td>290 (14.8)</td>
</tr>
<tr>
<td>African</td>
<td>1767</td>
<td>180 (10.2)</td>
<td>100 (5.7)</td>
<td>280 (15.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>1183</td>
<td>75 (6.3)</td>
<td>75 (6.3)</td>
<td>150 (12.7)</td>
</tr>
<tr>
<td>Native American</td>
<td>597</td>
<td>44 (7.4)</td>
<td>35 (5.9)</td>
<td>79 (13.2)</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>492</td>
<td>30 (6.1)</td>
<td>16 (3.3)</td>
<td>46 (9.4)</td>
</tr>
<tr>
<td>Total</td>
<td>46,276</td>
<td>3351 (7.2)</td>
<td>2444 (5.3)</td>
<td>5795 (12.5)</td>
</tr>
</tbody>
</table>

Hall et al. Cancer 115:2222–33, 2009
Figure 1. Variant of uncertain significance reporting rate for 2002 through 2006.
8.3% (95% CI, 3.1%-20.1%) in Ashkenazi Jewish patients (n=41)
2.2% (95% CI, 0.7%-6.9%) in other non-Hispanic white patients (n=508)
High proportion of $BRCA1/2$ founder mutations in Hispanic breast/ovarian cancer families from Colombia

- 3450 delCAAG and A1708E accounted for 100% of all $BRCA1$ mutations identified in this cohort
- 3034 del-ACAA accounted for 40% of all $BRCA2$ mutations

A high prevalence of $BRCA1$ mutations among breast cancer patients from the Bahamas

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 Exon 21 T5443G</td>
<td>5</td>
</tr>
<tr>
<td>BRCA1 Exon 15 4730insG</td>
<td>6</td>
</tr>
<tr>
<td>BRCA1 IVS13+1G&gt;A</td>
<td>30</td>
</tr>
<tr>
<td>BRCA1 IVS16+6T&gt;C</td>
<td>3</td>
</tr>
<tr>
<td>BRCA1 exon11 943ins10</td>
<td>3</td>
</tr>
<tr>
<td>BRCA1 exon2 185delAG</td>
<td>2</td>
</tr>
</tbody>
</table>
BRCA mutations prevalent among Colombian Ovarian Cancer Patients

- Unselected women with ovarian cancer (n=96)
- DNA samples screened with panel of recurrent Hispanic BRCA mutations*
  - BRCA mutation detected in 15/96 (15.6%)
    - 11/15 BRCA1 3450del4

*panel: BRCA1 n=50; BRCA2 n=46; includes all mutations reported from Colombia

Mexico-U.S. Migration

Source: www.saludmigrante.salud.gob.mx/
The Foreign Born from Mexico in the United States As Percentage of Total County Population, 2000

LEGEND
Foreign born from Mexico as percentage of total county population
- 0.0 to 1.3
- 1.4 to 3.2
- 3.3 to 9.2
- 9.3 to 19.9
- 20.0 to 37.1
U.S. average: 3.3%

Source: U.S. Census Bureau, Census 2000, Summary File 3.
Migration Policy Institute ©2004

Hawaii is located 2,400 miles southwest of mainland U.S.
Alaska is located 750 miles northwest of mainland U.S. and borders Canada.
Puerto Rico is located 1,000 miles southeast of mainland U.S.
City of Hope IRB # 96144; supported by Award Number RC4A153828 (PI: J.Weitzel) from the NCI and the Office of the Director, NIH
### BRCA Mutations in 746 High Risk Hispanic Families

**Mutation Status and Cancer History of Probands**

<table>
<thead>
<tr>
<th></th>
<th>Mutation Status</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carriers</td>
<td>Non-Carriers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Variant</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total no. (%) N=746</strong></td>
<td>189 (25)</td>
<td>523 (70)</td>
<td>34 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>187</td>
<td>520</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affected</strong></td>
<td>169</td>
<td>449</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with breast cancer</td>
<td>144</td>
<td>419</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with ovarian cancer</td>
<td>17</td>
<td>21</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with breast and ovarian cancer</td>
<td>8</td>
<td>9</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Average age at first breast cancer diagnosis</strong></td>
<td><strong>40</strong></td>
<td><strong>40.8</strong></td>
<td><strong>39.5</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unaffected</strong></td>
<td>20</td>
<td>74</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

J.N. Weitzel *et al.* JCO 2012
Graphical comparison of mutations across 4 cohorts:
Southwest US; Texas; No. California; Mexico City

- ex9-12del (n=13)
- ex9-12del (n=3)
- ex9-12del (n=13)
Large Genomic Rearrangements and \textit{BRCA}

- \textit{BRCA} large genomic rearrangements (LGR) are not detectable by PCR-based Sanger DNA sequencing.
- Recently published clinical data from Myriad Genetics laboratory confirmed previous observations that LGRs constitute $>10\%$ of all \textit{BRCA} mutations.
- $21\%$ rate was reported for Latin American/Caribbean.
- $1/3$ of LGRs were the \textit{BRCA1} ex9-12del mutation.

Grandparental Origins for Recurrent Mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>No. of observations</th>
<th>Country of Origin</th>
<th>States in Mexico</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>185delAG</td>
<td>18</td>
<td>Mexico (16) Spain (2)</td>
<td>Chiapas Durango Jalisco</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Michoacan Distrito Federal</td>
</tr>
<tr>
<td></td>
<td>Exon9-12del</td>
<td>13</td>
<td>Mexico</td>
<td>Chihuahua (2) Durango</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Jalisco Puebla Tamaulipas</td>
</tr>
<tr>
<td></td>
<td>R71G</td>
<td>9</td>
<td>Mexico (7) Spain (2)</td>
<td>Michoacan (2) Sonora</td>
</tr>
<tr>
<td></td>
<td>R1443X</td>
<td>6</td>
<td>Mexico (4) Colombia (1) Peru (1)</td>
<td>Oaxaca</td>
</tr>
<tr>
<td></td>
<td>Q1200X</td>
<td>5</td>
<td>Mexico</td>
<td>Aguascalientes Colima</td>
</tr>
<tr>
<td></td>
<td>917delTT</td>
<td>5</td>
<td>El Salvador (4) Guatemala (1)</td>
<td>Michoacan</td>
</tr>
</tbody>
</table>

J.N. Weitzel et al. JCO 2012
Discover your DNA ancestors not from hundreds of years ago, but from thousands of years ago.

Genetic research has grown leaps and bounds. Now with this innovative ancestry test, you can use that research to learn fascinating insights about your earliest ancestors, their history, and the amazing journeys they traveled. A simple swab of your inner-cheek is all it takes to gain a better understanding of your lineage. Your ancestry will also be confirmed with a beautiful full-color certificate, styled in either Modern or Traditional, with your name and information about your ancestors garnered from worldwide scientific papers and reports. DNA Ancestors Certificate size: 16½"H x 11¾"W.

DNA101A
Father's DNA Ancestors $159.99
DNA102A
Mother's DNA Ancestors $159.99
DNA103A
Buy Both and Save $279.99

Certificates shipped within 2 weeks after DNA sample returned.
Ancestry Informative Markers – What is Hispanic?

*Samples courtesy of Mary Beth Terry, Columbia University
Identification of the prevalent *BRCA1* and *BRCA2* mutations in the female population of Puerto Rico

Julie Dutil a,*, Jose L. Colon-Colon b, Jaime L. Matta c, Rebecca Sutphen d, Miguel Echenique b

a Department of Biochemistry, Ponce School of Medicine, Ponce, Puerto Rico; b Cancer Center, Auxilio Mutuo Hospital, San Juan, Puerto Rico; c Department of Pharmacology and Physiology, Ponce School of Medicine, Ponce, Puerto Rico; d University of South Florida College of Medicine, Tampa, FL

<table>
<thead>
<tr>
<th>Gene</th>
<th>Exon</th>
<th>Nucleotide</th>
<th>Amino acid</th>
<th>Clinical significance</th>
<th>No. Observations</th>
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<tr>
<td>BRCA1</td>
<td>1-2</td>
<td>delExon1-2</td>
<td>N/A</td>
<td>Deleterious</td>
<td>2</td>
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<tr>
<td>BRCA1</td>
<td>13</td>
<td>4380C&gt;T</td>
<td>H1421Y</td>
<td>Uncertain</td>
<td>1</td>
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<tr>
<td>BRCA1</td>
<td>14</td>
<td>4529A&gt;T</td>
<td>E1470D</td>
<td>Favors polymorphism</td>
<td>1</td>
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<tr>
<td>BRCA2</td>
<td>11</td>
<td>4150G&gt;T</td>
<td>E1308X</td>
<td>Deleterious</td>
<td>4</td>
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<tr>
<td>BRCA2</td>
<td>11</td>
<td>6027del4</td>
<td>Stop1961</td>
<td>Deleterious</td>
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<tr>
<td>BRCA2</td>
<td>11</td>
<td>6392delT</td>
<td>Stop2069</td>
<td>Deleterious</td>
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<tr>
<td>BRCA2</td>
<td>11</td>
<td>6714del4</td>
<td>Stop2166</td>
<td>Deleterious</td>
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<tr>
<td>BRCA2</td>
<td>11</td>
<td>7031G&gt;A</td>
<td>R2268K</td>
<td>Uncertain</td>
<td>1</td>
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<tr>
<td>BRCA2</td>
<td>15</td>
<td>7708C&gt;T</td>
<td>R2494X</td>
<td>Deleterious</td>
<td>1</td>
</tr>
</tbody>
</table>
Ancestry Informative Markers

185delAG Carriers

Mean EUR and AMI Ancestry

<table>
<thead>
<tr>
<th></th>
<th>Ex9-12del</th>
<th>185delAG</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUR</td>
<td>36%</td>
<td>50%</td>
<td>0.03</td>
</tr>
<tr>
<td>AMI</td>
<td>43%</td>
<td>30%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*P-value for Student’s T-test

Weitzel lab (unpublished)
**BRCA Mutations in High Risk Hispanic Families**  
Prevalence and Founder effect - Summary

- The *BRCA1* 185delAG mutation is prevalent in Latinos, and shares the Jewish founder haplotype
  - Likely descendents of Spanish Jews who converted to Christianity to avoid persecution

- Large deletion mutation seen in 18 independent Mexican families (high risk clinic=13; population-based=5) “Mexican Founder Mutation”
  - Estimated by haplotype analysis to have arisen ~74 generations/1,480 yrs ago
  - Amerindian origin suggested by admixture studies and historical context

- Among 746 Latinas tested in clinic-based cohort: *BRCA1* 185delAG (n=18), ex9-12del (n=13), *BRCA2* 3492insT (n=10); fifteen recurrent (n>4) mutations account for 54% of all carriers

J.N. Weitzel et al. JCO, 2012
Genetic Predisposition Testing Is a Multi-Step Process

- Identify at-risk patients
- Provide pretest counseling
- Obtain informed consent
- Select and offer test
- Disclose results
- Provide post-test counseling and follow-up
HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA\textsuperscript{a,b,c}

- Individual from a family with a known deleterious BRCA1/BRCA2 mutation
- Personal history of breast cancer\textsuperscript{d} + one or more of the following:
  - Diagnosed age ≤ 45 y
  - Diagnosed age ≤ 50 y with ≥ 1 close blood relative\textsuperscript{e} with breast cancer ≤ 50 y and/or ≥ 1 close blood relative\textsuperscript{e} with epithelial ovarian\textsuperscript{f} cancer at any age
  - Two breast primaries\textsuperscript{g} when first breast cancer diagnosis occurred ≤ age 50 y
  - Diagnosed age ≤ 60 y with a triple negative breast cancer
  - Diagnosed age ≤ 50 y with a limited family history\textsuperscript{c}
  - Diagnosed at any age, with ≥ 2 close blood relatives\textsuperscript{e} with breast and/or epithelial ovarian\textsuperscript{f} cancer at any age
  - Diagnosed at any age with ≥ 2 close blood relatives\textsuperscript{e} with pancreatic cancer at any age
  - Close male blood relative\textsuperscript{e} with breast cancer
  - For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required\textsuperscript{h}

- Personal history of epithelial ovarian\textsuperscript{f} cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer at any age with ≥ 2 close blood relatives\textsuperscript{e} with breast and/or ovarian\textsuperscript{f} and/or pancreatic cancer at any age
- Family history only
  - (Testing of unaffected family members should only be considered when no affected family member is available and then the unaffected family member with the highest probability of mutation should be tested. Significant limitations of interpreting test results should be discussed.)
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative with breast cancer\textsuperscript{d} and/or ovarian\textsuperscript{f} cancer with ≥ 2 close blood relatives\textsuperscript{e} with breast cancer (at least one with breast cancer ≤ 50 y) and/or ovarian\textsuperscript{f} cancer

\textsuperscript{a} See NCCN Breast Cancer Screening and Diagnosis Guidelines

\textsuperscript{b} See Follow-up (HBOC-2)
Clinical Management of BRCA Mutation-Positive Patient

**Cancer Screening & Prevention Program**

Positive BRCA1 or BRCA2 test result

Possible testing for other adult relatives

- Prophylactic surgery
- Lifestyle changes
- Increased surveillance
- Chemo-prevention
Cumulative incidence of early-stage (stages 0 to I) breast cancer in magnetic resonance imaging (MRI)

No MRI group
MRI group

\( P = .01 \)

No. at risk
No MRI 830 663 549 418 336 264 189
MRI 445 338 275 223 161 109 68

Warner E et al. JCO 2011;29:1664-1669
Options for breast cancer patients with *BRCA* mutations

- **Surgical options for the breast**
  - therapeutic mastectomy *versus* breast conservation therapy on affected breast
  - risk reduction mastectomy on contralateral breast

- **Hormonal risk reduction options**
  - BSO
  - tamoxifen

- **Screening**
  - mammography
  - MRI
Oophorectomy Reduces Ovarian Cancer, Breast Cancer, and all cause mortality

Greatest breast cancer risk reduction among BRCA1 mutation carriers without a prior dx of breast cancer who had their oophorectomy < age 50
HR: 0.15 (95% CI 0.04-0.63)

27% for BRCA2 mutation carriers.3,6 Women who are mutation carriers have cancer risk–management options that include risk-reducing salpingo-oophorectomy, risk-reducing mastectomy, annual cancer screening, and chemoprevention. Due to the lack of effective screening for ovarian cancer, salpingo-oophorectomy is strongly recommended once childbearing is complete.

Salpingo-oophorectomy has been demonstrated to decrease the risk of both breast cancer and ovarian cancer in BRCA2 mutation carriers.7,10 However, estimates for risk and mortality reduction for women with and without a prior breast cancer diagnosis differ.5

Author Affiliations are listed at the end of this article.
Corresponding Author: Timothy R. Rebbeck, PhD, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, 217 Bockley Hall, 423 Guardian Dr, Philadelphia, PA 19104 (trebeck@mail.med.upenn.edu).
Survival of epithelial invasive ovarian cancer patients by stage and BRCA mutation status

Response to Neoadjuvant Cisplatin in BRCA1+ Breast Cancer Patients

- 10 women with BRCA1 mutations
- 4 cycles CDDP 75mg/m2 q 21d

<table>
<thead>
<tr>
<th>Response</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Complete Response</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>Clinical Partial Response</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Complete Pathologic Response</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>Partial Pathologic Response</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Residual Disease in the Breast</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number positive nodes</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>1</td>
</tr>
</tbody>
</table>

18/25 = 72% pathCR

Poly (ADP-ribose) polymerase (PARP)

- A key regulator of DNA damage repair processes
- Involved in DNA base-excision repair (BER)
- Binds directly to DNA damage
- Produces large branched chains of poly(ADP-ribose)
- Attracts and assists BER repair effectors
PARP inhibition and tumor-selective synthetic lethalitly

DNA damage (SSBs)

DNA replication (accumulation of DNA DSBs)

PARP inhibition

Normal cell with functional HR pathway

HR-mediated DNA repair

Cell survival

HR-deficient tumor cell (e.g. BRCA 1/2-/-)

Impaired HR-mediated DNA repair

Tumor-selective cytotoxicity

DSB, double-strand break; HR, homologous recombination
SSB, single-strand break

Protocol NCI #8264: ABT-888 +/- Carbo

Endpoints: BRCA1 vs. BRCA2
- RECIST Criteria
- PFS ABT-888 single agent; post-progression for combination
- Safety & Tolerability, Pharmacokinetics
- Correlative studies will include biomarkers of PARP and carboplatin effect, as well as prospective analyses of mechanism(s) of resistance
  - in vivo selection for BRCA “reversion” mutants that restore the reading frame and functional domains such as HRR may be one mechanism of drug resistance
### City of Hope Cancer Screening & Prevention Program

#### Patient Characteristics and BRCA Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Probands N=79</th>
<th>At-risk relatives N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average age at time of visit (years)</strong></td>
<td>40.3 (range 22-61)</td>
<td>35.7 (range 22-54)</td>
</tr>
<tr>
<td><strong>Cancer status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unaffected (%)</td>
<td>16 (20.3%)</td>
<td>15 (83.3%)</td>
</tr>
<tr>
<td>Affected with BC and/or OC</td>
<td>63 (79.7%)</td>
<td>3 (16.7%)</td>
</tr>
<tr>
<td>breast cancer (%)</td>
<td>49 (77.7%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>bilateral breast cancer (%)</td>
<td>11 (17.5%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>ovarian cancer (%)</td>
<td>3 (4.8%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Average age at first BC diagnosis</strong></td>
<td>38.6 (range 23-61)</td>
<td>38.0 (range 29-49)</td>
</tr>
<tr>
<td><strong>BRCA Testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Tested (%)</td>
<td>17 (21.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Tested (%)</td>
<td>62 (78.4%)</td>
<td>18 (100%)</td>
</tr>
<tr>
<td>Positive (%)</td>
<td>17 (27.4%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>42 (67.8%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>VUS (%)</td>
<td>3 (4.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Clinical Management of BRCA Mutation-Negative Patients

Negative BRCA1 and/or BRCA2 test result

NO

Member of family w/ known BRCA1 or BRCA2 mutation?

YES

Emphasize empirically increased risk of breast and/or ovarian cancer

Encourage adherence to population screening guidelines

Provide individualized risk-management plan

Emphasize risk of sporadic cancer
Contribution of known genes to explaining familial aggregation of breast cancer

BRCA1
BRCA2
TP53
PTEN
ATM
CHEK2, BRIP1, PALB2
CASP8
8 WGA SNPs

Other familial risk factors (genes, environment)
Li-Fraumeni Syndrome

Affected with cancer

TP53-mutation carrier

Affected with cancer
### Emerging Breast Cancer Phenotype in Women with TP53 Germline mutations

<table>
<thead>
<tr>
<th>Cohort of TP53 Carriers</th>
<th>N</th>
<th>ER+ Percentage</th>
<th>Her2/neu+ Percentage</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiFE Consortium</td>
<td>32</td>
<td>84%</td>
<td>63%</td>
<td>Masciari et al. BCRT 2012</td>
</tr>
<tr>
<td>UK</td>
<td>9</td>
<td></td>
<td>83%</td>
<td>Wilson et al. J Med Genet 2010</td>
</tr>
<tr>
<td>MDACC/Chi</td>
<td>30</td>
<td>70%</td>
<td>67%</td>
<td>Melhem-Bertrandt et al. Cancer 2012</td>
</tr>
<tr>
<td>Women &lt; 40 BC, unselected for FHx</td>
<td>-</td>
<td>52-66%</td>
<td>22-33%</td>
<td>Collins et al. BCRT 2011; Gonzalez-Angulo et al. Cancer 2012</td>
</tr>
</tbody>
</table>
# BROCA Gene Panel

<table>
<thead>
<tr>
<th>GENE</th>
<th>CANCER RISK</th>
<th>GENE</th>
<th>CANCER RISK</th>
<th>GENE</th>
<th>CANCER RISK</th>
<th>GENE</th>
<th>CANCER RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Colon</td>
<td>CDK4</td>
<td>Melanoma</td>
<td>NBN</td>
<td>Breast</td>
<td>RBBP8</td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>Breast, Pancreatic</td>
<td>CDKN2A</td>
<td>Pancreatic, Melanoma</td>
<td>PALB2</td>
<td>Breast, Pancreatic</td>
<td>RET</td>
<td>Endocrine</td>
</tr>
<tr>
<td>ATR</td>
<td>Oropharyngeal</td>
<td>CHEK1</td>
<td></td>
<td>PMS2</td>
<td>Colon, Endometrial</td>
<td>SMAD4</td>
<td>Colon</td>
</tr>
<tr>
<td>BABAM1</td>
<td></td>
<td>CHEK2</td>
<td>Breast</td>
<td>PRSS1</td>
<td>Pancreatic</td>
<td>STK11</td>
<td>Breast</td>
</tr>
<tr>
<td>BAP1</td>
<td>Uveal melanoma, mesothelioma</td>
<td>FAM175A</td>
<td>Breast</td>
<td>PTEN</td>
<td>Breast</td>
<td>TP53</td>
<td>Breast, Ovary</td>
</tr>
<tr>
<td>BARD1</td>
<td>Breast, Ovarian</td>
<td>MLH1</td>
<td>Colon, Ovarian</td>
<td>RAD50</td>
<td>Breast</td>
<td>TP53BP1</td>
<td></td>
</tr>
<tr>
<td>BMPR1A</td>
<td>Colon</td>
<td>MRE11A</td>
<td>Breast</td>
<td>RAD51</td>
<td></td>
<td>UIMC1</td>
<td>Breast</td>
</tr>
<tr>
<td>BRCC3</td>
<td>MSH2 (+EPCAM)</td>
<td>Colon, Ovarian</td>
<td>RAD51B</td>
<td></td>
<td>VHL</td>
<td>Kidney, neuroendocrine</td>
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</tr>
<tr>
<td>BRIP1</td>
<td>Breast, Ovarian</td>
<td>MSH6</td>
<td>Colon, Endometrial</td>
<td>RAD51C</td>
<td>Ovarian, Breast</td>
<td>XRCC2</td>
<td>Breast</td>
</tr>
<tr>
<td>CDH1</td>
<td>Breast, Gastric</td>
<td>MUTYH</td>
<td>Colon</td>
<td>RAD51D</td>
<td>Ovarian, Breast</td>
<td>XRCC3</td>
<td></td>
</tr>
</tbody>
</table>

Developed by Tom Walsh and Mary-Claire King
Proportions ovarian, fallopian tube, or peritoneal cancer patients with respective germ-line loss-of-function mutations

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Proportion of patients with inherited mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL PATIENTS</strong></td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>10</td>
<td>0.10</td>
</tr>
<tr>
<td>40 - 49</td>
<td>57</td>
<td>0.28</td>
</tr>
<tr>
<td>50 - 59</td>
<td>99</td>
<td>0.30</td>
</tr>
<tr>
<td>60 - 69</td>
<td>114</td>
<td>0.35</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>80</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Self, in addition to ovarian cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>31</td>
<td>0.19</td>
</tr>
<tr>
<td>No breast cancer</td>
<td>329</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
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</tr>
<tr>
<td>Breast cancer</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>35</td>
<td>0.35</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>18</td>
<td>0.54</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>19</td>
<td>0.28</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>60</td>
<td>0.42</td>
</tr>
<tr>
<td>Breast or ovarian cancer</td>
<td>157</td>
<td>0.36</td>
</tr>
<tr>
<td>Neither breast nor ovarian cancer</td>
<td>203</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Disease site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>273</td>
<td></td>
</tr>
<tr>
<td>Peritoneum</td>
<td>46</td>
<td>0.22</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>31</td>
<td>0.27</td>
</tr>
<tr>
<td>Ovary/Endometrium</td>
<td>8</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>242</td>
<td></td>
</tr>
<tr>
<td>Carcinoma, undifferentiated</td>
<td>64</td>
<td>0.24</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>23</td>
<td>0.17</td>
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<tr>
<td>Clear cell</td>
<td>17</td>
<td>0.06</td>
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<tr>
<td>Carcinosarcoma, other</td>
<td>14</td>
<td>0.14</td>
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<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>0.11</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>328</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>22</td>
<td>0.18</td>
</tr>
<tr>
<td>II</td>
<td>26</td>
<td>0.23</td>
</tr>
<tr>
<td>III or IV</td>
<td>308</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Walsh T et al. PNAS 2011;108:18032-18037
Known Cancer Genes

High penetrance, rare cancer predisposition genes
(\textit{Relative risk} \geq 5)

- P53
- APC
- CDH1
- BRCA1
- BRCA2
- MLH1
- MSH2
- PTEN
- STK11
- CDKN2A
- MSH6
- PMS2

Moderate risk alleles
(\textit{Relative risk} \geq 1.5 \text{ and } < 5.0)

- ATM
- CYP1A1
- APC (I1307K)
- CHEK2
- BRIP1
- PALB2
- BLM (BLM^{Ash})
- GSTM1
- JAK2
- KITLG

Low penetrance, high frequency risk alleles*
(\textit{Relative risk} < 1.5)

- 8q24 locus
- MSMB
- CHRNA3
- CHRNAS
- CHRN4
- FGFR2
- NUDT10
- NUDT11

Population Frequency
CHEK2 1100delC and Breast Cancer Risk: Meta-Analyses of 26,000 Patient Cases and 27,000 Controls

Studies of familial breast cancer

Odds ratio (95% CI)

Baeyens et al 4.7 (0.2 to 93)
Sodha et al 32 (1.6 to 630)
Rashid et al 3.0 (0.3 to 33)
Van Binst et al 4.3 (0.5 to 35)
Bernstein et al 7.9 (1.1 to 58)
De Jong et al 6.0 (1.4 to 26)
Dufault et al 3.4 (1.2 to 10)
Vahteristo et al 4.2 (2.1 to 8.1)
CHEK2 Consortium et al 4.8 (3.3 to 9.8)
Overall, fixed effect model 4.8 (3.3 to 7.2)
Overall, random effect model 4.6 (3.1 to 6.8)

Odds Ratio for CHEK2*1100delC Heterozygotes v Noncarriers
Absolute risks for BRCA1 mutation carriers based on combined SNP profile distributions

Couch et al. PLOS Genetics 9(3) e1003212, March 2013
Summary…

- Hereditary breast and ovarian cancer affects all world populations
- Common ancestry, geography and world history are reflected in the presence and prevalence of founder mutations
- The first demonstrated Mexican BRCA founder mutation, BRCA1 ex9-12del, is prevalent and likely of Amerindian ancestral origin
  - history cites the integration of the Mayans and Toltecs in Puebla around this time period
  - Early data suggest that ex9-12del one of the most frequent population-specific large rearrangement mutations in the world
- Prevalence of BRCA1 185delAG in Hispanic populations is a reflection of Spanish Jewish history, the legacy of religious intolerance and guns, germs and steel
While complete sequencing and screening for large genomic rearrangements are the “gold standard” of BRCA gene analysis, ancestry-informed strategies may increase cost-efficiency and broaden access where clinical sensitivity can be established.

Pragmatic applications include assessment of 3 mutations for individuals of Jewish ancestry as a sole analysis, 1 mutation among Icelanders, or 4 mutations among Dutch patients as a prescreen among Polish patients as a broad dissemination strategy.

Potential applications in hand include Latin America (Mexico, Central America and Colombia) and Caribbean Islands (e.g. Bahamas).

Breast and ovarian cancer epidemiology studies may need to take into account \textit{BRCA} status when investigating populations where founder mutations are prevalent (e.g. Hispanic, Jewish).
Future Directions

• Training in genetic cancer risk assessment and counseling is important for clinical implementation of BRCA analyses, and should be disseminated

• The remarkable advances in genetic analysis technologies should be brought to bear to enhance access globally
Hereditary Breast Cancer and Novel Hispanic BRCA Mutations Project

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