Breast Cancer Genomic Risk Assessment in Global Health: Implementation in Low-Resource Settings

Jeffrey N. Weitzel, M.D.
Professor and Chief, Division of Clinical Cancer Genomics

UICC 2018 Kuala Lumpur
AACR Delegation (United States)
Organization of the Session

Skills, tools and insights to aid implementation of genomic cancer risk assessment for Latinos
Jeffrey Weitzel, City of Hope Cancer Center (United States)

Research in the service of clinical cancer genetics in Brazil
Patricia Ashton-Prolla, Universidade Federal do Rio Grande do Sul- CNOA (Brazil)

Reducing the gaps to enhance access to genetic cancer risk assessment in Mexico
Cynthia Villarreal, Alianza Mexicana por el Cáncer, AC (Mexico)

Genomics and Cancer Control in Low Resource Settings: Lessons from the US and Nigeria
Olufunmilayo Olopade, University of Chicago (United States)

Q&A and DISCUSSION
BRCA1- and BRCA2-Associated Cancers

- 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
June 2013 - U.S. Supreme Court rules that as nature, genes cannot be patented
Clinical Management of BRCA Mutation-Positive Patient

Positive BRCA1 or BRCA2 test result

Possible testing for other adult relatives

Prophylactic surgery

Targeted therapy

Increased surveillance

Chemo-prevention
How Much Breast and Ovarian Cancer Is Hereditary? Is it different in different populations?

- Breast Cancer:
  - Sporadic: ~5-10%
  - Family clusters: 15% -20%
  - Hereditary: 15% - 20%

- Ovarian Cancer:
  - Sporadic: 15-24%
  - Hereditary: 15-24%
Access to care influences knowledge of genetic epidemiology.
Exploring the climate, barriers, and possible approaches to implementing genetic cancer risk assessment in Latin America: a roundtable discussion

Barriers and challenges for global implementation of GCRA

- Cost of tests (not covered by most public health plans)
- Cost of GCRA delivery
- Few genomically competent practitioners
- Difficulty interpreting risks for genes other than BRCA
- Concerns about stigma and discrimination
- Competition for limited health care resources
- Greater pharma interest in treatment vs. prevention

GCRA may enable more effective allocation of limited health care resources, while preventing the suffering of cancer.

With all of these costs and challenges, is GCRA a dispensable luxury in the context of health care in LMIC’s?
Perceived understanding of SARS-CoV-2 through mitigation strategies and public health recommendations

Pathological characteristics of BRCA-associated breast cancers in Hispanics

Social-cognitive aspects of underserved Latinas preparing to undergo genetic cancer risk assessment for hereditary breast and ovarian cancer

Evidence for Common Ancestral Origin of a Recurring BRCA1 Genomic Rearrangement Identified in High-Risk Hispanic Families
The Clinical Cancer Genomics Community Research Network

- 47 oncogenetic practices across the U.S and Latin America

- Opportunity to participate in global cancer genomics research
Prevalence and Type of BRCA Mutations in Hispanics Undergoing Genetic Cancer Risk Assessment in the Southwestern United States: A Report From the Clinical Cancer Genetics Community Research Network

Jeffrey H. Watanabe, Jessica Cisneros, Arturi Marron-Nogren, Raquel Perez, Jose Jaramillo, Charnie Becker, Cheryl Jungbluth, Cheryl Cina, Paul Duncan, Gary Urmey, J. Salvador Saldivar, Mary Beattie, Nancy Lelman, Sharon Said, Danielle Port, Deborah J. Barragan, Esther M. John, Susan L. Neuhau, and Garrett P. Larson

ABSTRACT

Purpose
To determine the prevalence and type of BRCA1 and BRCA2 (BRCA) mutations among Hispanics in the Southwestern United States and their potential impact on genetic cancer risk assessment (GCRA).

Methods
Hispanics aged 45-74 with a personal or family history of breast and/or ovarian cancer were enrolled in an institutional review board-approved registry and received GCRA and BRCA testing within a consortium of 14 clinics. Population-based Hispanic breast cancer cases (n = 402) enrolled in the Northern California Breast Cancer Family Registry, negative by sequencing for BRCA mutations, were evaluated for the presence of the BRCA1 ex9-12del large rearrangement.

Results
Deletional BRCA mutations were detected in 109 (25%) of 402 familial cancer patients (124 BRCA1; 65 BRCA2; 21 [11%] of 196 were large rearrangements, of which 82% [15 of 19] were BRCA1 ex9-12del). Nine rearrangement mutations accounted for 52% of the total. Among those, BRCA1 ex9-12del seems to be a Mexican founder mutation and represents 10% to 12% of all BRCA1 mutations in clinic- and population-based cohorts in the United States.

Conclusion
BRCA mutations were prevalent in the largest study of Hispanic breast and/or ovarian cancer families in the United States to date, and a significant proportion were large rearrangement mutations. The high frequency of large rearrangement mutations warrants screening in every case. We document the first Mexican founder mutation (BRCA1 ex9-12del), which, along with other recurrent mutations, suggests the potential for a cost-effective panel approach to ancestry-informed GCRA.

Hereditary Breast Cancer and Novel Hispanic BRCA Mutations; supported by Grant#RSGT0926301 from the American Cancer Society
Clinical Profile of Disparity: Young and advanced disease at diagnosis with BRCA mutations prevalent and a possible partial explanation for excess of TNBC in Mexico.

<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer n=96</th>
<th>Ovarian Cancer n=92</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>Range</td>
<td>26-63</td>
<td>23-83</td>
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<tr>
<td>Mean</td>
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<td>2%</td>
<td>IV</td>
</tr>
<tr>
<td>Unknown</td>
<td>3%</td>
<td>Unknown</td>
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</tbody>
</table>

BRCA mutations prevalent in Mexico.

Villarreal et al. Cancer 2014

Significant clinical impact of recurrent BRCA1 and BRCA2 mutations in Mexico.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Ovarian cancer (n=92)</th>
<th>Breast cancer (n=96)</th>
<th>Total (n=188)</th>
</tr>
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<tbody>
<tr>
<td>ex9-12del</td>
<td>9 (35%)</td>
<td>4 (29%)</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>IVS5+1G&gt;A</td>
<td>2</td>
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<tr>
<td>3977delA*</td>
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<td>R1696W*</td>
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<tr>
<td>803delA*</td>
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<tr>
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<tr>
<td>ex8-10del</td>
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BRCA1 Large Rearrangements (BRCA1)**

<table>
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<tr>
<th>Mutation</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Total</th>
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<tr>
<td>9463delG</td>
<td>1</td>
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<td>6244delG*</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>2900delICT*</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>6714delH*</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1803insA*</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6252insG</td>
<td>0</td>
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</tbody>
</table>

Total: 26 (28%) 14 (15%) 40 (21%)

* Mutations detected by pyrosequencing; **detected by MLPA

Personalized cancer genetics training for personalized medicine: Improving community-based healthcare through a genetically literate workforce

Kathleen R. Blazer, EdD, CGS\(^1\), Deborah J. MacDonald, PhD, APNG\(^1\), Julie O. Culver, MS\(^1\), Carin R. Huizenga, MS\(^2\), Robert J. Morgan, MD\(^2\), Gwen C. Uman, PhD, RN\(^3\), and Jeffrey N. Weitzel, MD\(^{1,2}\)

Clinical Cancer Genomics Community of Practice: National Reach and Global Impact
The effect of Genetic Cancer Risk Assessment on the uptake of risk-reducing surgeries in Hispanic women with breast cancer

- 1,517 Hispanic women with breast cancer (CCGCRN registry)
- Median follow-up = 2.6 yrs.
- BRCA carriers: 270 (18%)
- BRCA negative: 1247 (82%)

Factors associated with risk reduction surgery:
- Living in the US
- *BRCA* carriers
- Prior childbearing

RRM: US (53%) vs. LatAm (29%) p < 0.01
RRSO: US (67%) vs. LatAm (21%) p < 0.01

ASCO 2018; SABCS 2017
Summary

• Hereditary cancer affects all world populations
• Common ancestry, geography and world history are reflected in the prevalence of founder mutations
• There is clearly a potential to benefit counseled families, with ever broader arrays of genetic tools and precision Rx
• Innovative GCRA training and practice support, systematic collection of outcome data through research registries, and ancestry-informed strategies may enable cheap genetic testing, and NGS technologies promise to enhance access globally
• The goal is to decrease cancer related health disparities in Latin America by shifting clinical practice paradigms to include appropriate use of genomic cancer risk assessment as a cost-effective standard of care
Acknowledgements:

- American Cancer Society support for development of HISPANEL, and Avon Foundation support for validation testing in Mexico
- Breast Cancer Research Foundation support for pilot dissemination and implementation studies of GCRA in Latin America
- Clinical Cancer Genomics Community of Practice and GCRA training courses supported by NCI R25-CA171998
Research in the service of clinical cancer genetics in Brazil: Breast Cancer.

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Hospital de Clínicas de Porto Alegre, Brazil
Universidade Federal do Rio Grande do Sul, Brazil
Rede Brasileira de Câncer Hereditário

Disclosure: I have received grants from Brazilian Federal and State Funding Agencies and from Susan G. Komen for the Cure.

• Track 2: Advances in screening and early detection
Objectives

✔ Review major challenges and potential barriers in establishing GCRA programs in Latin America and Brazil;

✔ Provide 3 examples of research initiatives in the service of clinical cancer genetics in Brazil:
  - Cancer risk assessment in a primary care setting;
  - Hereditary Breast and Ovarian Cancer in Brazil;
  - Li-Fraumeni syndrome and the Brazilian founder mutation.
10% of all breast cancer is hereditary. Why focus on hereditary cancer?

Goals for cancer control and prevention

- Increase awareness of cancer/cancer risk
- Identifying at-risk patients and their relatives
- Implement primary prevention measures
- Discussing risk reducing surgeries
- Optimise early detection
- Promoting cancer screening
- Optimise treatment of cancer
- Providing targeted treatments
Brazil: a country with many disparities

São Paulo, Brazil, 2013
Challenges and Barriers to Establish Cancer Genetics Services in Brazil

- Costs of service and payment/reimbursement issues: cancer predisposition testing is still unavailable for 70% of individuals (public health care system);

- Lack of knowledge about hereditary cancer among patients and physicians;

- Cultural/professional barriers to prevention;

- Absence of exemplar professions like genetic counselors;

- There are many political and economical barriers to health care policy change.

... Among others...
Research has been an important strategy to overcome some of these barriers.

Example 1: Genetic risk assessment in primary care
Núcleo Mama Porto Alegre (NMPOA) Cohort
Prospective mammographic screening cohort of 9218 women recruited from primary health care units in the periphery of the city of Porto Alegre.

Recruitment 2004-2006
Follow-up: 10 years
Development and validation of a simple questionnaire for the identification of hereditary breast cancer in primary care
Patricia Ashton-Prolla*1,2,3,4,5,6,7, Juliana Giacomazzi2,3,4,6,
Aishameriane V Schmidt8, Fernanda L Roth3,6, Edenir I Palmero1,2,3,
Luciane Kalakun3,9, Ernestina S Aguiar2,3,4,6, Susana M Moreira3,7,
Erica Batassini3,9, Vanessa Belo-Reyes3,6, Lavinia Schuler-Faccini1,4,5,7,
Roberto Giugliani1,4,5,6,7, Maira Caleffi3 and Suzi Alves Caimy9,10

Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement
Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*
Research has been an important strategy to overcome some of these barriers.

Example 2:
Hereditary Breast and Ovarian Cancer Knowledge through international research collaborations
Screening for Hispanic Founder BRCA1 and BRCA2 Mutations in Latin America

Hispanel analysis
114 mutations
Multiplex PCR/ Maldi-TOF

Porto Alegre, Brazil
222 BC/OC patients
NCCN criteria
9 mutation +ve (4%)
(Alemar et al ) 2016

Lima, Peru
Abugggatas et al 2012
266 unselected BC
13 mutation +ve (5%)

Bogota, Colombia
Rodriguez et al, 2014
96 unselected OC
15 mutation +ve (15,6%)

Medellin, Colombia
Hernández et al 2014
244 unselected BC
3 mutation +ve (1,2%)

Monterrey, Mexico
Villareal-Garza et al, 2015
188 unselected BC/OC
40 mutation +ve (21,3%)

CLINICAL CANCER GENETICS
COMMUNITY OF PRACTICE
The germline mutational landscape of BRCA1 and BRCA2 in Brazil

BRCA1 variants

BRCA2 variants

Palmero, Carraro, Alemar et al. 2018.
Research has been an important strategy to overcome some of these barriers.

Example 3:
Li-Fraumeni Syndrome in Brazil
A unique profile.
TP53 c. 1010G>A (p.Arg337His) and Breast Cancer in Brazil

Retrospective analysis of 815 unselected BC patient recruited from 3 centers
c.1010G>A prevalence = 8.6%
Comprehensive data on the Brazilian TP53 founder mutation R337H
In conclusion

Research can:

✓ Stimulate the development of outreach programs and research/education networks;

✓ Produce novel/population-specific information on phenotype, epidemiology, testing strategy, management in hereditary cancer;

✓ Enable access to care (testing, screening, treatment), at least temporarily, in low resource countries and underserved communities.
Thank you!
Reducing the gaps to enhance access to genetic cancer risk assessment in Mexico

Cynthia Villareal-Garza

Centro de Cancer de Mama - Tecnologico de Monterrey, Mexico
Instituo Nacional de Cancerologia (INCan)
Alianza Mexicana por el Cancer (MILC)
Clinical case: 2013

41 y/o IIB TNBC

32 y/o BC

45 y/o BC
55 y/o OC

Left mastectomy and right prophylactic mastectomy + Adjuvant CT and RT
Breast Cancer in Mexico

• BC is the third leading cause of mortality in the general population and the second in the 45-64 age category ¹

• Ratio mortality/incidence in Mexico is almost the double than in the US ²

• ~20% of coverage of mammographic screening

• 95% are self-palpated masses

• BC delay is 7.8 months mostly due to provider delay ³

• 60-80% of cases are diagnosed at stage III-IV

¹ Instituto Nacional de Estadística y Geografía (INEGI), 2011.
Breast Cancer Coverage in Mexico

• Since 2007, BC diagnosis and treatment are covered by the fund for protection against catastrophic expenditure\(^1\)

• 24% of physicians reported treatment limitations\(^2\)

• Still, unmet needs for cancer care include:
  • Primary prevention
  • Secondary prevention or early detection
  • Rehabilitation
  • Long term follow-up and survivorship
  • Palliation
  • End-of-life care

Barriers for implementation of GCRA in Mexico

- In Mexico, GCRA services are not routinely provided and BRCA testing is not broadly available

Directed efforts for implementation of GCRA in Mexico

- Efforts should be directed to implement and maintain a program of GCRA in Mexico that will enable:
  - Public health policy to provide coverage for preventive services, including genetic testing
  - Screening and therapeutic interventions for patients and their families
Breast Cancer Center at Monterrey (2014)

Specialized center that provides care for BC patients from the private and the public sectors

- Clinical oncology
- Breast surgery
- Breast radiology
- Breast pathology

No GCRA
Key elements for GCRA implementation in TecSalud

International collaborations

- City of Hope Clinical Cancer Genetics Community Research Network (CCGCRN) consortium
- Women’s College Research Institute

Productivity:
  - Joint presentations at international meetings
  - Publications with COH and WCRI
Key elements for GCRA implementation in TecSalud

Cohort 3: Prospective registry

- Members of the Clinical Cancer Genetics Community Research Network (CCGCRN)
- Provision of a proper relational database and pedigree drawing program via web-based centralized Progeny program
- 248 patients in the registry in our Monterrey site!!!
Key elements for GCRA implementation

- **HISPANEL**
  - Inexpensive genomic panel assay
  - Identification of 114 recurrent Hispanic mutations
  - At 2% of the sequencing and MLPA cost
  - Opportunity for cost-effective genetic testing strategies with full clinical translation
Key elements for GCRA implementation

GCRA training

- Intensive Course and Clinical Cancer Genetics Community of Practice, facilitated by our collaboration with the CCGCRN team
  - Crucial to guarantee the follow-up and execution of the required patient interventions
Key elements for GCRA implementation

**Mentorship and follow-up**

- Virtual meetings
- Virtual GCRA tumor board in COH
- Scheduled visit for guidance by JW and KB in Jan 2018
Implementation of GCRA in TecSalud - 2015

1. Identification of high-risk patients by oncology clinicians
2. Refer to GCRA with our geneticist, Dr. Dione Aguilar
3. Registration to CCGCRN protocol
4. Risk reduction strategies: surveillance and/or surgeries
5. Post-test psychological assessment
6. Delivery of Final Test Results
7. Invite patient’s relatives to GCRA

Dr. Dione Aguilar y Méndez
Results

Total Patients at Risk with Results: 237/320
Total Family members at Risk with Results: 48/163

Total Percentage of Positive Results:
• Patients at Risk: 12.8%
• Family Members at Risk: 12.9%

Detected mutations:
• BRCA1
• BRCA2
• TP53
• CHEK2
• PALB2
• ATM
Challenges

Regulatory approval

- Renovation needed every 6 months
- Time delays for results delivery

Prophylactic measures

- Not covered either by public or private insurance services
- Low-income patients cannot afford extra out-of-pocket expenses
Strategies to carry out prophylactic measures

- **Coverage of surgeries (not covered) by Seguro Popular**
  - Bilateral mastectomies in a single procedure for mutation carriers (prioritization for testing)
  - BSO labeled as “adjuvant” measure in a 2-year period after initial diagnosis
  - 6 PM, 15 BSO, 13 on surveillance

- **NGO support (Fundacion Santos y de la Garza Evia)**
  - Prophylactic surgeries for patients with hereditary BC
  - Physicians’ pro bono services
  - 15 candidates

- **Collaboration with general hospital (Hospital Materno-Infantil)**
  - Familial mutation carriers
  - Low or no-cost procedures
  - 8 referrals

- **Abbreviated MRI protocol**
Future

Prospective registry in Mexican sites:
• Mutation burden, clinicopathological features and outcomes
• Uptake of preventive measures

Implementation of follow-up clinic

Extension of research studies

GCRA services dissemination across Mexico

TecSalud will serve as a model for other clinical sites to:
• Reproduce strategies
• Aid to understand the barriers
Clinical case: 2017

41 y/o TNBC IIB

32 y/o BC

45 y/o BC
55 y/o OC

66 y/o TNBC stage I

64 y/o Prophylactic BSO

41 y/o TNBC IIB BSO

32 y/o BC Surveillance

2

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2
Conclusions

• Key determinants that have permitted this progress are:
  • International collaborations that have provided us with:
    – Readily available assays through research projects, GCRA training, provision of proper database and pedigree drawing programs, and continuing collaborations
  • GCRA implementation that have resulted in:
    – Increased awareness, multidisciplinary team participation and ideas for improvement
  • Leaders and administrators increasing involvement to:
    – Implement personalized strategies for coverage of prophylactic measures
  • Enthusiasm and hard-work!
Working team

- **Tec Salud:**
  - Cynthia Villarreal
  - Dione Aguilar
  - Melina Miaja
  - Servando Cardona
  - Mauricio Canavati
  - Magaly Garza
  - Gerardo Amarante
  - Gerardo Magallanes
  - Jaime Tamez
  - Teresa Mireles
  - Rocío Ortiz
  - Sonia Flores

- **City of Hope:**
  - Jeffrey Weitzel
  - Kathleen Blazer
  - Josef Herzog
  - Danielle Castillo
  - Rosa Mejia

- **Women's College Research Institute:**
  - Steven Narod
  - Marcia Llacuachaqyu

*Physicians, nurses, administrators, staff from TecSalud, Fundacion Santos y de la Garza, Evia, Hospital Materno Infantil*
Thank you!!!

Contact details:
dra.cynthia.villarreal@gmail.com
Genomics and Cancer Control in Low Resource settings: Lessons from the US and Nigeria

AACR Sponsored Session
October 3rd, 2018

Olufunmilayo I Olopade, MD, FACP, OON
ACS Clinical Research Professor
Center for Clinical Cancer Genetics & Global Health
The University of Chicago
Disclosure

- **Co-Founder**: CancerIQ
- **Consultant or Advisory role**: Tempus
- **Research Collaboration**: Myriad, Color, Novartis, Roche
- **Advocacy Board**: Susan G Komen, V Foundation

Off-label and experimental medications may be discussed but will be clearly labeled as such.
Advances in Cancer Research

- Suboptimal access to care for 90% of the world’s population
- Poor access to Clinical Trials
- Lack of access to genomics
Selection of Systemic Treatment for Breast Cancer

Evaluation for systemic treatment

- HR Positive: Hormone Therapy
- HER-2+: Biologic Therapy
- HR+ and HER2+: Biologic Therapy + Hormone Therapy
- Triple-negative: Chemotherapy
Can We Treat Cancer for a Dollar a Day?
Guidelines for Low-Income Countries
How tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change.
Out of Africa Theory of Early Migration

Question
Is the burden of lethal breast cancer in the African Diaspora due at least in part, to differences in the distribution of heritable risk factors for the disease?
Molecular Subtypes of breast cancer

Multiplatform subtype:
- Somatic mutation
- CNV
- DNA Methylation
- miRNA
- Gene expression
- Protein expression

The Cancer Genome Atlas.
*Nature* 2012, Oct
Genetic Testing in African American Patients with Breast Cancer at UChicago

- Cancer Risk Clinic at UChicago

- 289 African American breast cancer patients

  - Enriched for:
    - early age onset (62% < 45 years)
    - positive family history (60%)
    - ER- (47%) and TNBC (36%)

- 68 damaging mutations in 65 cases (22.5%)

- 29 BRCA1 (10%) and 23 BRCA2 (8%)
Strong Genetic Contribution to Breast Cancer Risk in Nigerians

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cases (n = 1,136)</th>
<th>Controls (n = 997)</th>
<th>OR (95% CI), adjusted for age</th>
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<tr>
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<tr>
<td>BRCA1</td>
<td>80 (7.04)</td>
<td>3 (0.30)</td>
<td>25.94 (8.16 to 82.48)</td>
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<tr>
<td>BRCA2</td>
<td>47 (4.14)</td>
<td>4 (0.40)</td>
<td>10.76 (3.86 to 29.99)</td>
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<tr>
<td>PALB2</td>
<td>11 (0.97)</td>
<td>0 (0)</td>
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<tr>
<td>TP53</td>
<td>4 (0.35)</td>
<td>0 (0)</td>
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<tr>
<td>Total</td>
<td>142 (12.50)</td>
<td>7 (0.70)</td>
<td>20.77 (9.67 to 44.63)</td>
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<tr>
<td>Other genes</td>
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<td>2 (0.18)</td>
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<td>CHEK2</td>
<td>1 (0.09)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>FAM175A</td>
<td>0 (0)</td>
<td>1 (0.10)</td>
<td></td>
</tr>
<tr>
<td>GEN1</td>
<td>2 (0.18)</td>
<td>1 (0.10)</td>
<td></td>
</tr>
<tr>
<td>MRE11A</td>
<td>0 (0)</td>
<td>1 (0.10)</td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>1 (0.09)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td>3 (0.26)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>RAD51D</td>
<td>1 (0.09)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>SLX4</td>
<td>0 (0)</td>
<td>5 (0.50)</td>
<td></td>
</tr>
<tr>
<td>XRCC2</td>
<td>1 (0.09)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Total*</td>
<td>23 (2.02)</td>
<td>11 (1.10)</td>
<td>1.86 (0.80 to 3.84)</td>
</tr>
<tr>
<td>All genes</td>
<td>164 (14.44)</td>
<td>18 (1.81)</td>
<td>9.41 (5.73 to 15.44)</td>
</tr>
</tbody>
</table>

*One subject carries both BRCA1 and BRIP1 mutations.

Zheng et al. in press JCO
Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And molecular analysis
Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

Hope S. Rugo, M.D., Olufunmilayo I. Olopade, M.D., Angela DeMichele, M.D., Christina Yau, Ph.D., Laura J. van ’t Veer, Ph.D., Meredith B. Buxton, Ph.D., Michael Hogarth, M.D., Nola M. Hylton, Ph.D., Melissa Paoloni, D.V.M., Jane Perlmutter, Ph.D., W. Fraser Symmans, M.D., Douglas Yee, M.D., A. Jo Chien, M.D., Anne M. Wallace, M.D., Henry G. Kaplan, M.D., Judy C. Boughey, M.D., Tufia C. Haddad, M.D., Kathy S. Albain, M.D., Minetta C. Liu, M.D., Claudine Isaacs, M.D., Qamar J. Khan, M.D., Julie E. Lang, M.D., Rebecca K. Viscusi, M.D., Lajos Pusztai, M.D., D.Phil., Stacy L. Moulder, M.D., Stephen Y. Chui, M.D., Kathleen A. Kemmer, M.D., Anthony D. Elias, M.D., Kirsten K. Edmiston, M.D., David M. Euhus, M.D., Barbara B. Haley, M.D., Rita Nanda, M.D., Donald W. Northfelt, M.D., Debasish Tripathy, M.D., William C. Wood, M.D., Cheryl Ewing, M.D., Richard Schwab, M.D., Julia Lyandres, B.S., Sarah E. Davis, M.S., Gillian L. Hirst, Ph.D., Ashish Sanil, Ph.D., Donald A. Berry, Ph.D., Laura J. Esserman, M.D., for the I-SPY 2 Investigators

N Engl J Med
Volume 375(1):23-34
July 7, 2016
Original Article
Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation

Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., Ph.D., Louis Fehrenbacher, M.D., Rinat Yerushalmi, M.D., Lida A. Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., Ruben G.W. Quek, Ph.D., Denka Markova, Ph.D., Iulia C. Tudor, Ph.D., Alison L. Hannah, M.D., Wolfgang Eiermann, M.D., and Joanne L. Blum, M.D., Ph.D.
• Among patients with breast cancer and germline mutations in the \textit{BRCA} DNA repair pathway genes, the poly(adenosine diphosphate–ribose) inhibitor talazoparib provided a significant benefit over standard chemotherapy with respect to progression-free survival.

## Why Genomic Testing?

<table>
<thead>
<tr>
<th>Unaffected</th>
<th>Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Tailored screening recommendations</em></td>
<td></td>
</tr>
<tr>
<td><em>Risk-reduction strategies</em></td>
<td></td>
</tr>
<tr>
<td>• Surgical</td>
<td></td>
</tr>
<tr>
<td>• Chemoprevention</td>
<td></td>
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<td></td>
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<tr>
<td><em>Surgical management</em></td>
<td></td>
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<tr>
<td><em>Risk reduction for other cancers</em></td>
<td></td>
</tr>
<tr>
<td><strong>Targeted treatment options</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Risk assessment may also identify those *not* at increased risk.
Breast Cancer: Risk Management Options

Patient
- Upcoming Treatment Decisions
- Increased Surveillance
- Secondary Prevention

Family Members
- Risk Reducing Surgery
- Increased, Surveillance
- Chemoprevention
Clinical applications of liquid biopsies in cancer care

<table>
<thead>
<tr>
<th>Event</th>
<th>Cancer screening</th>
<th>Localized cancer</th>
<th>Metastatic cancer</th>
<th>Refractory cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment strategy</td>
<td>Early intervention</td>
<td>Risk of dissemination and detection of recurrence</td>
<td>Treatment selection and monitoring response</td>
<td>Mechanism of resistance and new treatment</td>
</tr>
</tbody>
</table>

- Multiple DNA abnormalities
- RNA expression and fusion transcripts
- Protein expression and phosphorylation
- Circulating tumor DNA [number of mutant molecules]
- Chromosomal abnormalities
- Amplification and deletion
- Translocation
- Point mutations
- In vitro/in vivo culture

World leaders committed to achieving 17 Sustainable Development Goals (SDG) by 2030.

For the first time in history, the SDG on health (3) calls for reducing by one third premature mortality from non-communicable diseases (NCDs) that calls for:

- Universal Health Coverage;
- Lifesaving vaccines and essential medicines (e.g Hydroxyurea, Pneumovax, HPV, HBV)
- Tobacco Control

“The 2030 Agenda compels us to look beyond national boundaries and short-term interests and act in solidarity for the long-term.”

Ban Ki-Moon, U.N. Secretary-General
The End of Mobile Mammography ---
The Dawn of a New Era