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

UICC 2018 Kuala Lumpur
AACR Delegation (United States)

CLINICAL CANCER GENETICS COMMUNITY OF PRACTICE

City of Hope

World Cancer Congress
Kuala Lumpur, Malaysia
1—4 Oct 2018

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UICC WORLD CANCER CONGRESS

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

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)

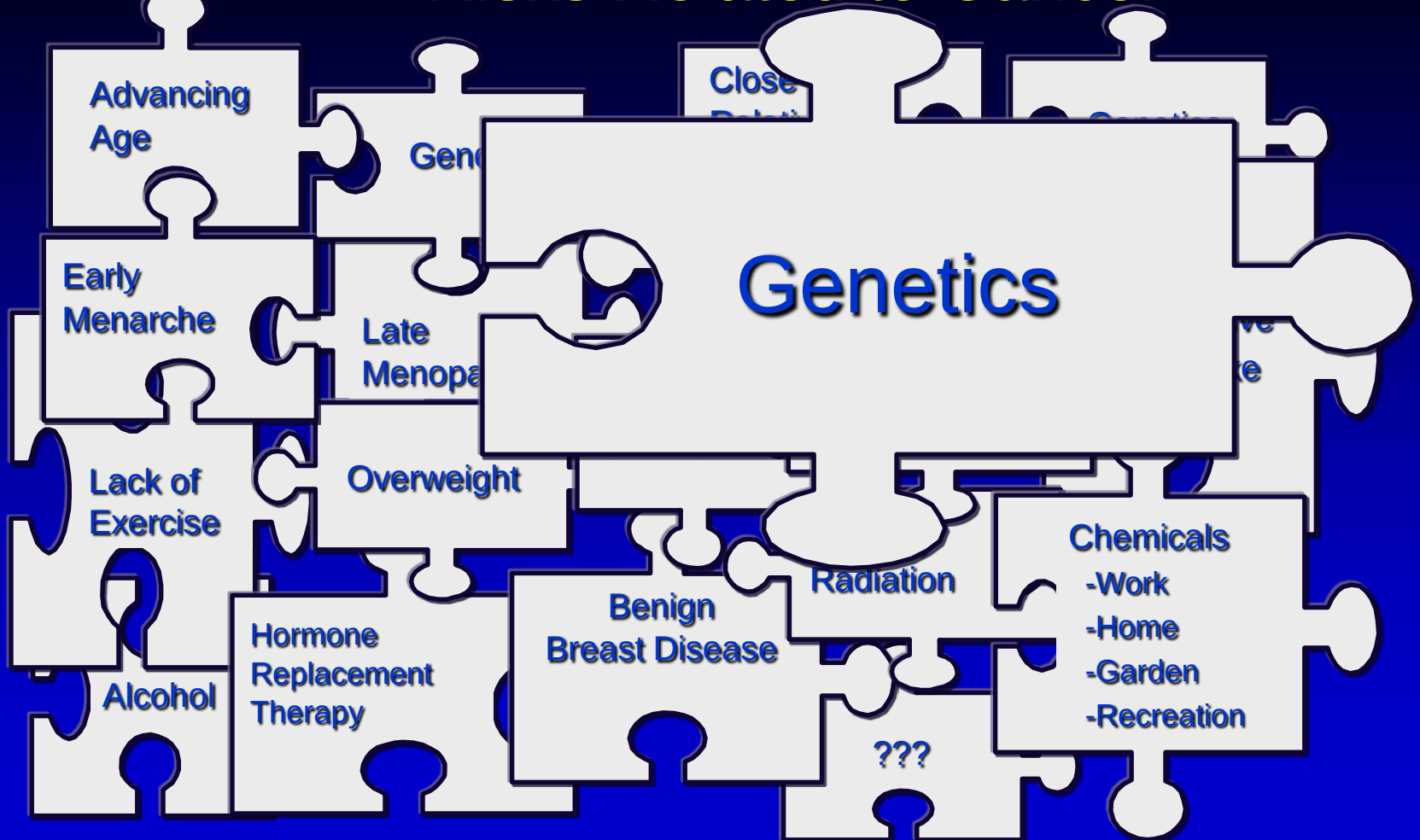
Research in the service of clinical cancer genetics in Brazil
Patricia Ashton-Prolla, Universidade Federal do Rio Grande do Sul- CNOA (Brazil)

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

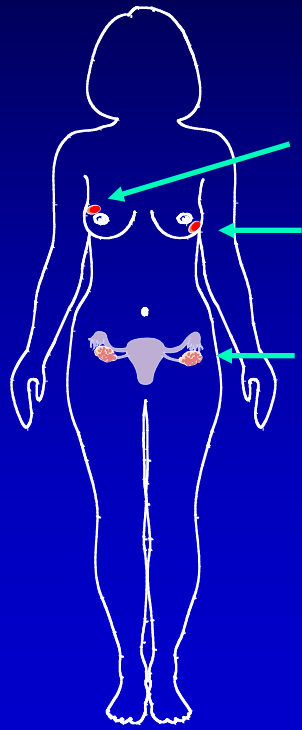
Genomics and Cancer Control in Low Resource Settings: Lessons from the US and Nigeria
Olufunmilayo Olopade, University of Chicago (United States)

Q&A and DISCUSSION

Risks Related to Cancer



BRCA1- and *BRCA2-*Associated Cancers



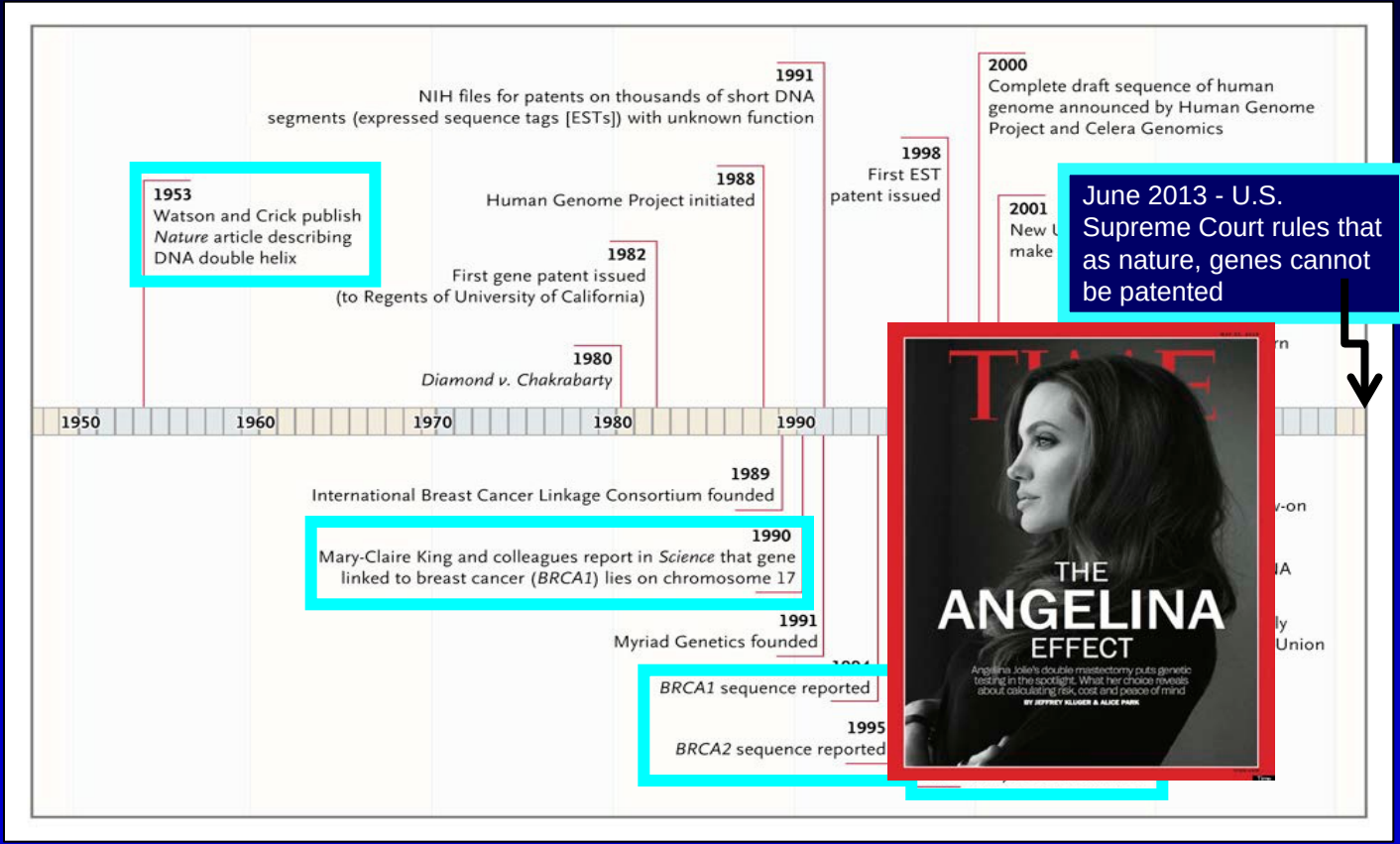
Breast cancer 50%-85% (often early age at onset

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

Important Events in Discovery and Use of Genes Conferring Susceptibility to Breast and Ovarian Cancer



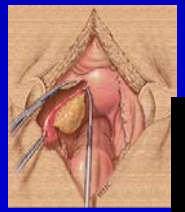
Kesselheim AS, Mello MM. N Engl J Med 2010; 362(20):1855-1858.

Clinical Management of *BRCA* Mutation-Positive Patient

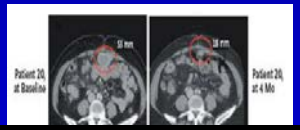
Positive *BRCA1* or *BRCA2* test result

Possible testing for other adult relatives

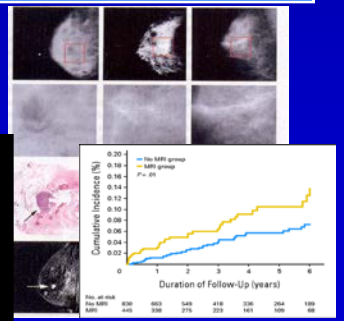
Prophylactic surgery



Targeted therapy

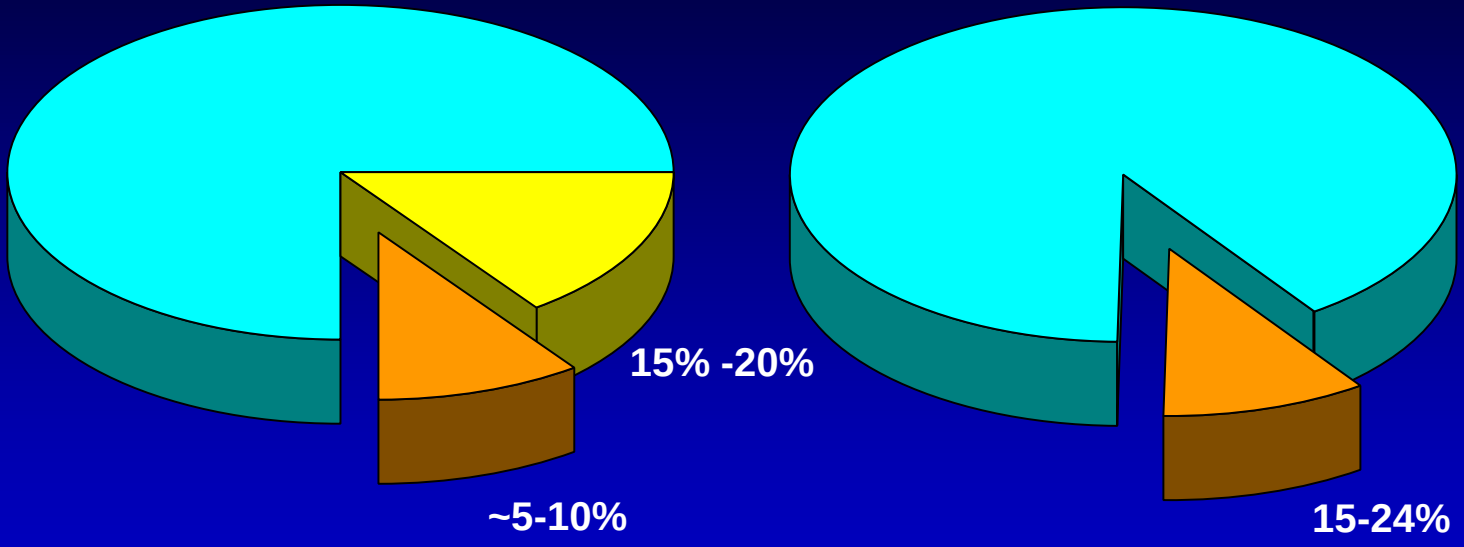


Increased surveillance

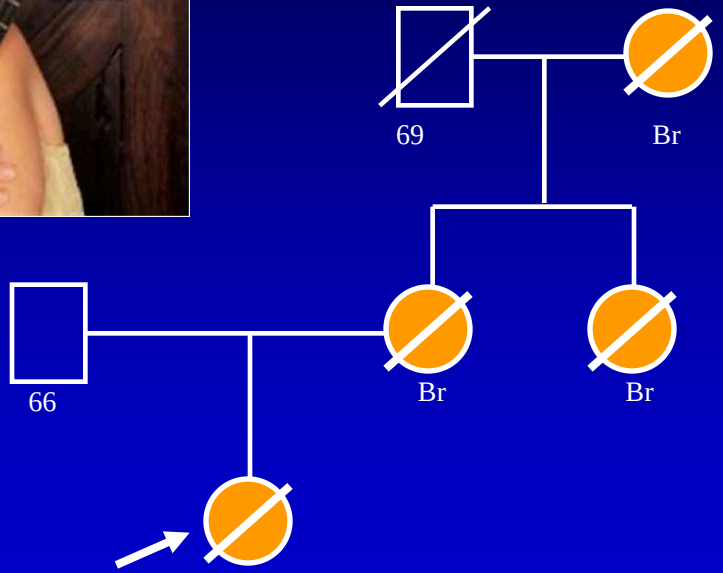


Chemo-prevention

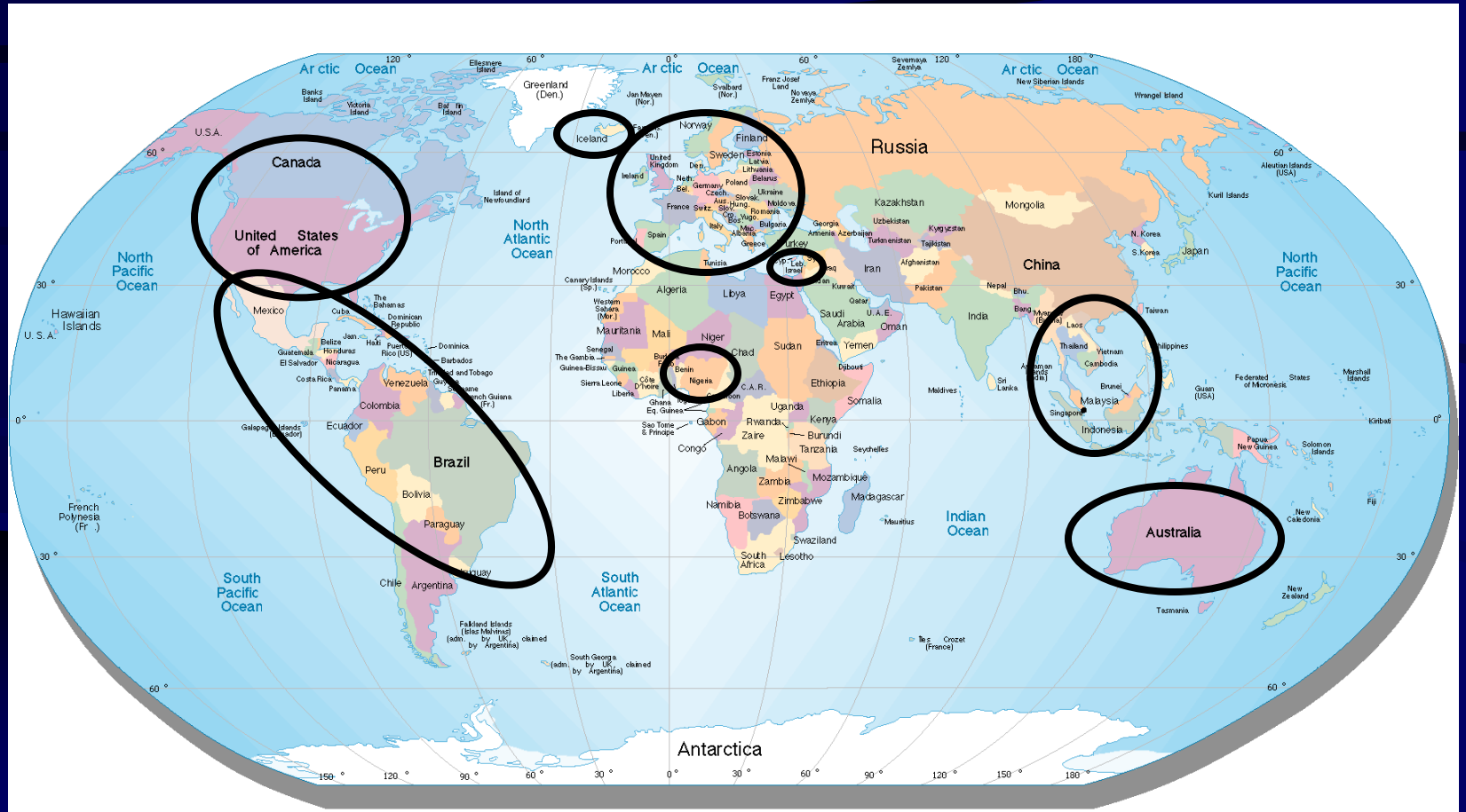
How Much Breast and Ovarian Cancer Is Hereditary?
Is it different in different populations?



Colombia



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

Chavez, T., Nehoray, B., Obregon-Tito, A., Ricker, C., Solomon, I., Niell-Swiller, M., Rybak, C., Abugattas, J., Sullcahuaman, Y., Noriega, M., Orduz, A., Melo, J., Chaves, A., Gallardo, L., Villarreal, C., Shaw, R., Álvarez, R., Morales, E., Cock-Rada, A., del Toro, A., Mora, P., Cruz, M., Fernández, M., Blazer, R., & Weitzel, J.

Barriers and challenges for global implementation of GCRA

- Cost of tests (not covered by most public health plans)
- Cost of GCRA delivery

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

- Competition for limited health care resources
- Greater pharma interest in treatment vs. prevention

With all of these costs and challenges, is GCRA a dispensible luxury in the context of health care in LMIC's?

Prevalence of *BRCA* Mutations and Founder Effect in High-Risk Hispanic Families

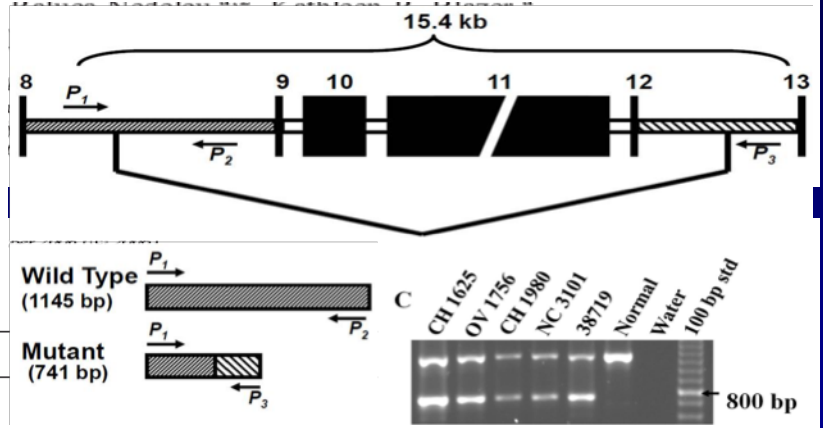
Jeffrey N. Weitzel,[1] Veronica Lagos,[1] Kathleen R. Blazer,[1] Rebecca Nelson,[2] Charité Ricker,[1] Josef Herzog,[1] Colleen McGuire,[3] and Susan Neuhausen[4]

Evidence for Common Ancestral Origin of a Recurring *BRCA1* Genomic Rearrangement Identified in High-Risk Hispanic Families

Jeffrey N. Weitzel,[1] Veronica I. Lagos,[1] Josef S. Herzog,[1] Thaddeus Judkins,[2] Brant Hendrickson,[2] Jason S. Ho,[1] Charité N. Ricker,[1] Katrina J. Lowstuter,[1] Kathleen R. Blazer,[1] Gail Tomlinson,[3] and Tom Scholl[2]

Breast Cancer Res Treat
DOI 10.1007/s10549-011-1570-7

EPIDEMIOLOGY



Psycho-Oncology
Psycho-Oncology (2008)
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**. 10.1002/pon.1358

Pathological characteristics of *BRCA*-associated breast cancers in Hispanics

Veronica I. Lagos-Jaramillo · Michael F. Press · Charité N. Ricker · Louis Dubeau · Phuong L. Mai · Jeffrey N. Weitzel

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

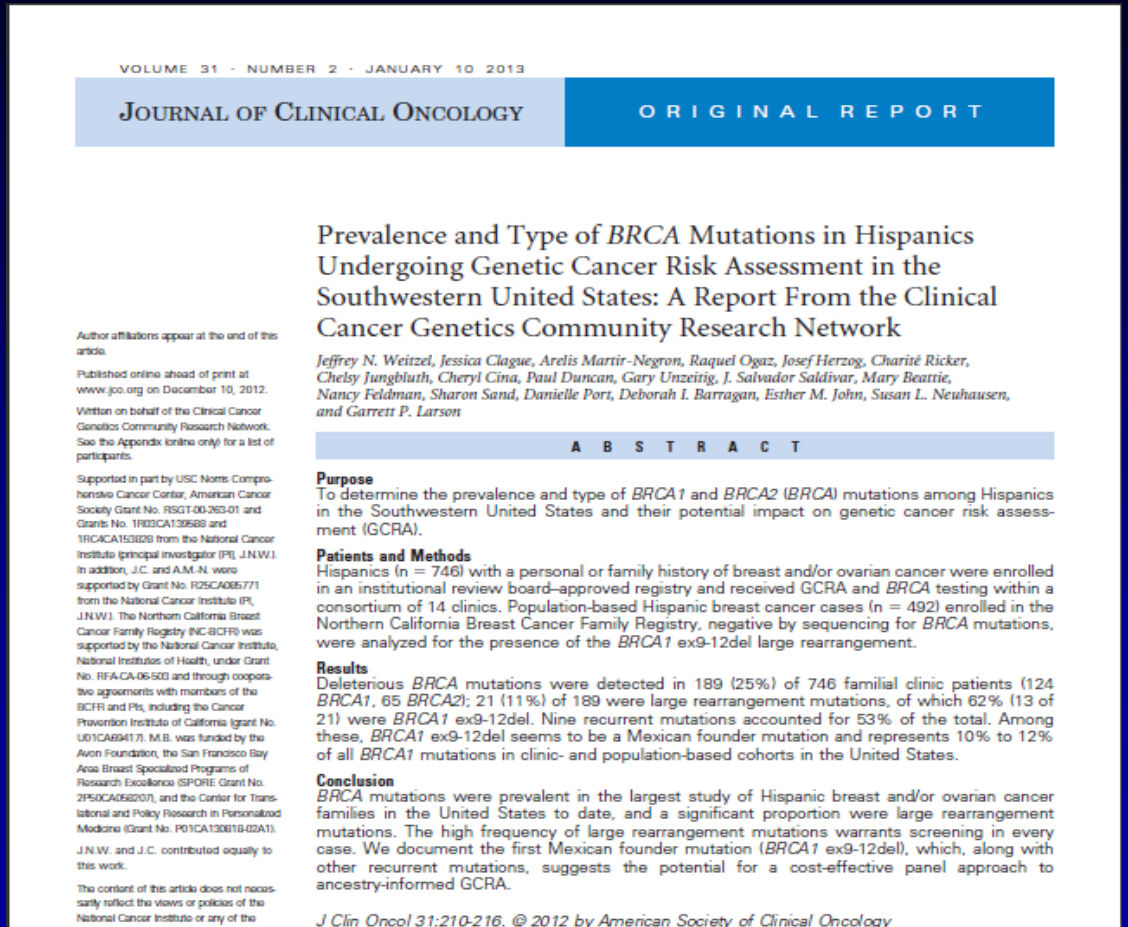
Veronica I. Lagos[1], Martin A. Perez[2], Charité N. Ricker[1,1]Kathleen R. Blazer[1], Nydia M. Santiago[1], Nancy

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

From Genetic Epidemiology to Clinical Translation



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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 N. Weitzel, Jessica Clague, Arelis Martir-Negron, Raquel Ogaz, Josef Herzog, Charité Ricker, Chelsy Jungbluth, Cheryl Cina, Paul Duncan, Gary Unzeitig, J. Salvador Saldivar, Mary Beattie, Nancy Feldman, Sharon Sand, Danielle Port, Deborah I. Barragan, Esther M. John, Susan L. Neuhausen, and Garrett P. Larson

Author affiliations appear at the end of this article.

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Written on behalf of the Clinical Cancer Genetics Community Research Network. See the Appendix (online only) for a list of participants.

Supported in part by USC Norris Comprehensive Cancer Center, American Cancer Society Grant No. RSGT-00-263-01 and Grants No. 1R03CA139588 and 1RC4CA153828 from the National Cancer Institute (principal investigator [PI], J.N.W.). In addition, J.C. and A.M.-N. were supported by Grant No. R25CA085771 from the National Cancer Institute (PI, J.N.W.). The Northern California Breast Cancer Family Registry (NC-BCFR) was supported by the National Cancer Institute, National Institutes of Health, under Grant No. RFA-CA-06-503 and through cooperative agreements with members of the BCFR and PIs, including the Cancer Prevention Institute of California (grant No. U01CA94117). M.B. was funded by the Avon Foundation, the San Francisco Bay Area Breast Specialized Programs of Research Excellence (SPORE Grant No. 2P50CA058207), and the Center for Translational and Policy Research in Personalized Medicine (Grant No. P01CA130818-02A1).

J.N.W. and J.C. contributed equally to this work.

The content of this article does not necessarily reflect the views or policies of the National Cancer Institute or any of the

A B S T R A C T

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).

Patients and Methods
Hispanics (n = 746) 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 = 492) enrolled in the Northern California Breast Cancer Family Registry, negative by sequencing for *BRCA* mutations, were analyzed for the presence of the *BRCA1* ex9-12del large rearrangement.

Results
Deleterious *BRCA* mutations were detected in 189 (25%) of 746 familial clinic patients (124 *BRCA1*, 65 *BRCA2*); 21 (11%) of 189 were large rearrangement mutations, of which 62% (13 of 21) were *BRCA1* ex9-12del. Nine recurrent mutations accounted for 53% of the total. Among these, *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.

J Clin Oncol 31:210-216. © 2012 by American Society of Clinical Oncology

- 14 CCGCRN clinics
- 746 registry participants
- 189 *BRCA+*
- 21 large deletions
- Observations of recurrent mutations generated hypotheses and novel genetic tool (HISPANEL) development $20/case; >70% sensitivity
- A potential tool to address disparities

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

Breast Cancer n=96		Ovarian Cancer n=92	
Age			
Range	26-63	Range	23-83
Mean	40	Mean	54
Stage			
I	1%	I	0%
II	27%	II	0%
III	67%	III	53%
IV	2%	IV	42%
Unknown	3%	Unknown	5%

BRCA mutations prevalent

and a possible partial explanation for excess of TNBC in Mexico

ER/PR/Her2 TNBC vs. non (any+)	No. (%) *BRCA* positive			Total No. of cases*
	BRCA1	*BRCA2*	Total	
TNBC cases	9	0	9 (27%)	33
Non-TNBC	2	3	5 (8%)	62
All cases	11	3	14 (15%)	95

ER: estrogen receptor, PR: progesterone receptor, TNBC: triple negative breast cancer. *Excluded one case with unknown tumor receptor status.

Mutation		Ovarian cancer (n=92)	Breast cancer (n=96)	Total (n=188)
BRCA1 (85%)	ex9-12del	9 (35%)	4 (29%)	13 (33%)
	IVS5+1G>A	2	0	2
	3977del4*	0	1	1
	R1699W*	1	0	1
	803delA*	1	0	1
	70insAG*	1	0	1
	A1708E	1	1	2
	4184del4	1	0	1
	R71G	1	0	1
	917delTT	0	1	1
	943ins10	1	0	1
	2925del4	0	1	1
	3878delTA	0	1	1
	185delAG	0	1	1
	R1443X	0	1	1
BRCA1 Large Rearrangements (*BRCA1*)**	ex8-9dup	2	0	2
	ex18-19del	2	0	2
	ex8-10del	1	0	1
BRCA2 (15%)	9463delG	1	0	1
	6244delG*	1	0	1
	2900delCT*	1	0	1
	6714del4*	0	1	1
	1803insA*	0	1	1
	6252insG	0	1	1
Total		26 (28%)	14 (15%)	40 (21%)

* Mutations detected by pyrosequencing; **detected by MLPA

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

Villarreal et al. Cancer 2014

Intensive Course in Cancer Risk Assessment
CCG WORKING GROUP
ESSENTIALS TOOLKIT 2012
Lewin
genes VII
MOLECULAR CELL BIOLOGY
METODOLOGÍA DE LA INVESTIGACIÓN
Intensive Course in Cancer Risk Assessment

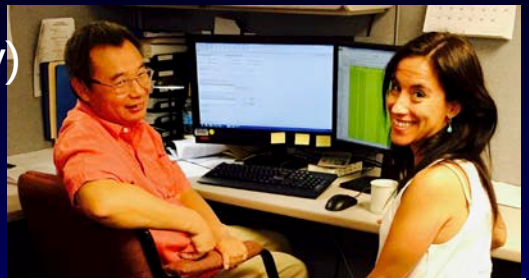
EDUCATION REPORT

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[1], 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

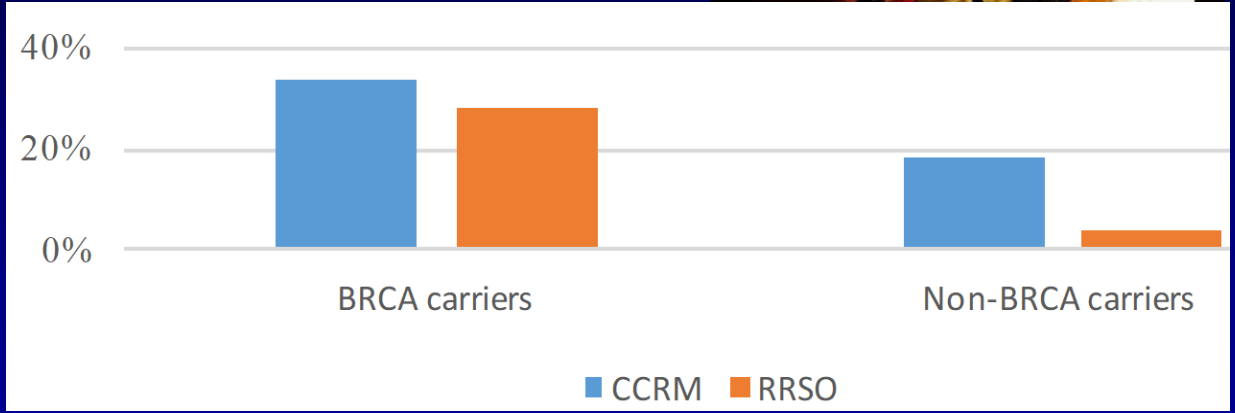
The effect of Genetic Cancer Risk Assessment on the uptake of risk-reducing surgeries in Hispanic women with breast cancer



- 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.

Patricia Ashton Prolla, MD, PhD
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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.

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Kuala Lumpur, Malaysia
1—4 Oct 2018

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global cancer control
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•Track 2: Advances in screening and early detection

Disclosure of interest: None declared

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:

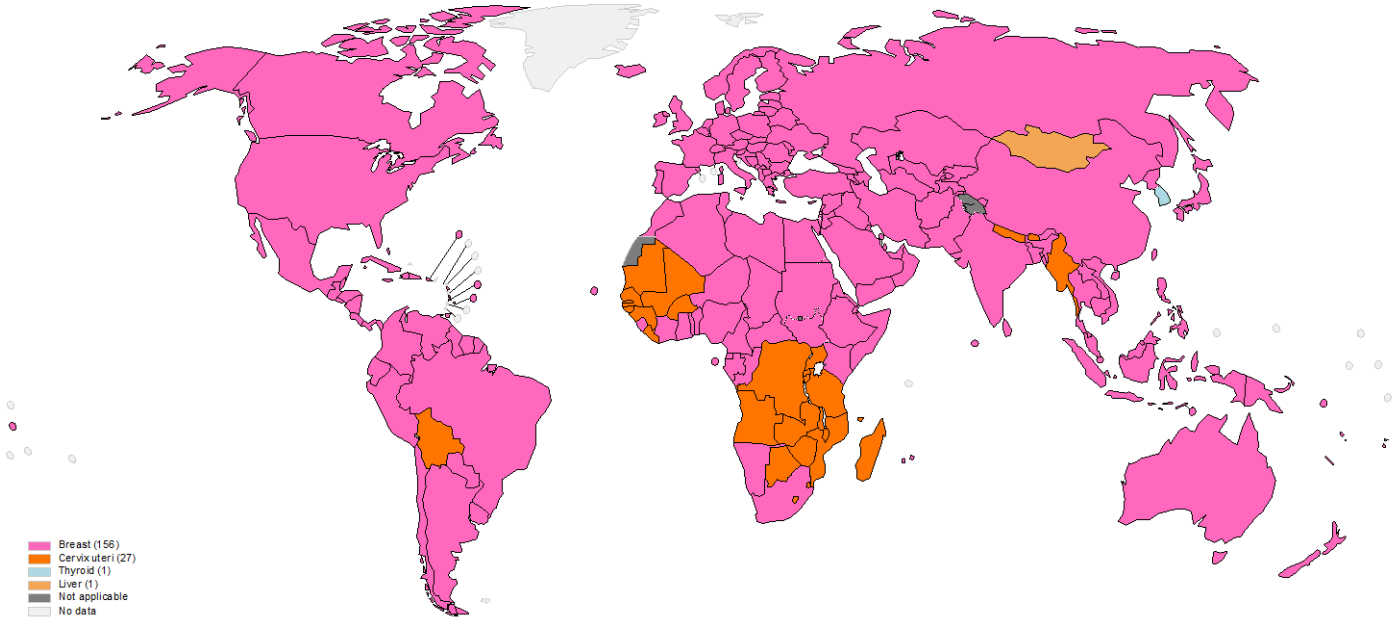
Cancer risk assessment in a primary care setting;

Hereditary Breast and Ovarian Cancer in Brazil;

Li-Fraumeni syndrome and the Brazilian founder mutation.

Breast Cancer
in Latin America and Brazil

Top cancer per country, estimated age-standardized incidence rates (World) in 2018, females, all ages



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Data source: GLOBOCAN 2018
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

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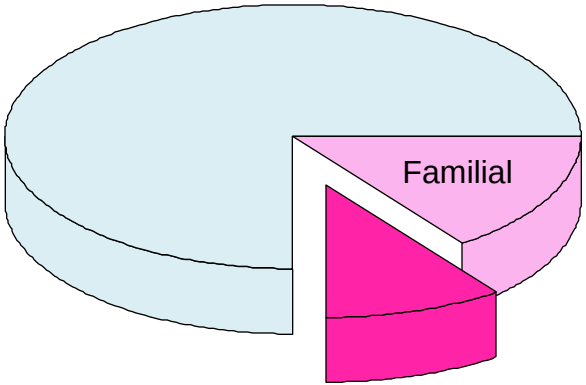
10% of all breast cancer is hereditary. Why focus on hereditary cancer ?



Hereditary
5-10%

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

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

Susan G. Komen
Population Specific Grant 2004

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

BMC Cancer

BioMed Central

NÚCLEO MAMA PORTO ALEGRE

Research article

Open Access

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 Giacomazzi[2,3,4,6], Aishameriane V Schmidt[8], Fernanda L Roth[3,6], Edenir I Palmero[1,2,3], Luciane Kalakun[3,9], Ernestina S Aguiar[2,3,4,6], Susana M Moreira[3,7], Erica Batassini[3,9], Vanessa Belo-Reyes[3,6], Lavinia Schuler-Faccini[1,4,5,7], Roberto Giugliani[1,4,5,6,7], Maira Caleffi[3] and Suzi Alves Camey[9,10]

Annals of Internal Medicine | CLINICAL GUIDELINE

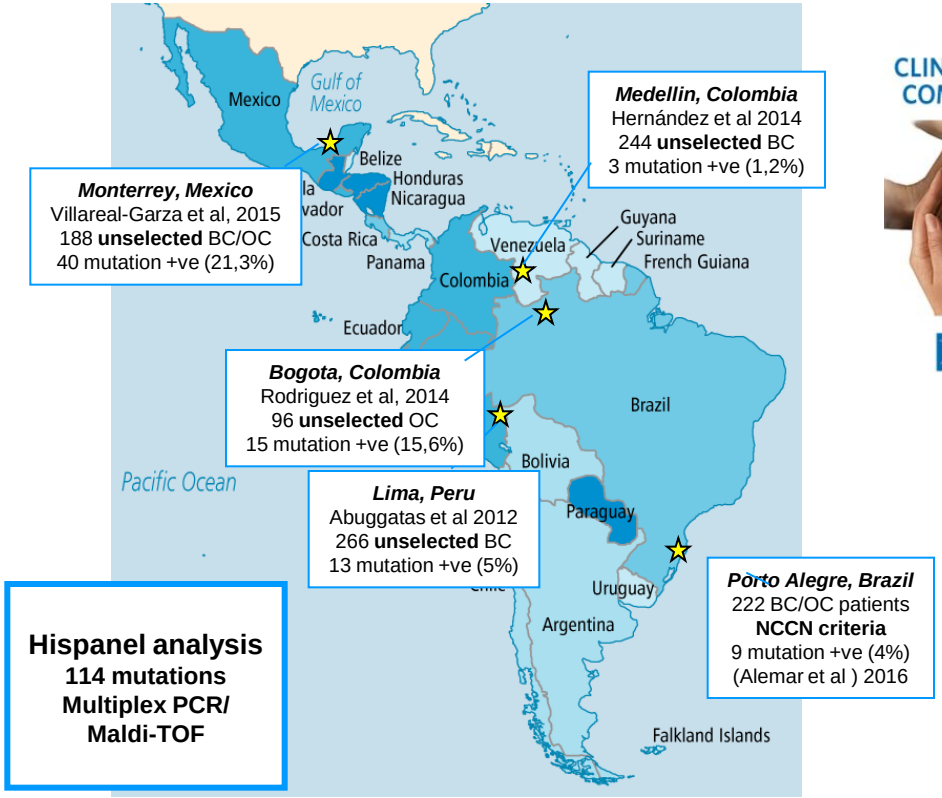
Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement

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



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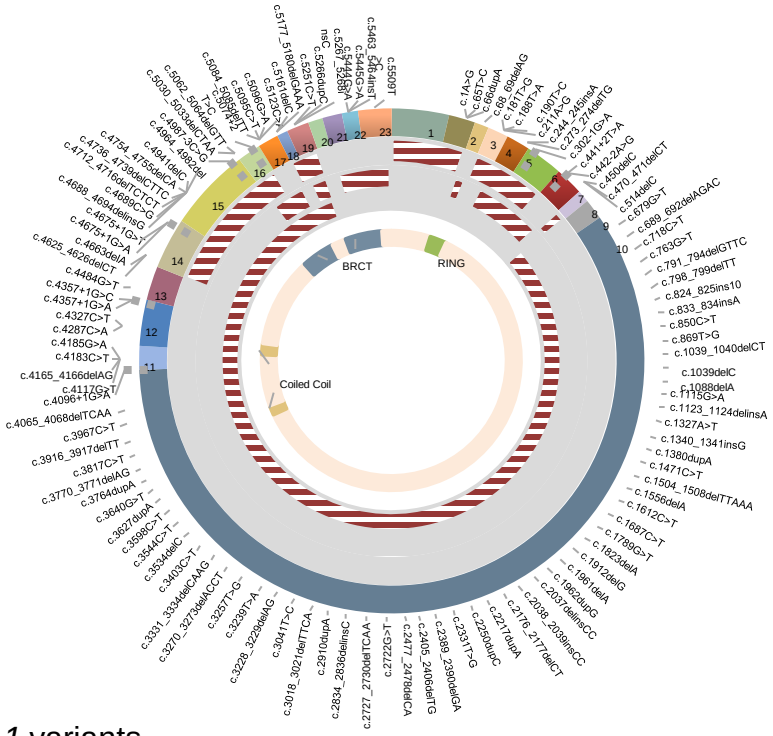
City of Hope

SCIENTIFIC REPORTS

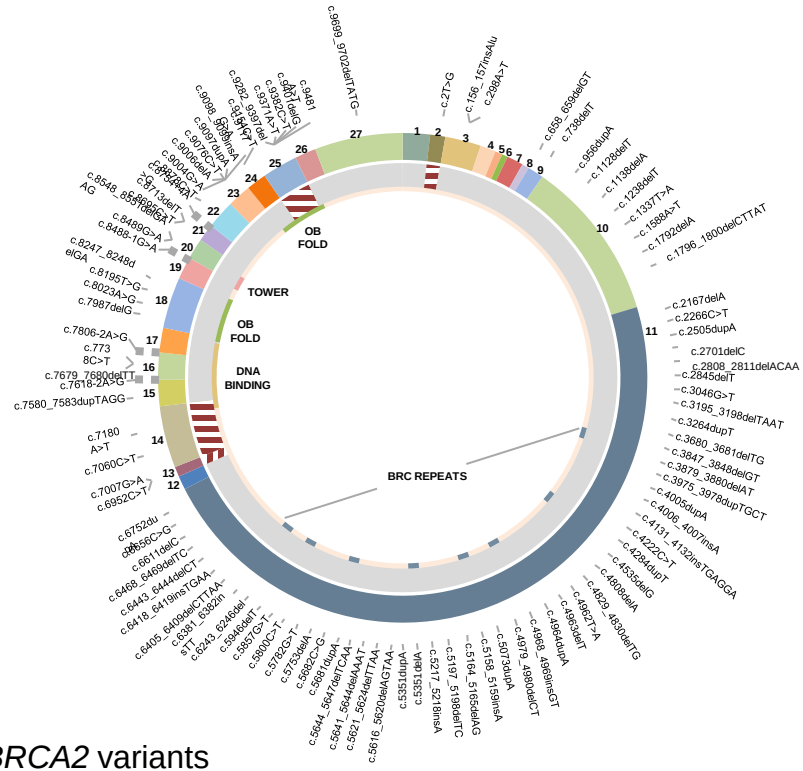
Palmero, Carraro, Alemar et al. 2018.

OPEN

The germline mutational landscape of *BRCA1* and *BRCA2* in Brazil



BRCA1 variants

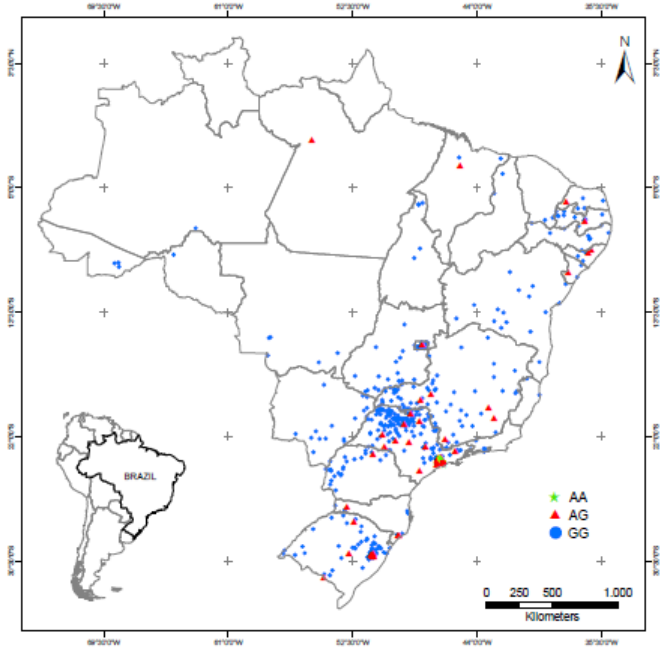


BRCA2 variants

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



OPEN ACCESS Freely available online

2014 PLOS ONE

Prevalence of the *TP53* p.R337H Mutation in Breast Cancer Patients in Brazil

Juliana Giacomazzi[1,2*], Marcia S. Graudenz[2,3], Cynthia A. B. T. Osorio[4], Patricia Koehler-Santos[5], Edenir I. Palmero[6], Marcelo Zagonel-Oliveira[7], Rodrigo A. D. Michelli[6], Cristovam Scapulatempo Neto[6], Gabriela C. Fernandes[6], Maria Isabel W. S. Achatz[8], Ghyslaine Martel-Planche[9], Fernando A. Soares[4], Maira Caleffi[10], José Roberto Goldim[11], Pierre Hainaut[9,12], Suzi A. Camey[13], Patricia Ashton-Prolla[1,2,7,14]

Retrospective analysis of 815 unselected BC patient recruited from 3 centers

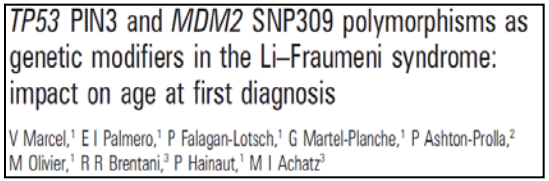
c.1010G>A prevalence = 8.6%

Comprehensive data on the Brazilian *TP53* founder mutation R337H

Available online at www.sciencedirect.com
SCIENCE DIRECT
Cancer Letters 245 (2007) 96–102
CANCER Letters
www.elsevier.com/locate/canlet

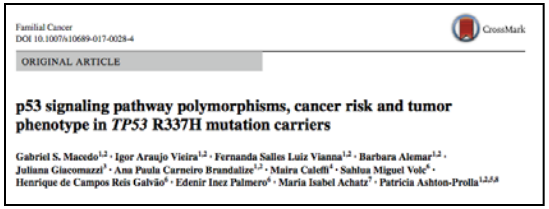
The *TP53* mutation, R337H, is associated with Li-Fraumeni and Li-Fraumeni-like syndromes in Brazilian families

Maria Isabel Waddington Achatz [a,b], Magali Olivier [c], Florence Le Calvez [c], Ghyslaine Martel-Planche [c], Ademar Lopes [d], Benedito Mauro Rossi [d], Patricia Ashton-Prolla [e,f], Roberto Giugliani [e,f], Edenir Inez Palmero [f], Fernando Regla Vargas [g], José Claudio Casali Da Rocha [h], Andre Luiz Vettore [a], Pierre Hainaut [c,*]



TP53 PIN3 and *MDM2* SNP309 polymorphisms as genetic modifiers in the Li–Fraumeni syndrome: impact on age at first diagnosis

V Marcel,[1] E I Palmero,[1] P Falagan-Lotsch,[1] G Martel-Planche,[1] P Ashton-Prolla,[2] M Olivier,[1] R R Brentani,[3] P Hainaut,[1] M I Achatz[3]

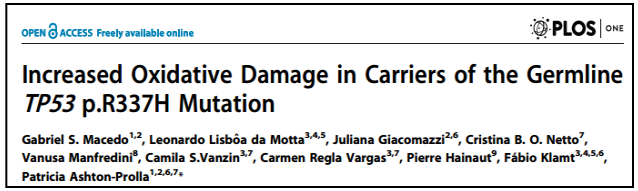


Familial Cancer
DOI 10.1007/s10689-017-0028-4

ORIGINAL ARTICLE

p53 signaling pathway polymorphisms, cancer risk and tumor phenotype in *TP53* R337H mutation carriers

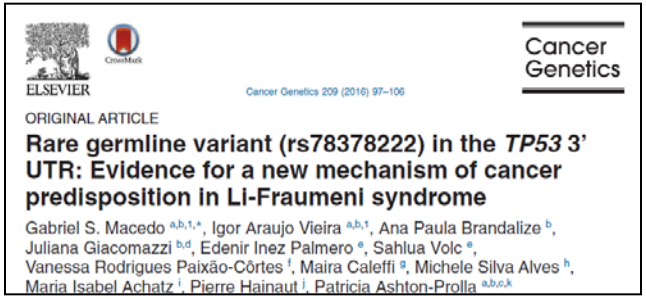
Gabriel S. Macedo[1,2] · Igor Araujo Vieira[1,2] · Fernanda Salles Luiz Vianna[1,2] · Barbara Alemar[1,2] · Juliana Giacomazzi[3] · Ana Paula Carneiro Brandalize[1,2] · Maira Caleffi[4] · Sahlua Miguel Volc[4] · Henrique de Campos Reis Galvão[5] · Edenir Inez Palmero[6] · Maria Isabel Achatz[7] · Patricia Ashton-Prolla[1,2,8,9]



OPEN ACCESS Freely available online
PLOS ONE

Increased Oxidative Damage in Carriers of the Germline *TP53* p.R337H Mutation

Gabriel S. Macedo[1,2], Leonardo Lisbôa da Motta[3,4,5], Juliana Giacomazzi[2,6], Cristina B. O. Netto[7], Vanusa Manfredini[8], Camila S.Vanzin[3,7], Carmen Regla Vargas[3,7], Pierre Hainaut[9], Fábio Klamt[3,4,5,6], Patricia Ashton-Prolla[1,2,6,7]*



ELSEVIER
Cancer Genetics 209 (2016) 97–106
Cancer Genetics

ORIGINAL ARTICLE

Rare germline variant (rs78378222) in the *TP53* 3' UTR: Evidence for a new mechanism of cancer predisposition in Li-Fraumeni syndrome

Gabriel S. Macedo [a,b,1,*], Igor Araujo Vieira [a,b,1], Ana Paula Brandalize [b], Juliana Giacomazzi [b,d], Edenir Inez Palmero [e], Sahlua Volc [e], Vanessa Rodrigues Paixão-Côrtes [f], Maira Caleffi [g], Michele Silva Alves [h], Maria Isabel Achatz [i], Pierre Hainaut [j], Patricia Ashton-Prolla [a,b,c,k]

Cancer. 2013 Oct 7. doi: 10.1002/cncr.28346. [Epub ahead of print]

Li-Fraumeni and Li-Fraumeni-like syndrome among children diagnosed with pediatric cancer in Southern Brazil.

Giacomazzi J, Selistre SG, Rossi C, Alemar B, Santos-Silva P, Pereira FS, Netto CB, Cossio SL, Roth DE, Brunetto AL, Zagonel-Oliveira M, Martel-Planche G, Goldim JR, Hainaut P, Camey SA, Ashton-Prolla P.

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.

BREAST CANCER AWARENESS MONTH

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)

World Cancer Congress
Kuala Lumpur, Malaysia
1—4 Oct 2018

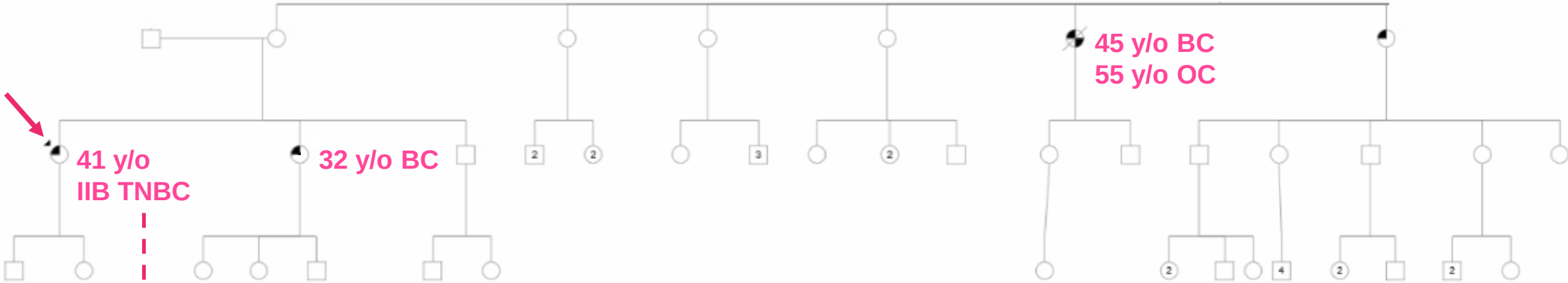
Strengthen
Inspire
Deliver

uicc
global cancer control
WORLD CANCER CONGRESS

Track 2: Advances in screening and early detection

Disclosure of interest: None declared

Clinical case: 2013



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.
2. Chavarri-Guerra Y, Villarreal-Garza C, et al. Lancet Oncol. Aug 2012;13(8):e335-343.
3. Unger-Saldaña K, Infante-Castañeda C. Salud Publica Mex 2009; 51:S270-S285

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

1. Arce-Salinas C, et al. Rev Invest Clin 2012; 64(1): 9-16.
2. Chavarri-Guerra et al. BMC Cancer2014, 14:658.

Barriers for implementation of GCRA in Mexico

- In Mexico, GCRA services are not routinely provided and BRCA testing is not broadly available [1]

Elevated costs and lack of coverage for genetic testing within the public health system	**Limited awareness** among providers and patients concerning target population for testing and GCRA benefits	Restricted number of clinicians with GCRA **expertise**

1. Villarreal-Garza, C. 2015. Cancer Epidemiology Biomarkers Prevention, 24, IA23-IA23.

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

No GCRA

Breast radiology

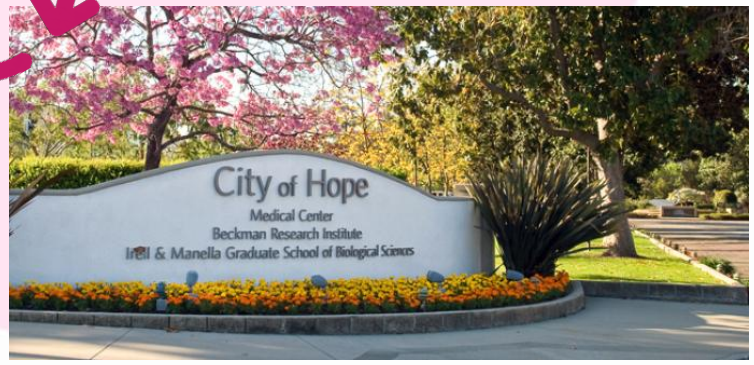
Breast pathology

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

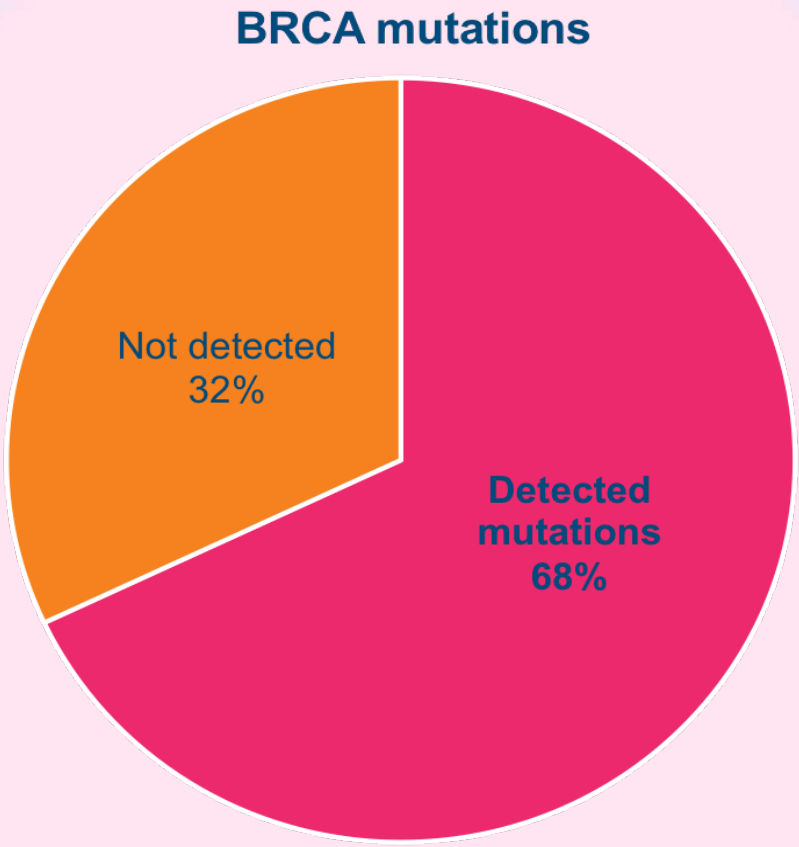
- ✓ Members of the Clinical Cancer Genetics Community Research Network (CCGCRN)
- ✓ Provision of a proper relational database and pedigree drawing program via web-based centralized Progeny program
- ✓ 248 patients in the registry in our Monterrey site!!!

1. Villarreal-Garza C, Alvarez-Gómez RM, et al. Cancer. 2015; 121(3):372-8.
2. Villarreal-Garza C, Weitzel JN, et al. Breast Cancer Res Treat. 2015; (2):389-94.

Key elements for GCRA implementation

Readily available assays

- **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



Villarreal-Garza C, Alvarez-Gómez RM, et al. Cancer. 2015; 121(3):372-8.

Key elements for GCRA implementation

GCRA training

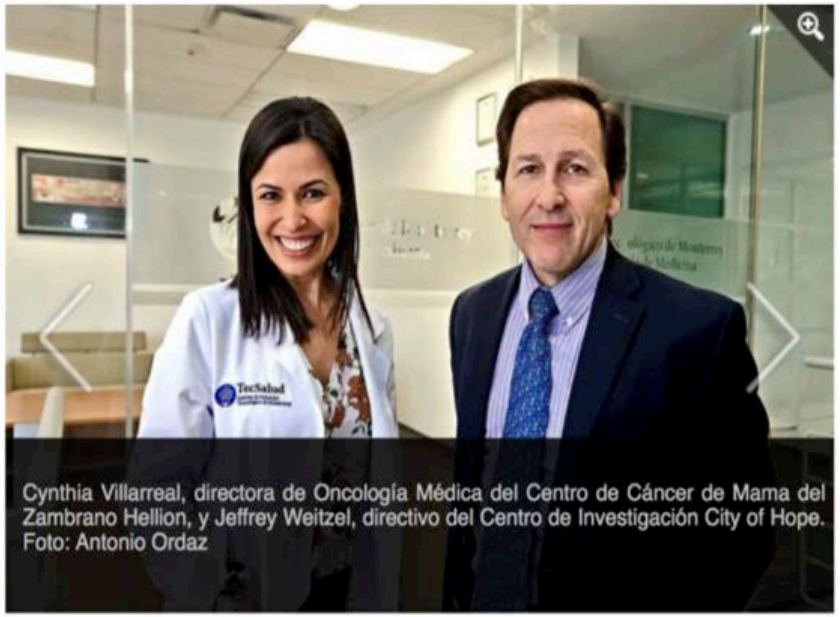
- **Intensive Course and Clinical Cancer Genetics Community of Practice**, facilitated by our collaboration with the CCGCRN team
  - Crucial to guarantee the follow-up and execution of the required patient interventions

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

Gen de cáncer tiene rastro mexicano



Cynthia Villarreal, directora de Oncología Médica del Centro de Cáncer de Mama del Zambrano Hellion, y Jeffrey Weitzel, directivo del Centro de Investigación City of Hope. Foto: Antonio Ordaz

Marión Altamirano

Monterrey, México (11 enero 2018).- Especialistas mexicanos y estadounidenses buscan crear conciencia sobre medidas preventivas, como cirugías, ante el hallazgo de que la población mexicana porta una mutación genética que la predispone al desarrollo de cáncer de mama y ovarios.

Cynthia Villarreal, directora de Oncología Médica del Centro de Cáncer de Mama del Hospital Zambrano Hellion en conjunto con

Implementation of GCRA in TecSalud - 2015

Identification of high-risk patients by oncology clinicians

Refer to GCRA with our geneticist, Dr. Dione Aguilar

Registration to CCGCRN protocol

Delivery of Final Test Results

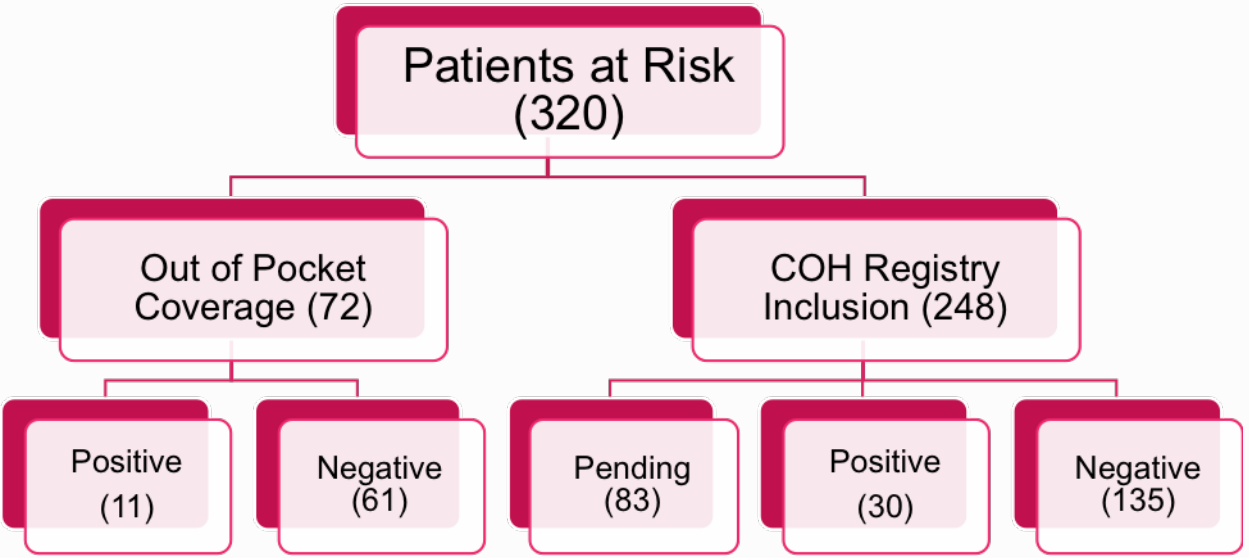
Post-test psychological assessment

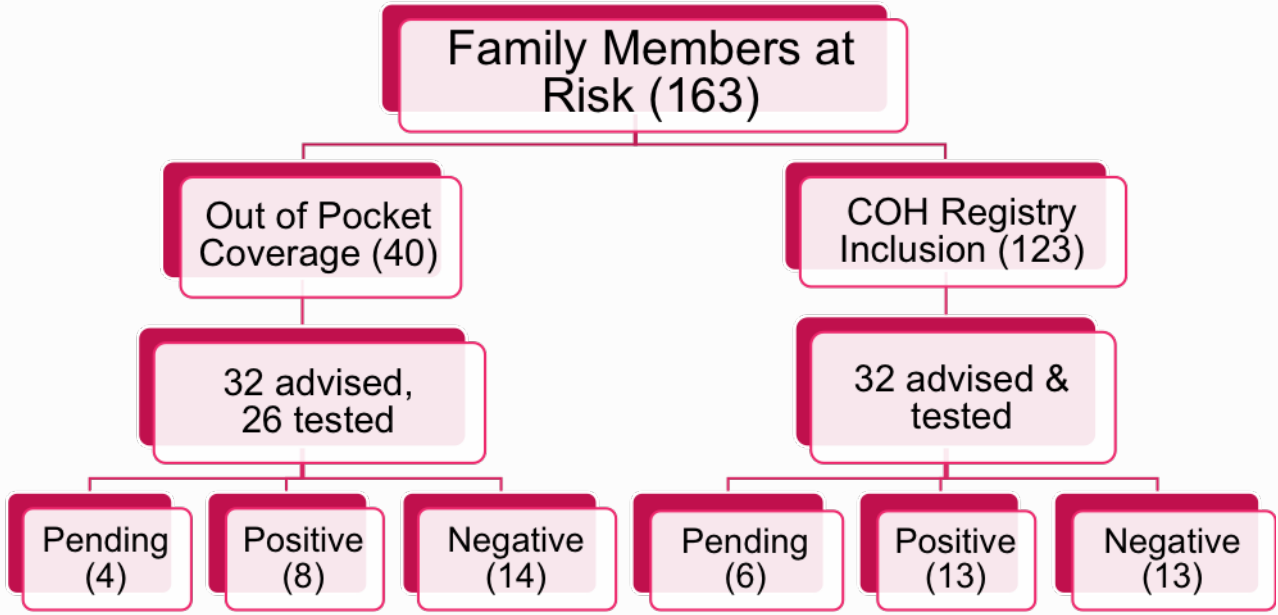
Risk reduction strategies: surveillance and/or surgeries

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

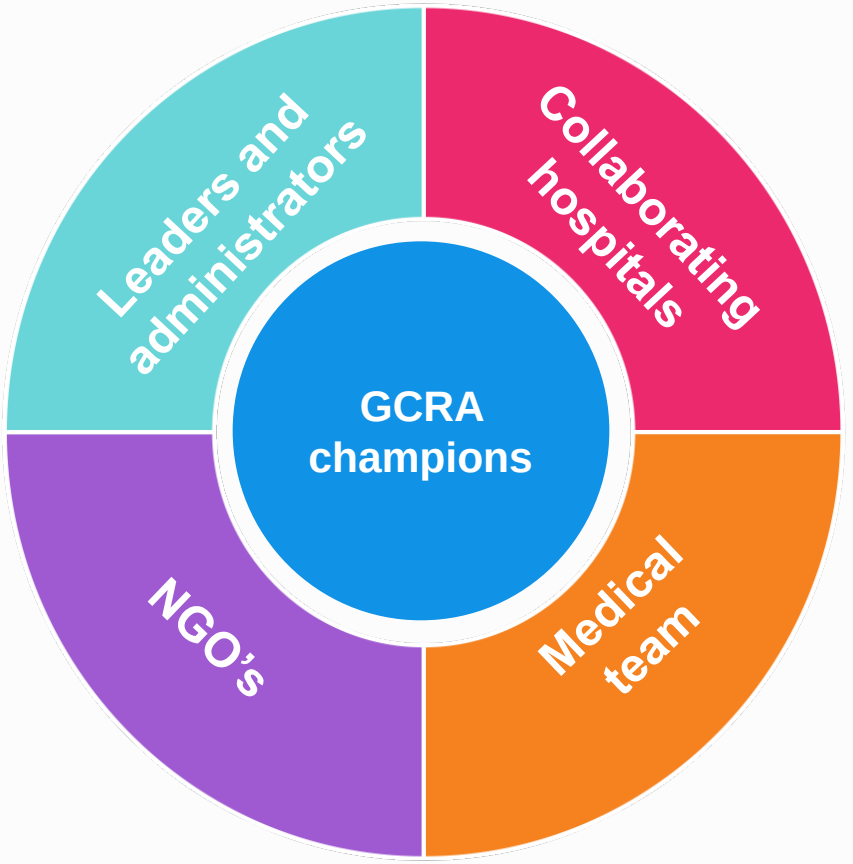
- Renovation needed every 6 months
- Time delays for results delivery

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)**
  - Familiy mutation carriers
  - Low or no-cost procedures
  - 8 referrals
- **Abbreviated MRI protocol**



Future

Implementation of follow-up clinic

Prospective registry in Mexican sites:

- Mutation burden, clinicopathological features and outcomes
- Uptake of preventive measures

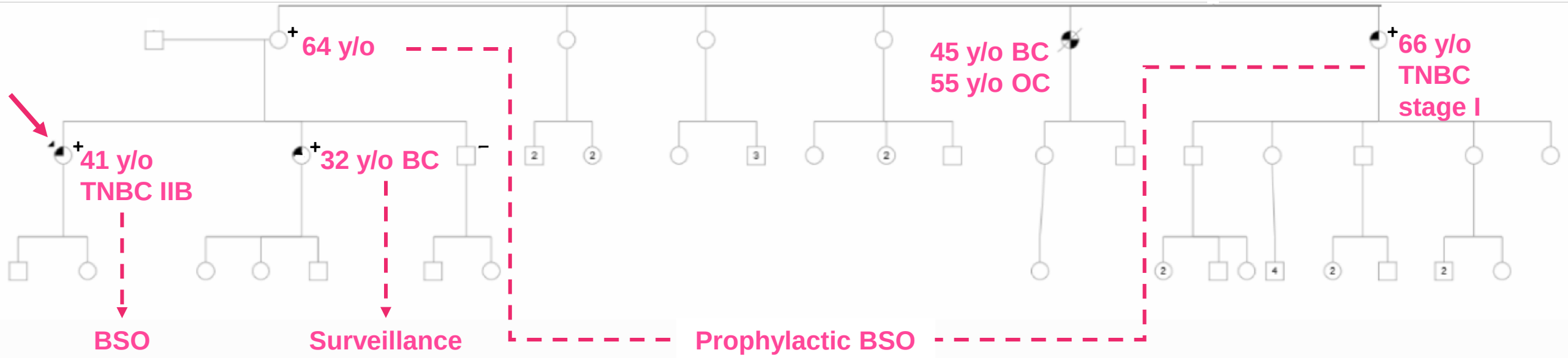
Extension of research studies

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



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

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UChicago Medicine

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

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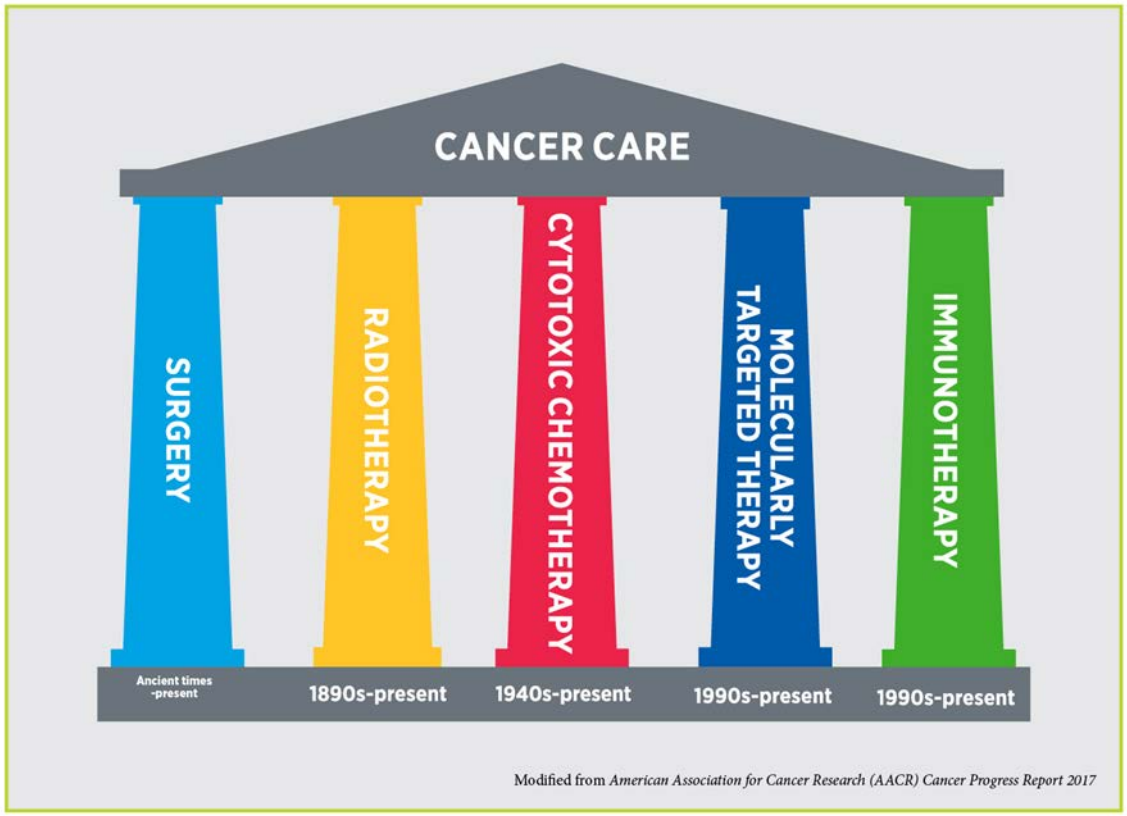
World Cancer Leaders' Summit

Cancer Treatment for All

1 October 2018
Kuala Lumpur, Malaysia

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

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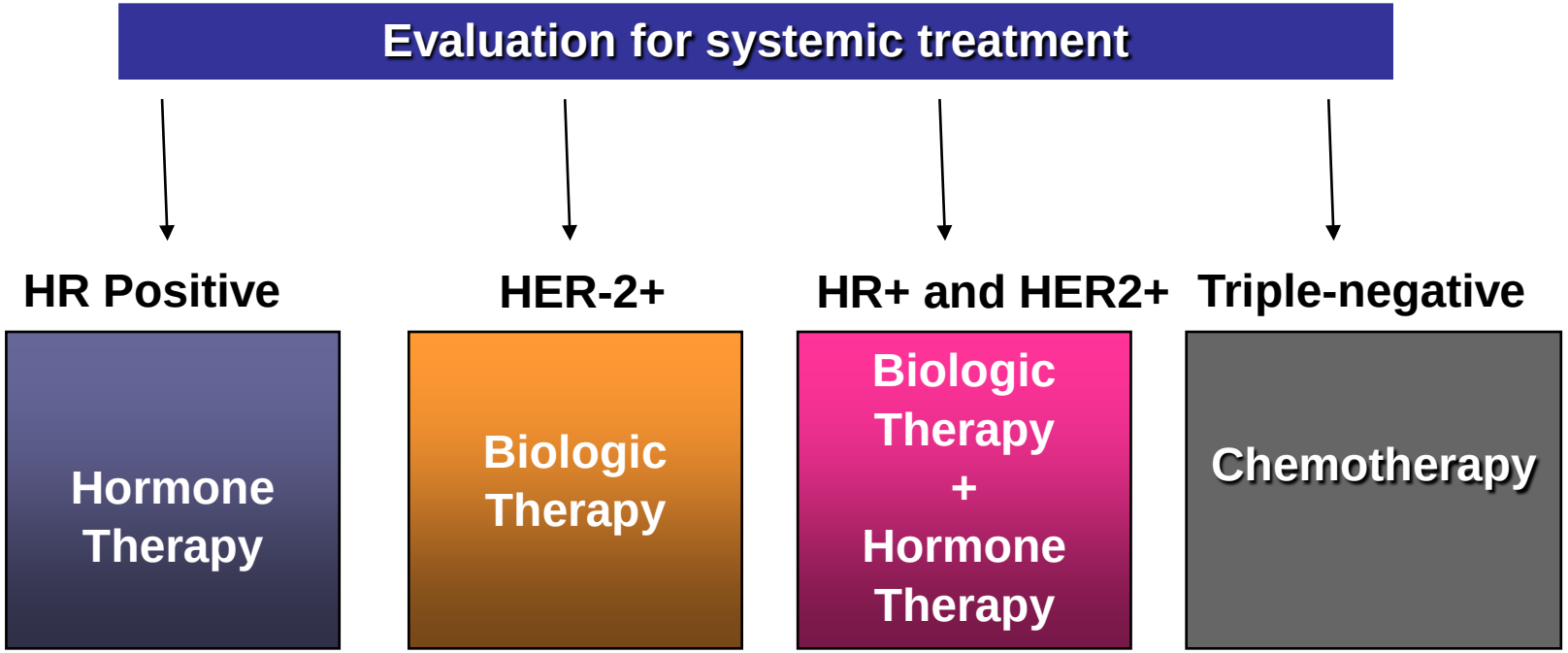
Selection of Systemic Treatment for Breast Cancer



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Research to Inform Policy

The New England Journal of Medicine
PERSPECTIVE
GLOBAL HEALTH
Can We Treat Cancer for a Dollar a Day?
Guidelines for Low-Income Countries

NEJM 2010;363:801-803

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A PERFECT STORM

How tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change.

CA Cancer J Clin. 2015 May-Jun;65(3):221-38. doi: 10.3322/caac.21271.

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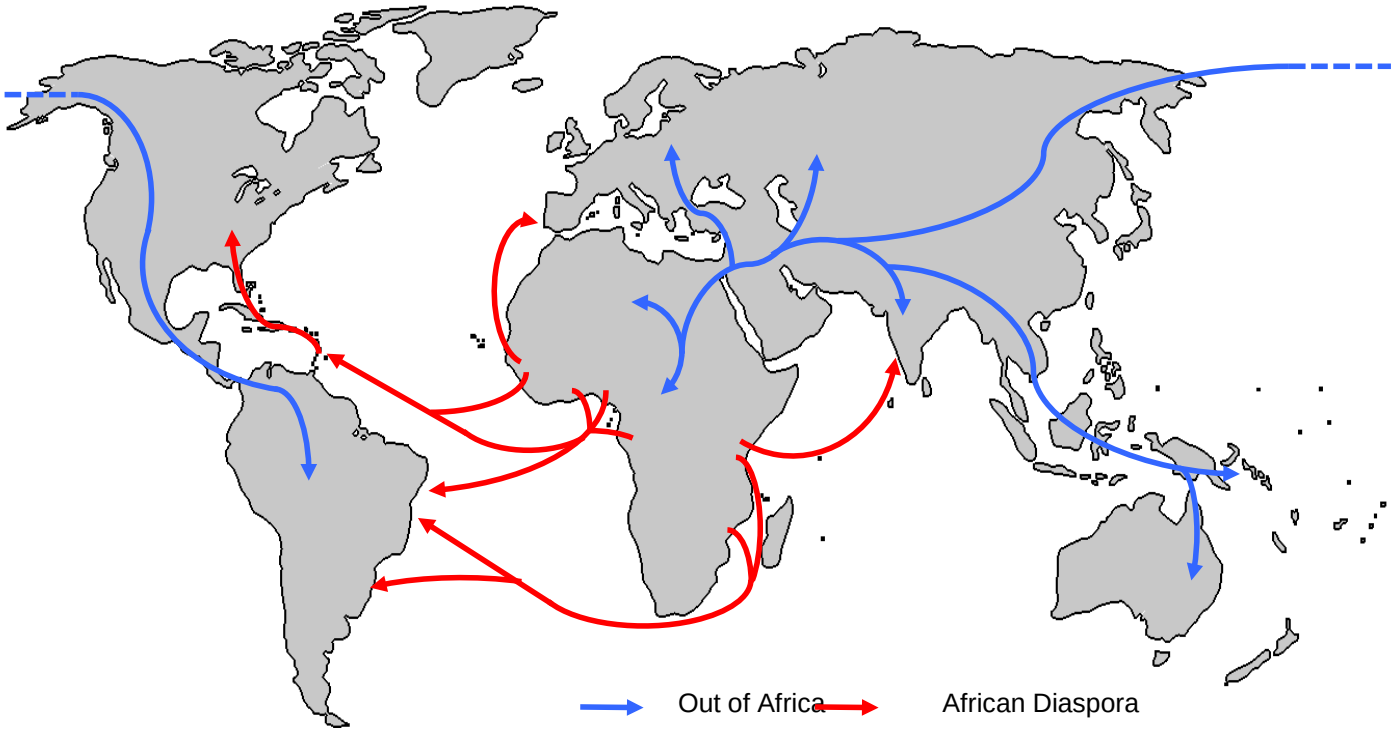
"Out of Africa" Theory of Early Migration



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?

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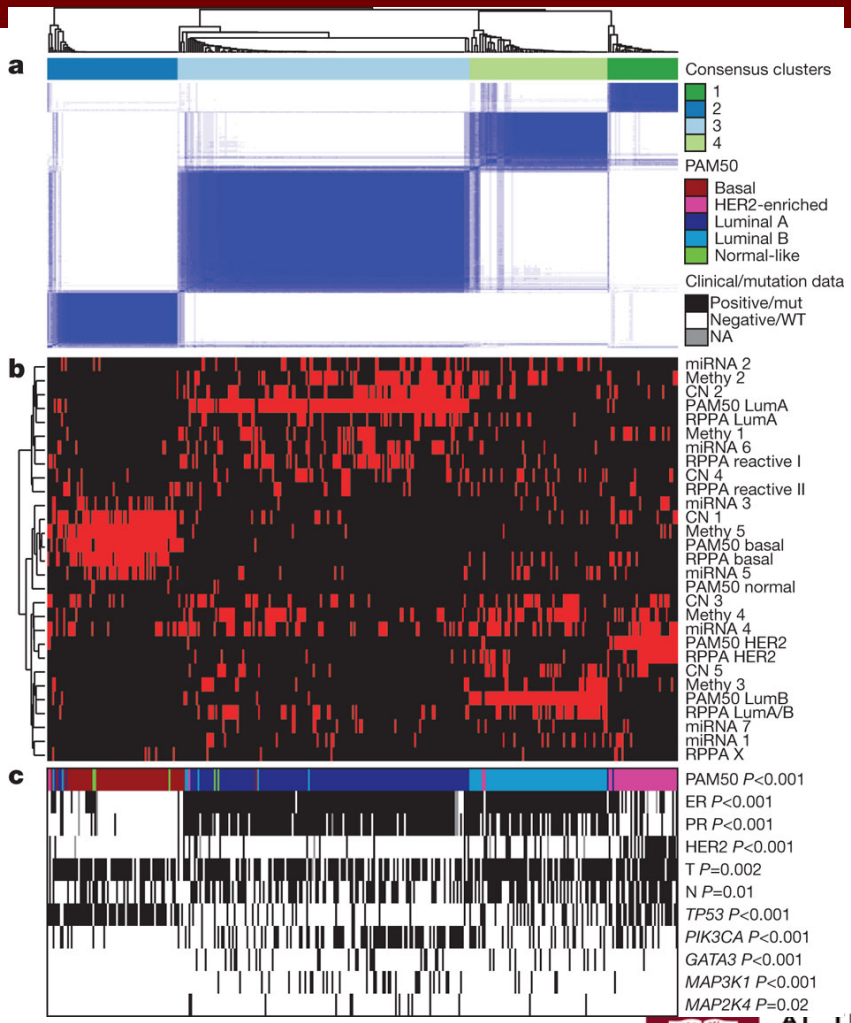
Molecular Subtypes of breast cancer

Multiplatform subtype:

Somatic mutation
CNV
DNA Methylation
miRNA
Gene expression
Protein expression

The Cancer Genome Atlas. *Nature* 2012, Oct



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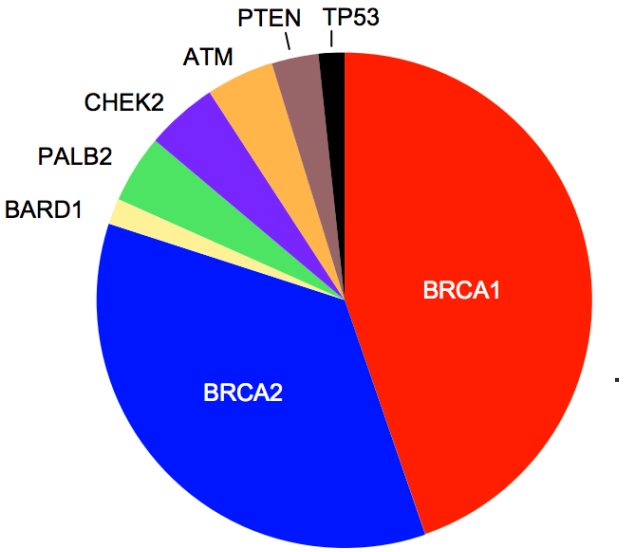
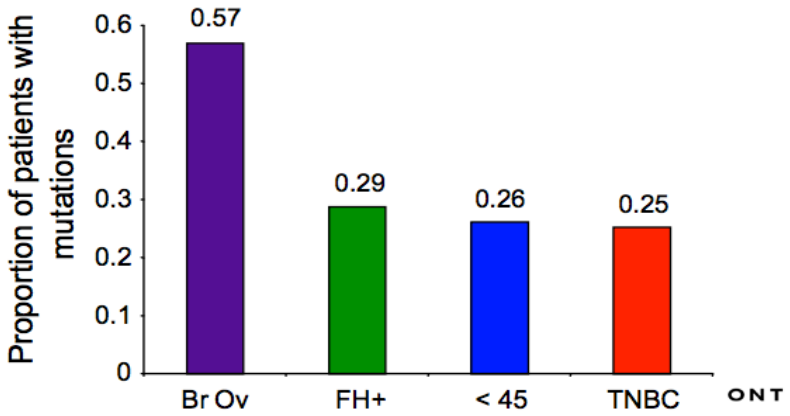
Genetic Testing in African American Patients with Breast Cancer at UChicago

- 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%)

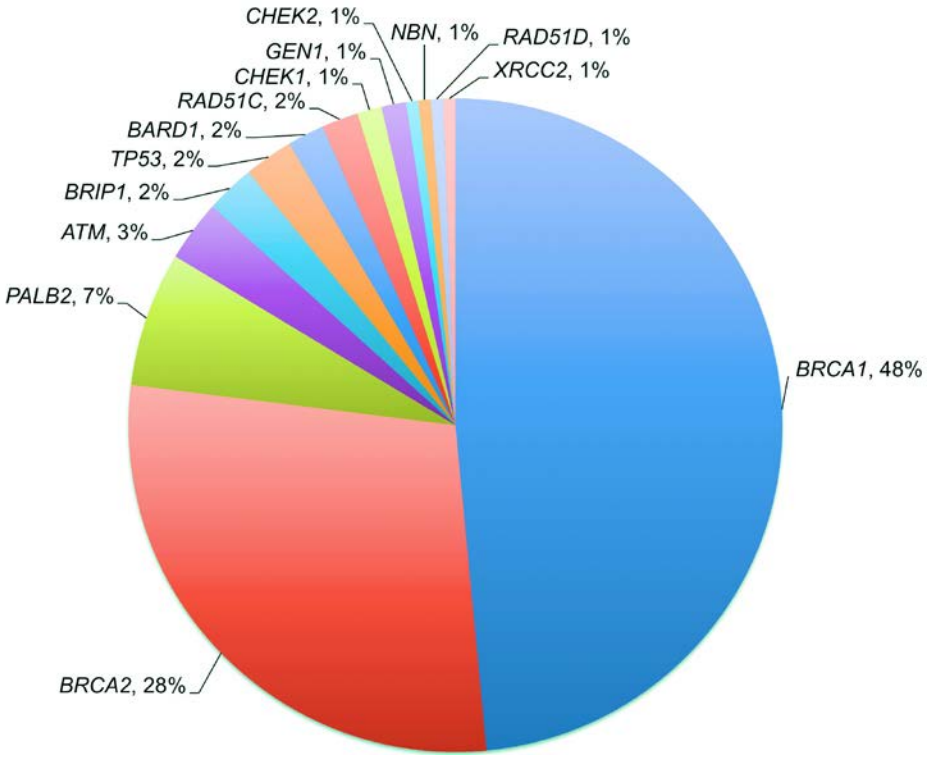




Breast Cancer Res Treat. 2015 Jan;149(1):31-9.

Strong Genetic Contribution to Breast Cancer Risk in Nigerians

Gene	Cases (n = 1,136) n (%)	Controls (n = 997) n (%)	OR (95% CI), adjusted for age
BRCA1/2 + PALB2 + TP53			
BRCA1	80 (7.04)	3 (0.30)	25.94 (8.16 to 82.48)
BRCA2	47 (4.14)	4 (0.40)	10.76 (3.86 to 29.99)
PALB2	11 (0.97)	0 (0)	
TP53	4 (0.35)	0 (0)	
Total	142 (12.50)	7 (0.70)	20.77 (9.67 to 44.63)
Other genes			
ATM	5 (0.44)	1 (0.10)	
BARD1	3 (0.26)	1 (0.10)	
BRIP1	4 (0.35)	1 (0.10)	
CHEK1	2 (0.18)	0 (0)	
CHEK2	1 (0.09)	0 (0)	
FAM175A	0 (0)	1 (0.10)	
GEN1	2 (0.18)	1 (0.10)	
MRE11A	0 (0)	1 (0.10)	
NBN	1 (0.09)	0 (0)	
RAD51C	3 (0.26)	0 (0)	
RAD51D	1 (0.09)	0 (0)	
SLX4	0 (0)	5 (0.50)	
XRCC2	1 (0.09)	0 (0)	
Total*	23 (2.02)	11 (1.10)	1.86 (0.90 to 3.84)
All genes	164 (14.44)	18 (1.81)	9.41 (5.73 to 15.44)



*One subject carries both *BRCA1* and *BRIP1* mutations.

Zheng et al. in press JCO

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The I SPY TRIALS

Investigation of
Serial studies to
Predict
Your
Therapeutic
Response with
Imaging
And
mo**L**ecular analysis

I SPY WITH MY LITTLE EYE . . . . . . A BIO-MARKER BEGIN-ING WITH X . . . .

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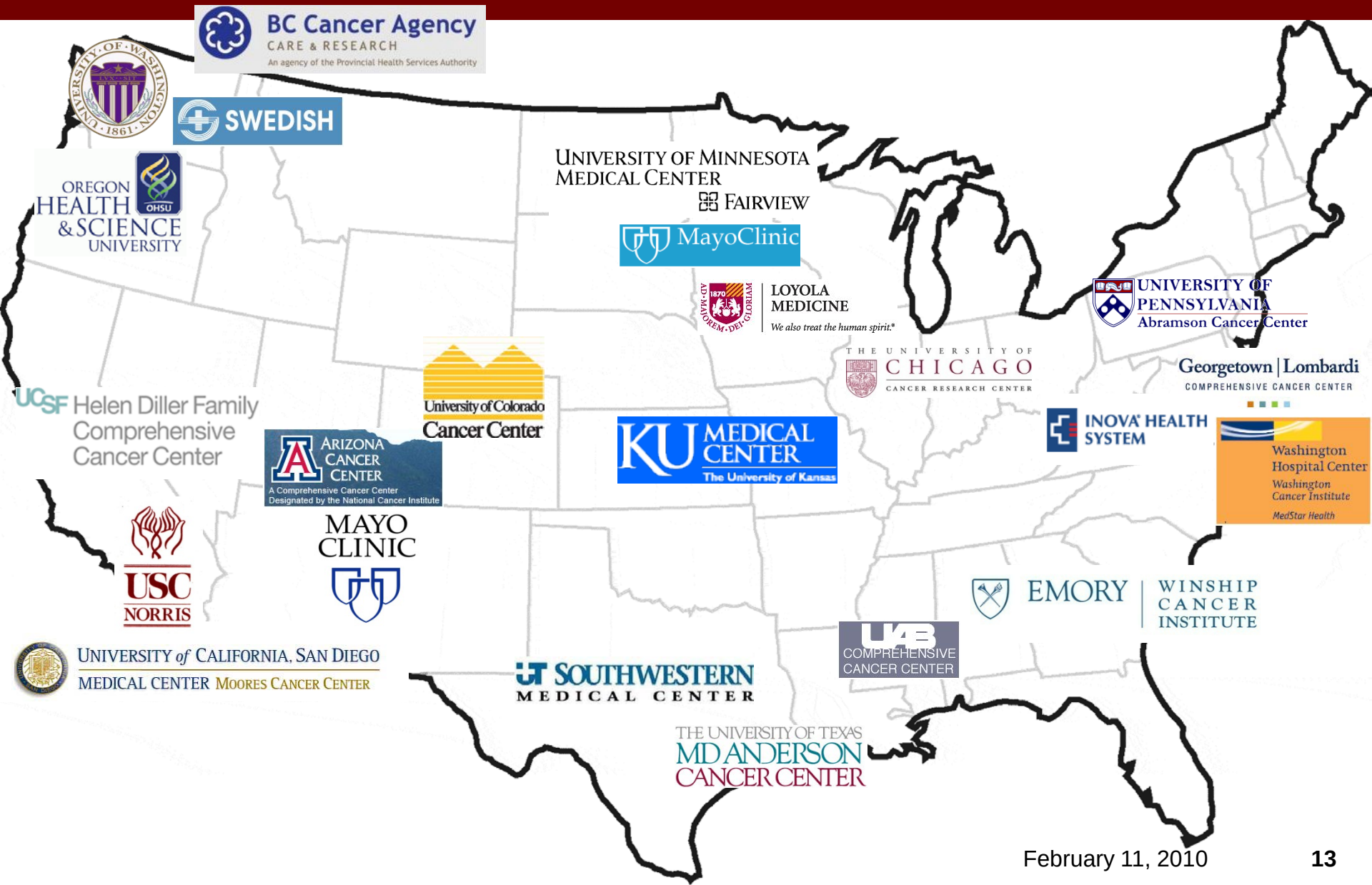
UChicago Medicine

I-SPY 2 Sites


BC Cancer Agency
CARE & RESEARCH
An agency of the Provincial Health Services Authority
SWEDISH
OREGON HEALTH & SCIENCE UNIVERSITY
OHSU
UNIVERSITY OF MINNESOTA MEDICAL CENTER
FAIRVIEW
MayoClinic
LOYOLA MEDICINE
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Abramson Cancer Center
THE UNIVERSITY OF CHICAGO
CANCER RESEARCH CENTER
Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER
UCSF Helen Diller Family Comprehensive Cancer Center
University of Colorado Cancer Center
INOVA HEALTH SYSTEM
Washington Hospital Center
Washington Cancer Institute
MedStar Health
ARIZONA CANCER CENTER
A Comprehensive Cancer Center
Designated by the National Cancer Institute
KU MEDICAL CENTER
The University of Kansas
MAYO CLINIC
USC NORRIS
EMORY
WINSHIP CANCER INSTITUTE
UAB
COMPREHENSIVE CANCER CENTER
UNIVERSITY of CALIFORNIA, SAN DIEGO
MEDICAL CENTER MOORES CANCER CENTER
UT SOUTHWESTERN MEDICAL CENTER
THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER

Original Article

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

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UChicago Medicine

Original Article
Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

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The NEW ENGLAND JOURNAL of MEDICINE

Litton et al. N Engl J Med Volume 379(8):753-763 August 23, 2018

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Study Overview

- Among patients with breast cancer and germline mutations in the *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.

Litton et al. N Engl J Med Volume 379(8):753-763 August 23, 2018

The NEW ENGLAND JOURNAL of MEDICINE

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Why Genomic Testing?

Unaffected

- Tailored screening recommendations
- Risk-reduction strategies
  - Surgical
  - Chemoprevention

Affected

- Surgical management
- Risk reduction for other cancers
- **Targeted treatment options**

* Risk assessment may also identify those ***not*** at increased risk

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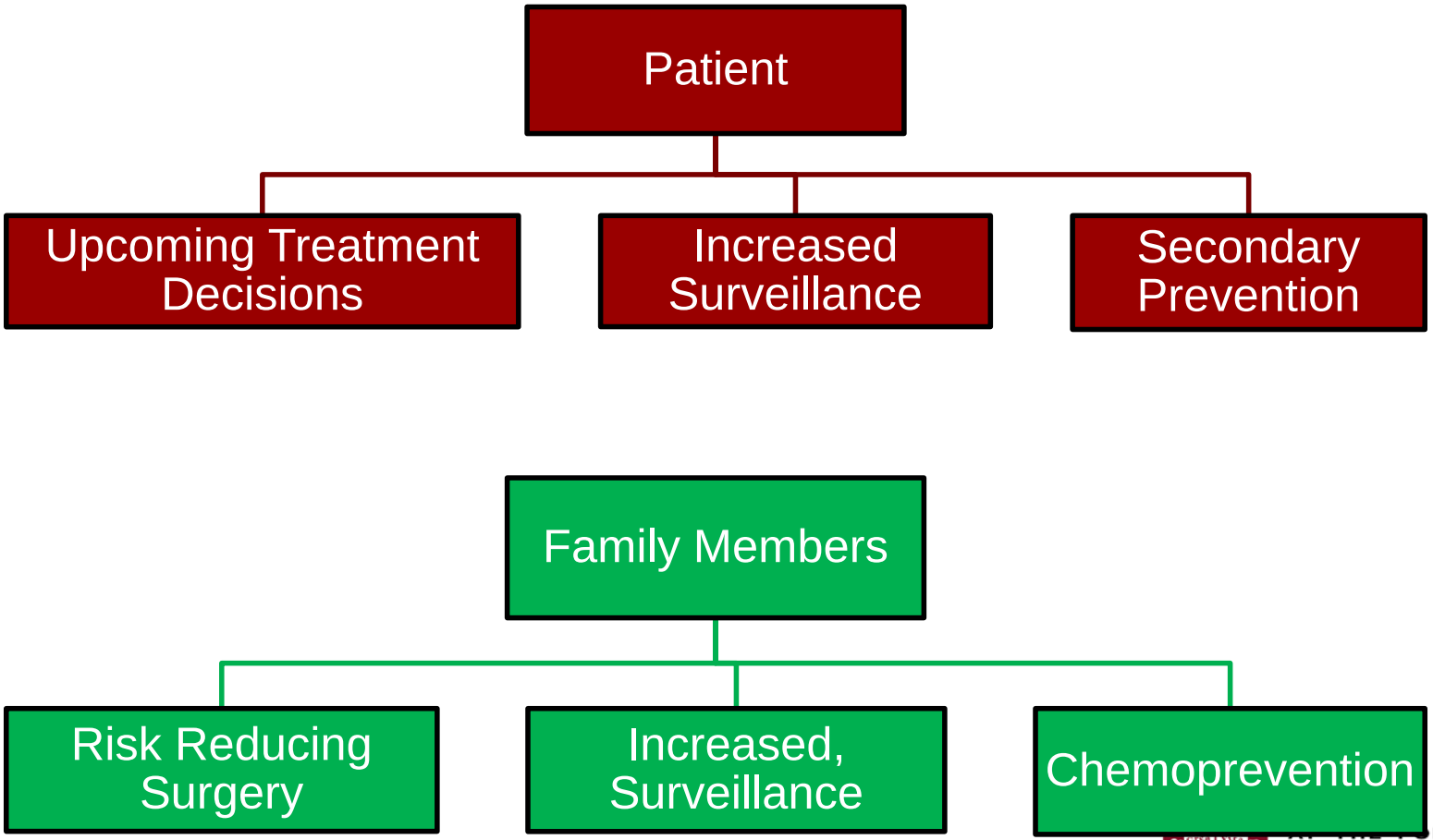
Breast Cancer: Risk Management Options



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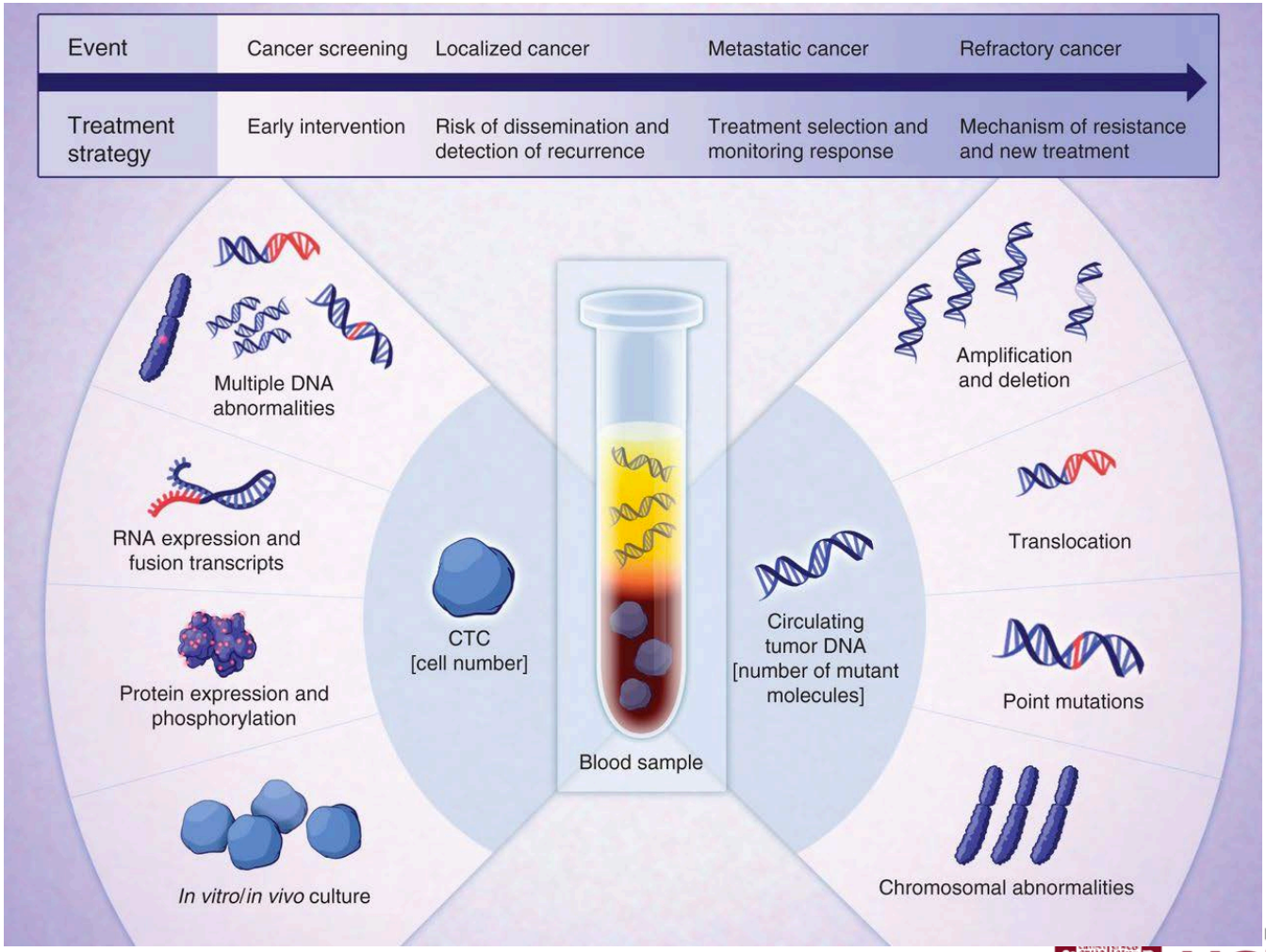
Clinical applications of liquid biopsies in cancer care



Cancer Discov. 2014 Jun;4(6):650-61.

E FOREFRONT
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Transforming Our World: 2030 Development Agenda

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

Center for Global Health Team

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