Harry Hynes Memorial Lecturer

Olufunmilayo Olopade, MD

AT THE FOREFRONT
UChicago Medicine

Population Risk Stratification to Improve Quality of Care

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Harry Hynes Lecture, SWOG, 2019

Disclosures

- Co-Founder: CancerIQ
- SAB: Tempus
- Roche: Clinical Trials Research support
- Novartis: Research support

I will discuss implementation of CancerIQ for POC testing

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Overview

- Introduction
- Historical perspectives
- Cancer Care Continuum
- Panel Testing for Inherited Cancers
- Population Risk Stratification
- Future Directions

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical and Pathological Features of Ovarian Cancer in Women with Germ-Line Mutations of *BRCA1*

Stephen C. Rubin, M.D., Ivor Benjamin, M.D., Kian Behbakht, M.D., Hiroyuki Takahashi, M.D., Ph.D., Mark A. Morgan, M.D., Virginia A. LiVolsi, M.D., Andrew Berchuck, M.D., Michael G. Muto, M.D., Judy E. Garber, M.D., Barbara L. Weber, M.D., Henry T. Lynch, M.D., and Jeff Boyd, Ph.D.et al.

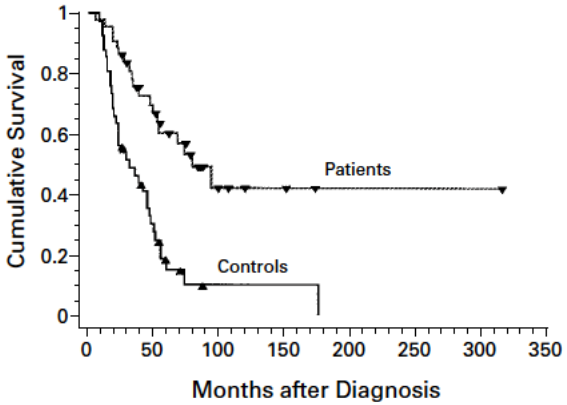

Figure 1. Actuarial Survival among 43 Patients with Advanced-Stage Ovarian Cancer and Germ-Line *BRCA1* Mutations, as Compared with Matched Controls without Such Mutations. P<0.001 by the log-rank test. The triangles and inverted triangles indicate the durations of follow-up among surviving patients.

November 7, 1996
N Engl J Med 1996; 335:1413-1416
DOI: 10.1056/NEJM199611073351901

Editorials

Genetics in Clinical Cancer Care — The Future Is Now

THE identification of *BRCA1* as the first gene for susceptibility to breast and ovarian cancer was an important step toward a better understanding of the biology of these cancers.[1] This advance should lead to new therapies, but for now it provides a unique opportunity to develop new strategies for early detection and prevention. The intense attention in the media to this breakthrough has caused many highly motivated women with family histories of cancer to seek counseling about their risks and options for prevention. It is no longer unusual for

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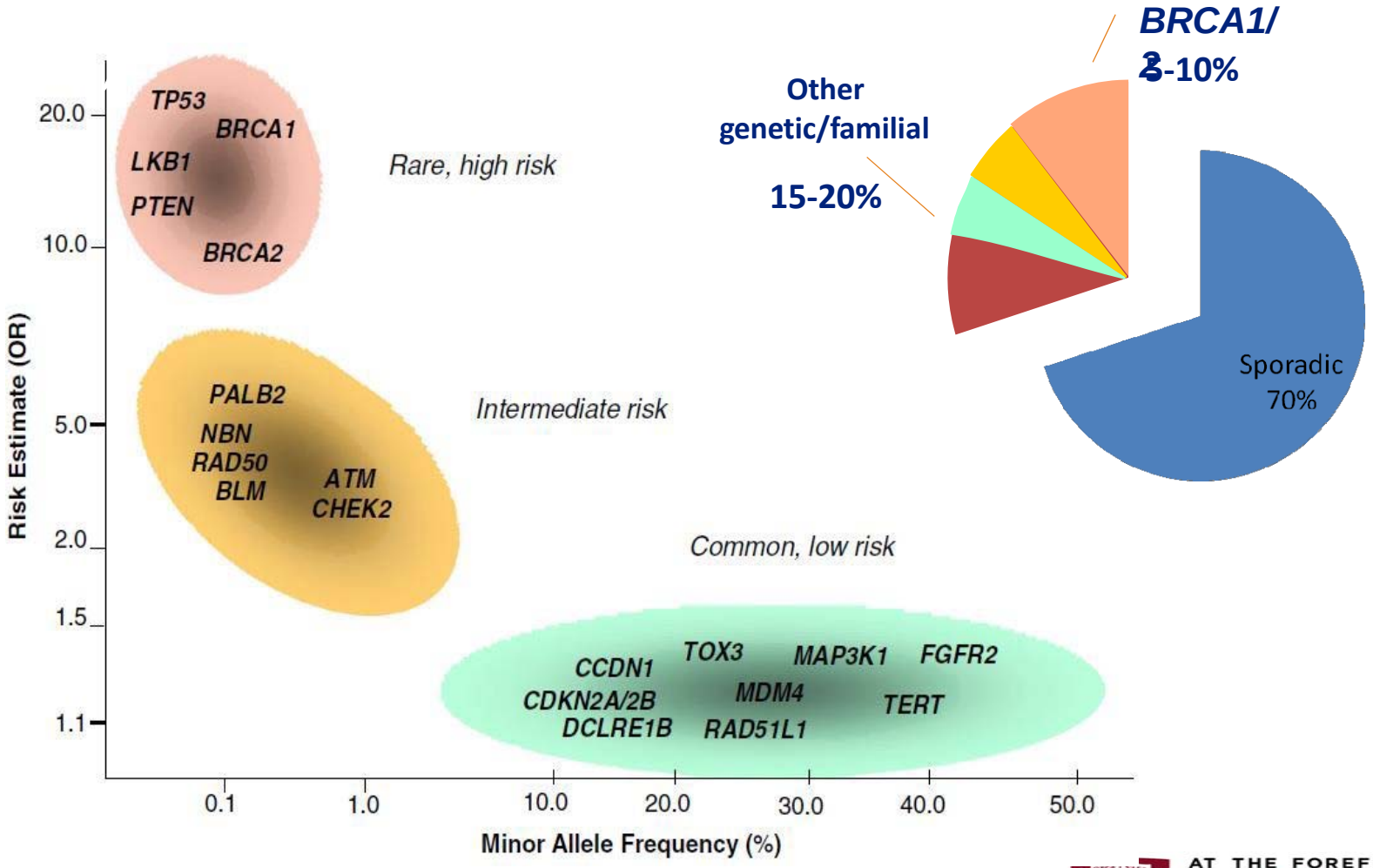
Frequency and Risk Distribution of Cancer Susceptibility Alleles (Example of Breast



Bogdanova N et al. Hereditary Cancer in Clinical Practice, 2013

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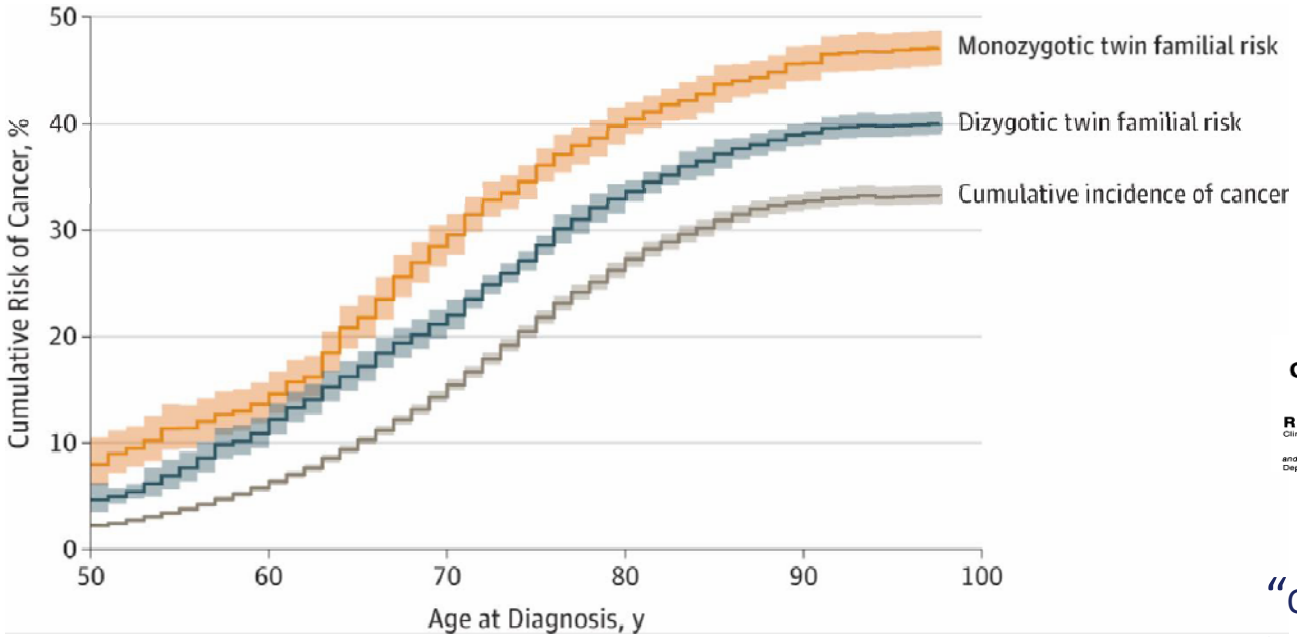
Breast Cancer SNPs

- ~ 170 breast cancer (BC) susceptibly loci identified through GWAS to date, explaining ~ 40% of the heritability.
- Most recent PRS developed by *Mavaddat et al* (2019) is based on **313 variants**. This includes:
  - 305 SNPs based on a hard-thresholding stepwise forward regression
  - 6 additional SNPs associated with ER-positive disease
  - 2 known rare BC susceptibility variants in *BRCA2* & *CHEK2* genes

PRS developed using 79 studies in Breast Cancer Association Consortium (BCAC):

- Development dataset :
  - 94,075 cases & 75,017 controls from 69 studies
- Validation datasets:
  - 11,428 cases & 18,323 controls from 10 prospective studies
  - 190,040 women from UK Biobank (3,215 incident breast cancers)

More than just the genes



	Familial Risk, % (95% CI)	
	Monozygotic Twins	Dizygotic Twins
Overall cancer	45.9 (44.1-47.7)	37.1 (35.7-38.4)
Breast cancer	28.1 (23.9-32.8)	19.9 (17.0-23.2)

Mucci LA et. JAMA, 2016

The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today

Richard Doll, Honorary Director, Imperial Cancer Research Fund Cancer Epidemiology and Clinical Trials Unit, and Warden of Green College, Oxford, United Kingdom

and Richard Peto, Imperial Cancer Research Fund Reader in Cancer Studies, Nuffield Department of Clinical Medicine, University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE, United Kingdom

JNCI, VOL. 66, NO. 6, JUNE 1981

"On the basis of comparisons of high- and low-incidence regions, Doll & Peto concluded that 75-80% of cancers diagnosed in the United States in 1970 theoretically could have been avoided."

- Colditz & Wei, Annual Review of Public Health 2012

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Why Genomic Testing?

Unaffected	Affected

• Tailored screening recommendations
• Risk-reduction strategies
  • Surgical
  • Chemoprevention
	• Surgical management
	• Risk reduction for other cancers
	• **Targeted treatment options**

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

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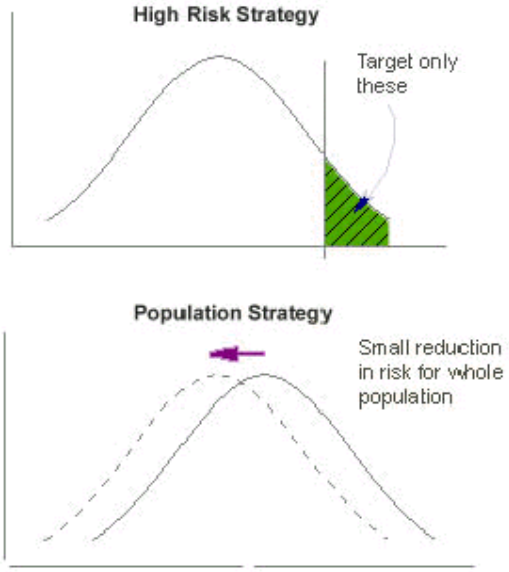
Population Risk Stratification

- Screening
  - To look for breast cancer before “touch down” --- easier to treat and potentially curable
  - Methods
    - Mammogram/MRI: Gold standard
      - Screening tests have risks
      - Limited resources, Cost-effective analysis
    - Questionnaires
  - Strategy
    - High risk
    - Whole population



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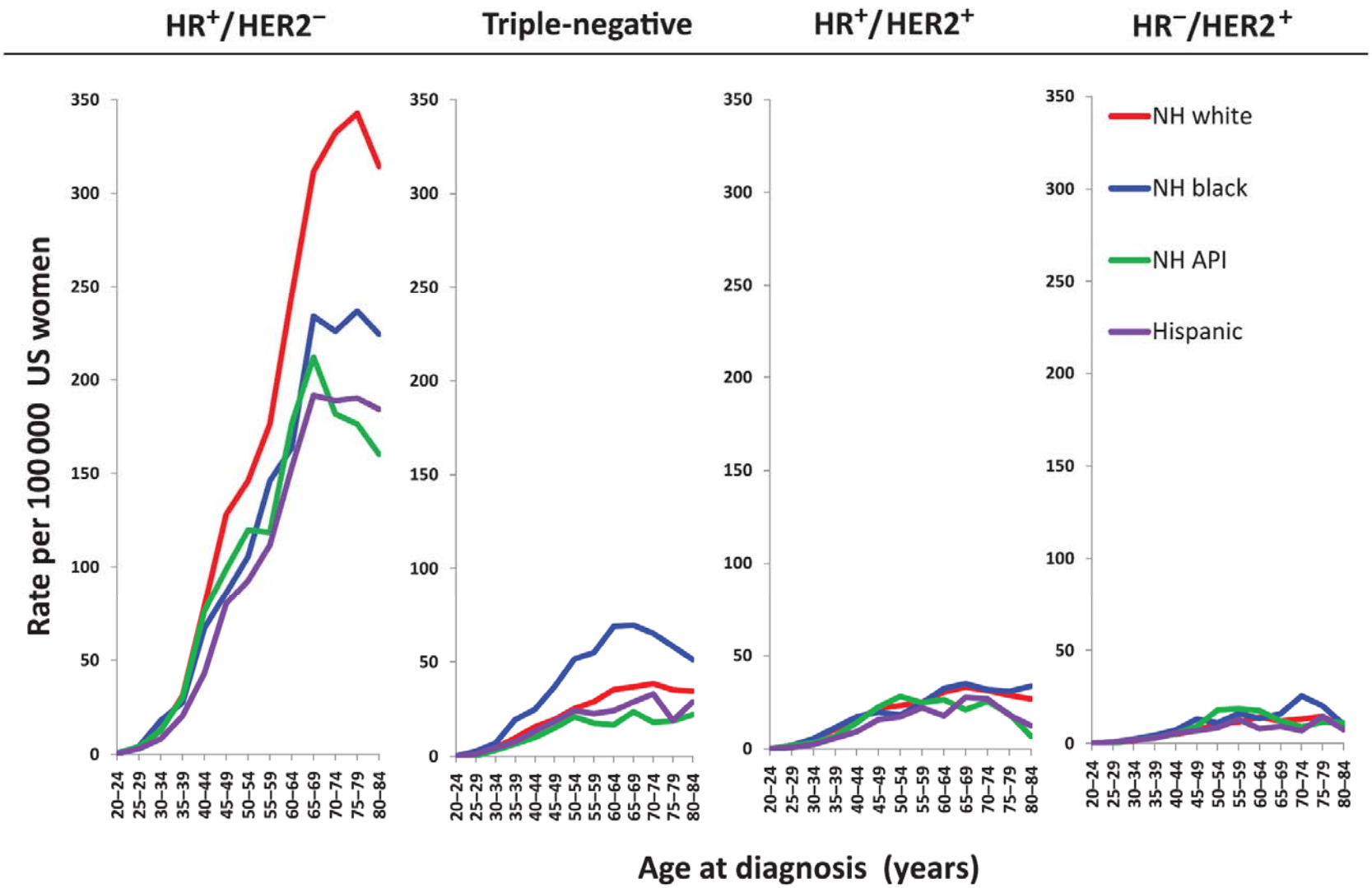
Subtype-specific breast cancer incidence



Howlader et al JNCI 2014

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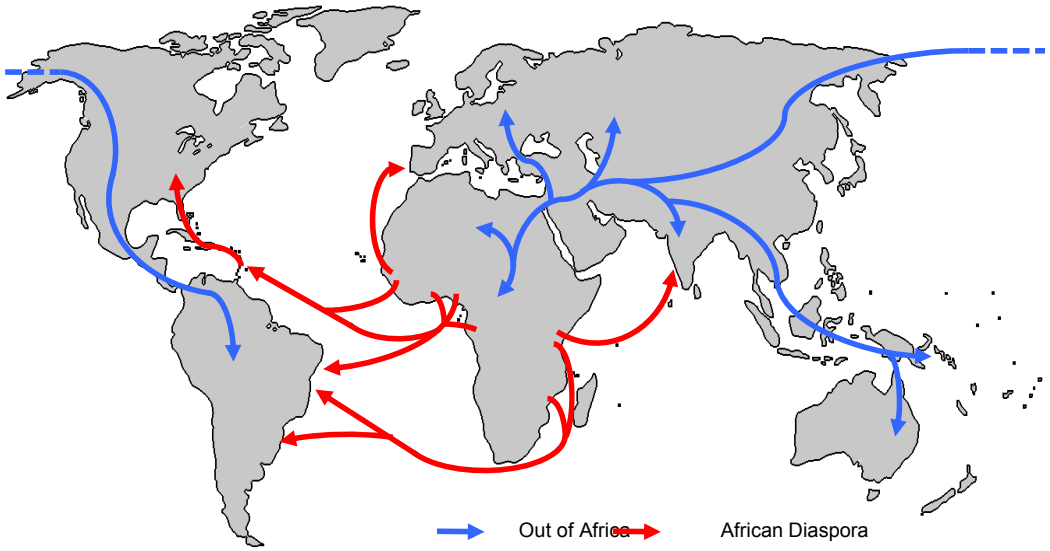
"Out of Africa" Theory of Early Migration



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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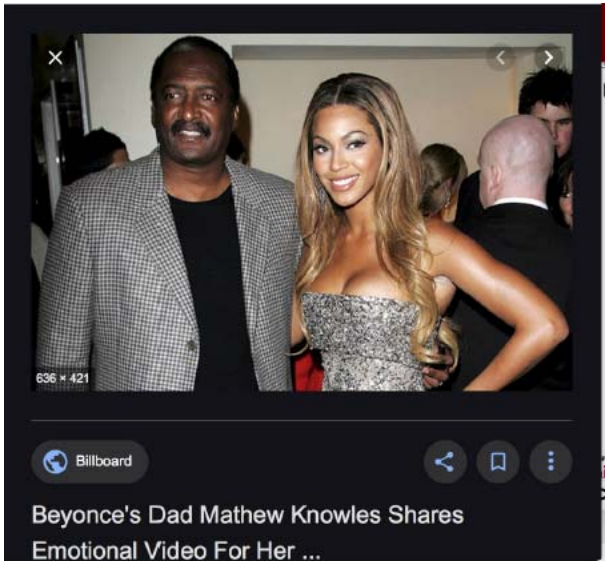
Multigene Panel Testing

- Context: Supreme Court unanimous decision overturned Myriad's patent on *BRCA1* and *BRCA2* in June 2013
  - Any laboratory can now test *BRCA1/2,* along with a variety of other cancer-predisposing genes
  - Panel Testing has rapidly expanded
  - Direct to Consumer Marketing expanding demand for high quality genomic services focused on the personal needs of healthy individuals
  - Testing across diverse populations with reduced costs now possible
  - We have now tested thousands of patients across the African Diaspora in Nigeria, Brazil, Cameroon and Uganda in collaboration with MC King and funded with gifts from private donors and Foundations.
  - Population risk stratification will lead to reduced costs and improved outcomes for high risk women

October 2nd 2019



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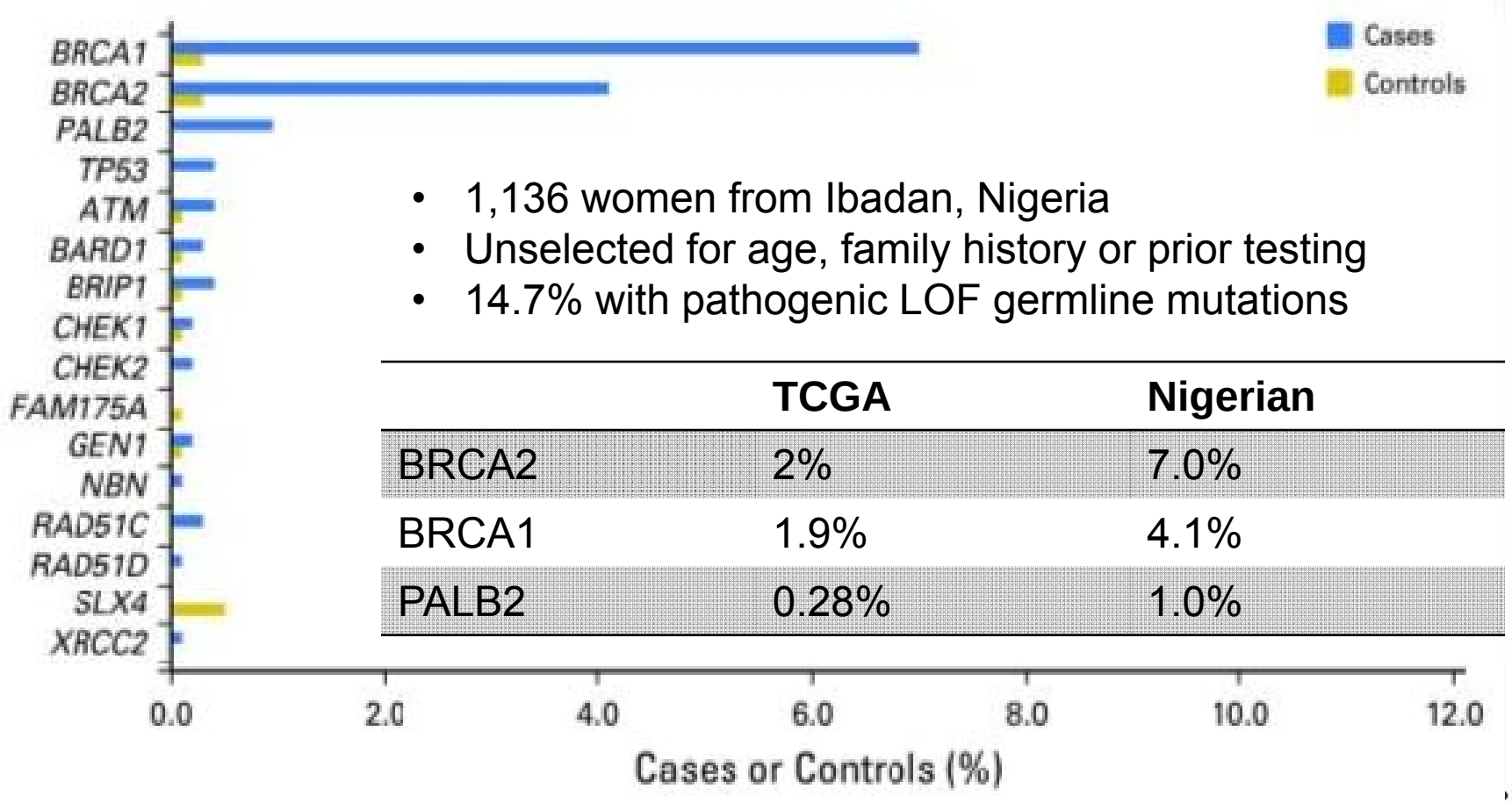
High rates of germline mutations in Nigerian breast cancer patients -- BROCA Panel and Tumor NGS



- 1,136 women from Ibadan, Nigeria
- Unselected for age, family history or prior testing
- 14.7% with pathogenic LOF germline mutations

	TCGA	Nigerian
BRCA2	2%	7.0%
BRCA1	1.9%	4.1%
PALB2	0.28%	1.0%

Courtesy Rajagopal

Zheng et al. *J Clin Oncol.* 2018 Oct 1; 36(28): 2820–2825.
Huang et al. *Cell* 2018 Apr 5; 173(2): 355-370

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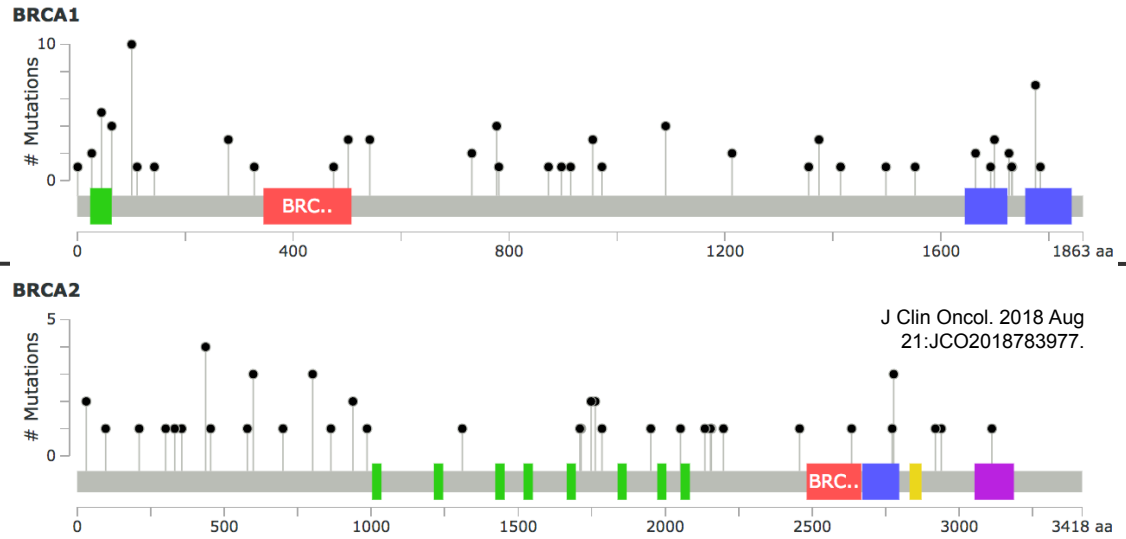
Highly Heterogeneous *BRCA1/2* Mutations in Nigerians



J Clin Oncol. 2018 Aug 21:JCO2018783977.

BRCA1/2 mutation testing limited to recurrent mutations is not sufficient to understand the *BRCA1/2*-associated breast cancer risk in African populations in the diaspora.

Zheng et al. J Clin Oncol. 2018 Aug 21:JCO2018783977

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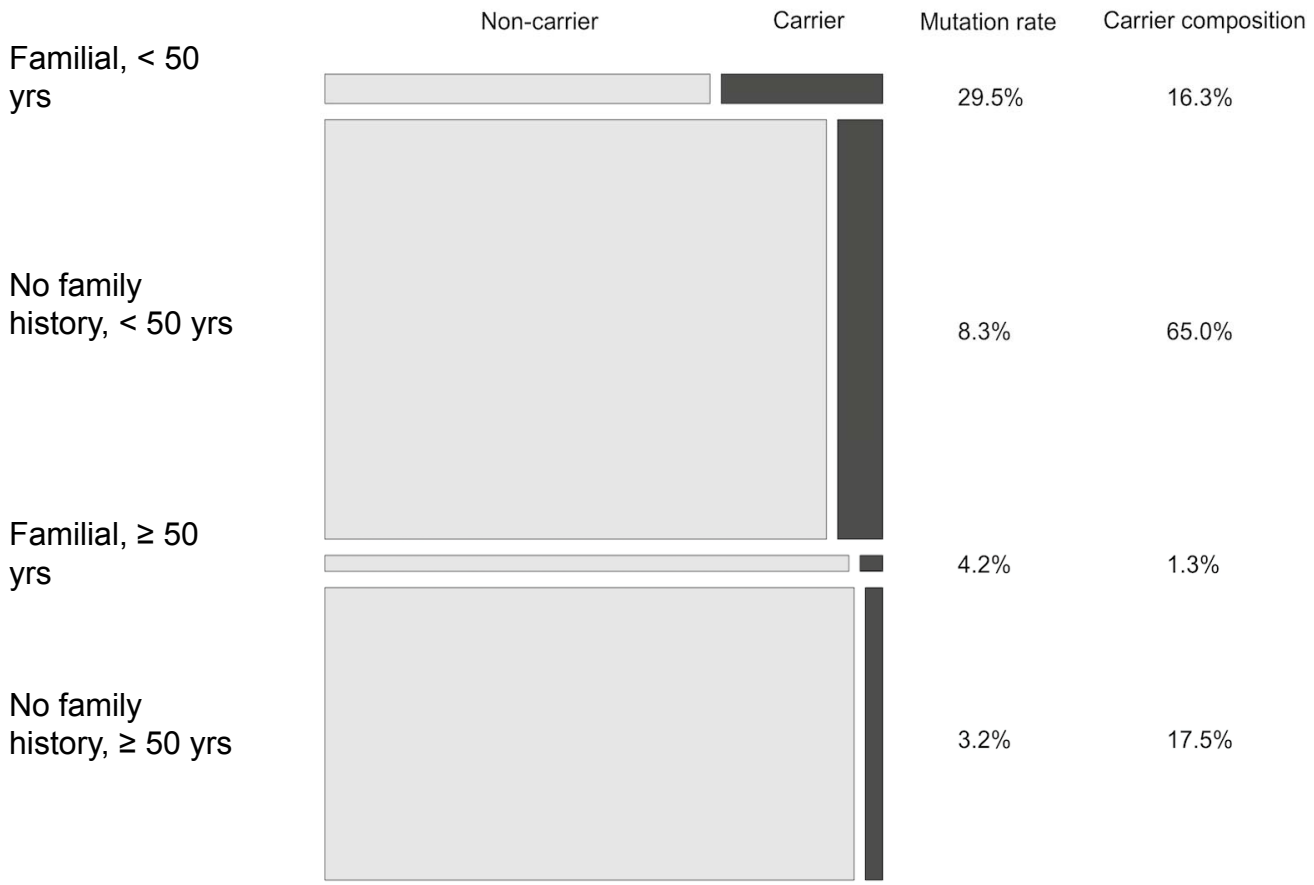
BRCA Mutations Stratified by Family History and Age in NBCS



Zheng et al. J Clin Oncol. 2018 Aug 21:JCO2018783977

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BRCA1 Lifetime Cancer Risks

- **Breast cancer** 46-71%
(often early age at onset)

- **Second primary breast cancer** 40%-60%
(5%/year, vs. 1%/year for sporadic BC)

- **Ovarian/fallopian tube cancer** 41-46%

Modified from ASCO Slide set

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BRCA2 Lifetime Cancer Risks

- **Breast cancer** (46-71%)
- **Male breast cancer** (7%)
- **Prostate** (33%)
- **Ovarian/fallopian tube cancer** (17-23%)

Modified from ASCO Slide set

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Other *BRCA* Cancer Risks

- Pancreatic
- Melanoma
- Gastric
- Laryngeal/Head and Neck Cancers
- Hematologic malignancies
- Others

Age-based screening and racial disparity

- Women of African Ancestry under the age of 45 years have a higher breast cancer incidence than women of European ancestry
- More likely to have aggressive hormone receptor negative or triple negative breast cancer
- Age-based screening without access to life saving cancer medicines has worsened global disparities in breast cancer outcomes
  - e.g. beginning screening at age 50 or not screening at all can lead to higher proportion of “lethal” forms of breast cancer being missed in understudied and underserved minority populations.

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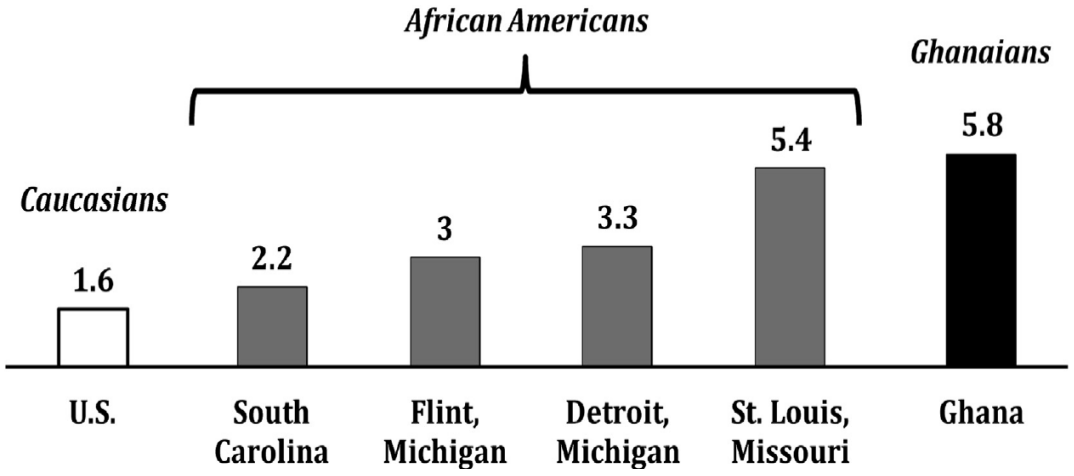
Prevalence of Prostate Cancer in Screened Populations

Screened detected prevalence of prostate cancer in White men 50 yrs or older, African Americans 40-79 yrs, and Ghanaian men 50-74 with PSA >4.0 and abnormal DRE.



Hsing et al., *J Urol* 2014

Courtesy of Tim Rebbeck

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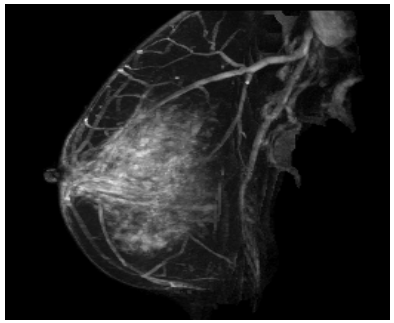
Age-based screening and racial disparity

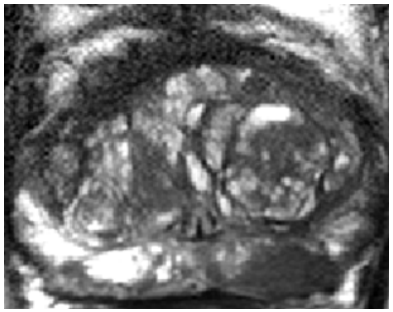
- 1/6 of men in the US will be diagnosed with prostate cancer
- Extremely inefficient diagnosis algorithm
  - 1.2 M prostate bx ($ 2B)/year – only 30% of initial bx is +
  - No significant improvement in mortality
  - Biopsy based GS not reliable
- Flawed management decisions and overtreatment:
  - Estimated “overtreatment” rates of 27 – 56%
  - Some experts estimate that ~30 prostatectomies required to significantly extend one life
  - Significant side effects
- US Preventive services task force recommended against PSA screening (2012)
- Diagnosis and management of recurrence is problematic

Courtesy Aytekin Oto

Development of effective and inexpensive MRI screening for breast and prostate cancer

- Currently, there are no good options for prostate cancer screening following USPST negative recommendation about PSA screening. A significant increase in mortality is expected in the next 10 years.
- X-ray mammography is not a good option for women with dense breasts and women who are at high risk for breast cancer
- The University of Chicago “catchment” area has high rates of aggressive breast and prostate cancer and an underserved population





Courtesy Greg Karczmar

?Genotype/Subtype Specific Screening

Clinical Cancer Research

Precision Medicine and Imaging

Intensive Surveillance with Biannual Dynamic Contrast-Enhanced Magnetic Resonance Imaging Downstages Breast Cancer in *BRCA1* Mutation Carriers

Rodrigo Santa Cruz Guindalini, Yonglan Zheng, Hiroyuki Abe, Kristen Whitaker, Toshio F. Yoshimatsu, Tom Walsh, David Schacht, Kirti Kulkarni, Deepa Sheth, Marion S. Verp, Angela R. Bradbury, Jane Churpek, Elias Obeid, Jeffrey Mueller, Galina Khramtsova, Fang Liu, Akila Raoul, Hongyuan Cao, Iris L. Romero, Susan Hong, Robert Livingston, Nora Jaskowiak, Xiaoming Wang, Marcio Debiasi, Colin C. Pritchard, Mary-Claire King, Gregory Karczmar, Gillian M. Newstead, Dezheng Huo, and Olufunmilayo I. Olopade

DOI: 10.1158/1078-0432.CCR-18-0200 Published March 2019 Check for updates

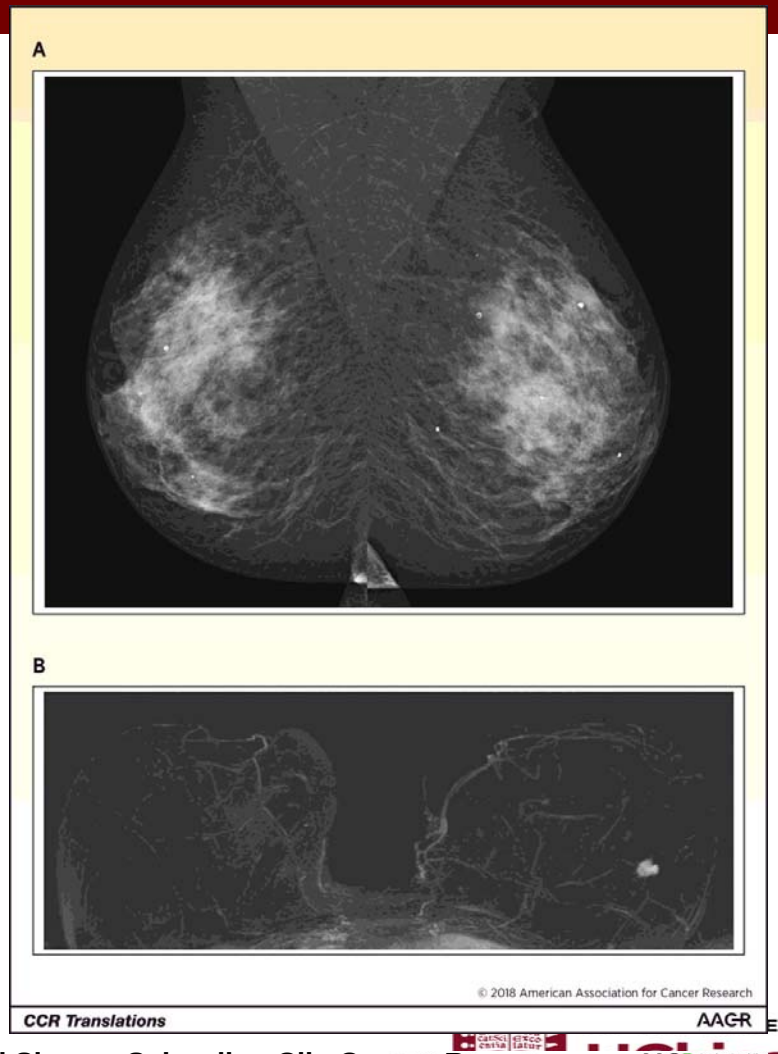
Clinical Cancer Research

CCR Translations

More Is More: Semiannual Breast MRI Screening in BRCA1 Mutation Carriers

Christiane K. Kuhl and Simone Schrading

DOI: 10.1158/1078-0432.CCR-18-3145 Published March 2019 Check for updates



Christiane K. Kuhl, and Simone Schrading Clin Cancer Res 2019;25:1693-1695

Original Article

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

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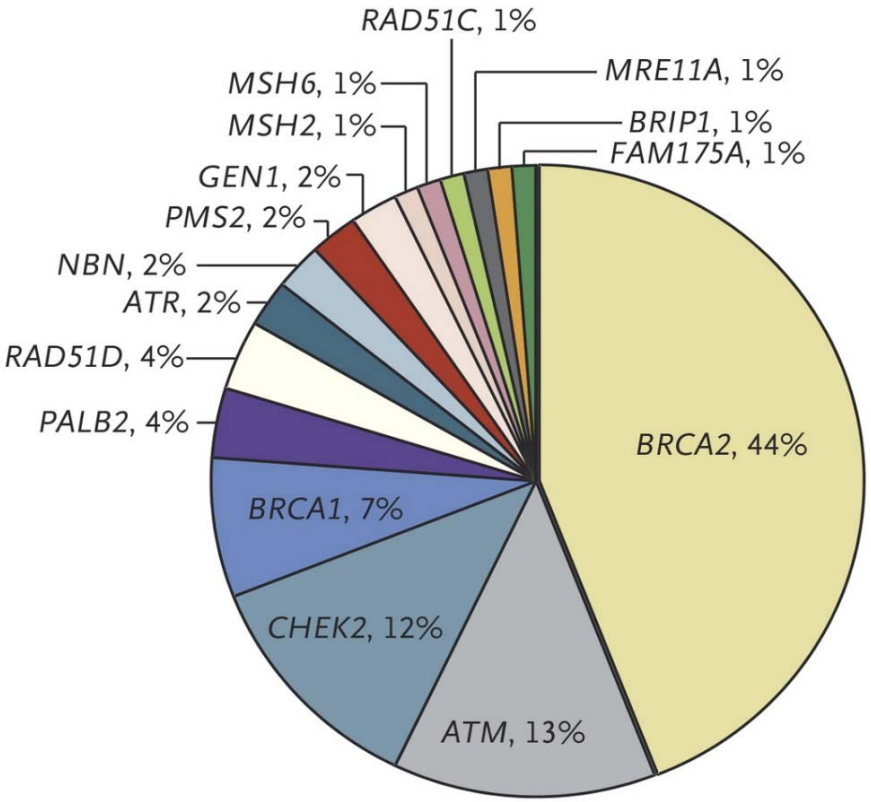
Germline DNA Repair Mutations Are Common in Metastatic Prostate Cancer



12% (82/692) with deleterious germline mutations in 16 DNA repair genes

59% (36/61) with avail. tumors had second allele loss-of-function mutation

Pritchard et al. *NEJM* 2016

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Breakthrough Status for PARPi in Metastatic Prostate Cancer

January 2016

FDA Grants Olaparib Breakthrough Designation in mCRPC

Gina Columbus @ginacolumbusonc
Published: Thursday, Jan 28, 2016

Olaparib (Lynparza) has received an FDA breakthrough therapy designation as a treatment for patients with *BRCA1/2* or *ATM*-mutated metastatic castration-resistant prostate cancer (mCRPC) in those who have received a prior taxane-based chemotherapy and at

October 2018

FDA Grants Rucaparib Breakthrough Designation for mCRPC

Ariela Katz
Published: Tuesday, Oct 02, 2018

The FDA has granted the PARP inhibitor rucaparib (Rubraca) a breakthrough therapy designation for single-agent use in adult patients with *BRCA1/2*-positive metastatic castration-resistant

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Point of Care Counseling

VOLUME 36 · NUMBER 13 · MAY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Evaluation of a Streamlined Oncologist-Led *BRCA* Mutation Testing and Counseling Model for Patients With Ovarian Cancer

Nicoletta Colombo, Gloria Huang, Giovanni Scambia, Eva Chalas, Sandro Pignata, James Fiorica, Linda Van Le, Sharad Ghamande, Santiago González-Santiago, Isabel Bover, Begoña Graña Suárez, Andrew Green, Philippe Huot-Marchand, Yann Bourhis, Sudeep Karve, and Christopher Blakeley

Streamlined Point of Care Counseling in Primary Care Settings

Point A: Screening Sites
Imaging, OB, GI, PCP

Point B: Genetic Specialists in Every practice

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Example of PRS results report

Breast Cancer riskScore™

riskScore™ BREAST CANCER

Breast Cancer riskScore™

31.3%

RESULT: 31.3% Remaining Lifetime Risk for Breast Cancer
1.7% 5-Year Risk for Breast Cancer

https://myriadmyrisk.com/riskscore/

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From stratification to precision

Stratification

- Clinical features
- Disease subtypes
- Demographics: age, race, socio-economic factors
- Pathology/molecular features
- Environment

Precision

- Somatic mutations
- Germline mutations
- Targeted therapies

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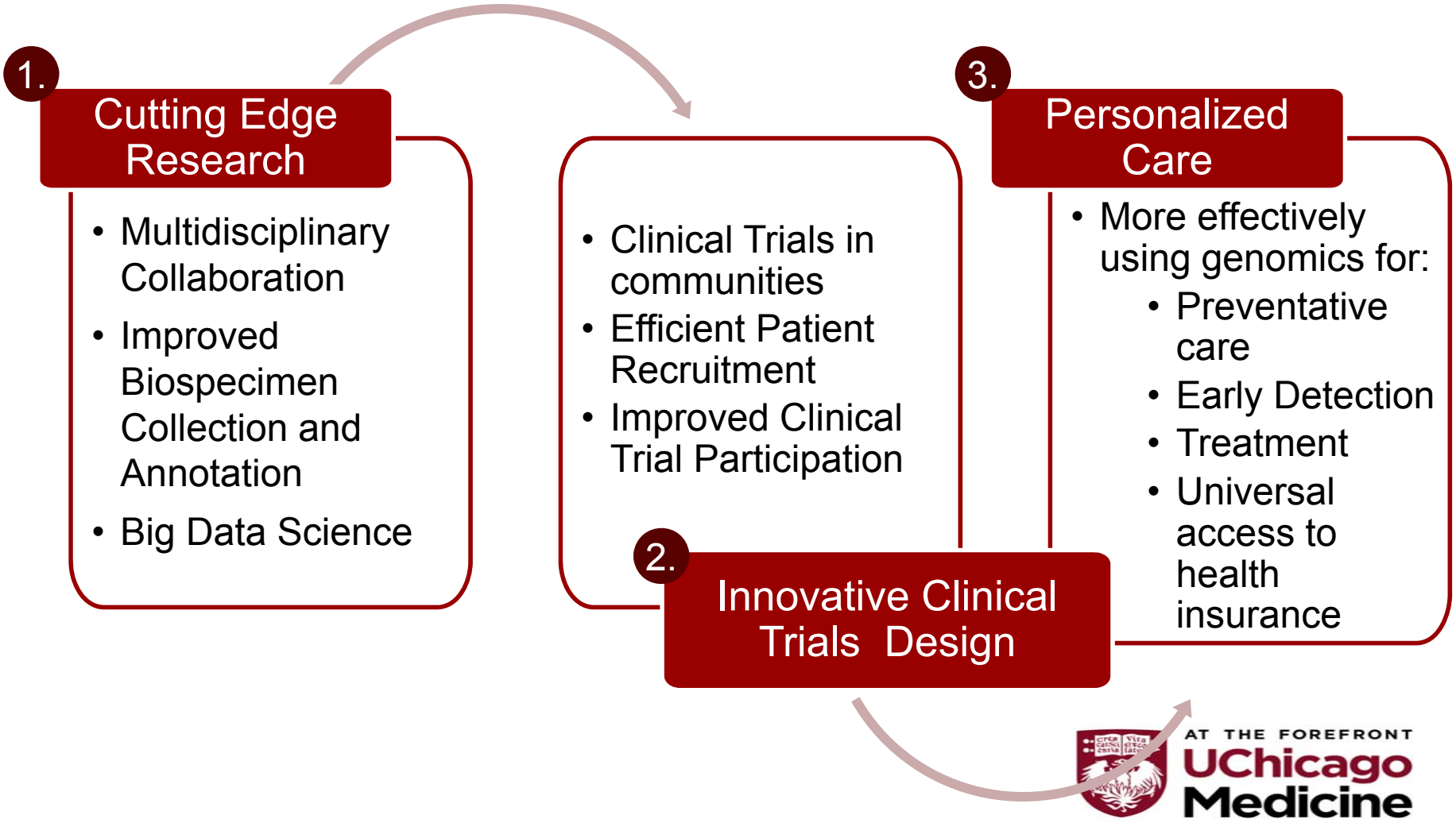
Clinical Trials for "All of Us"

Accelerating progress to promote health and well being in all populations



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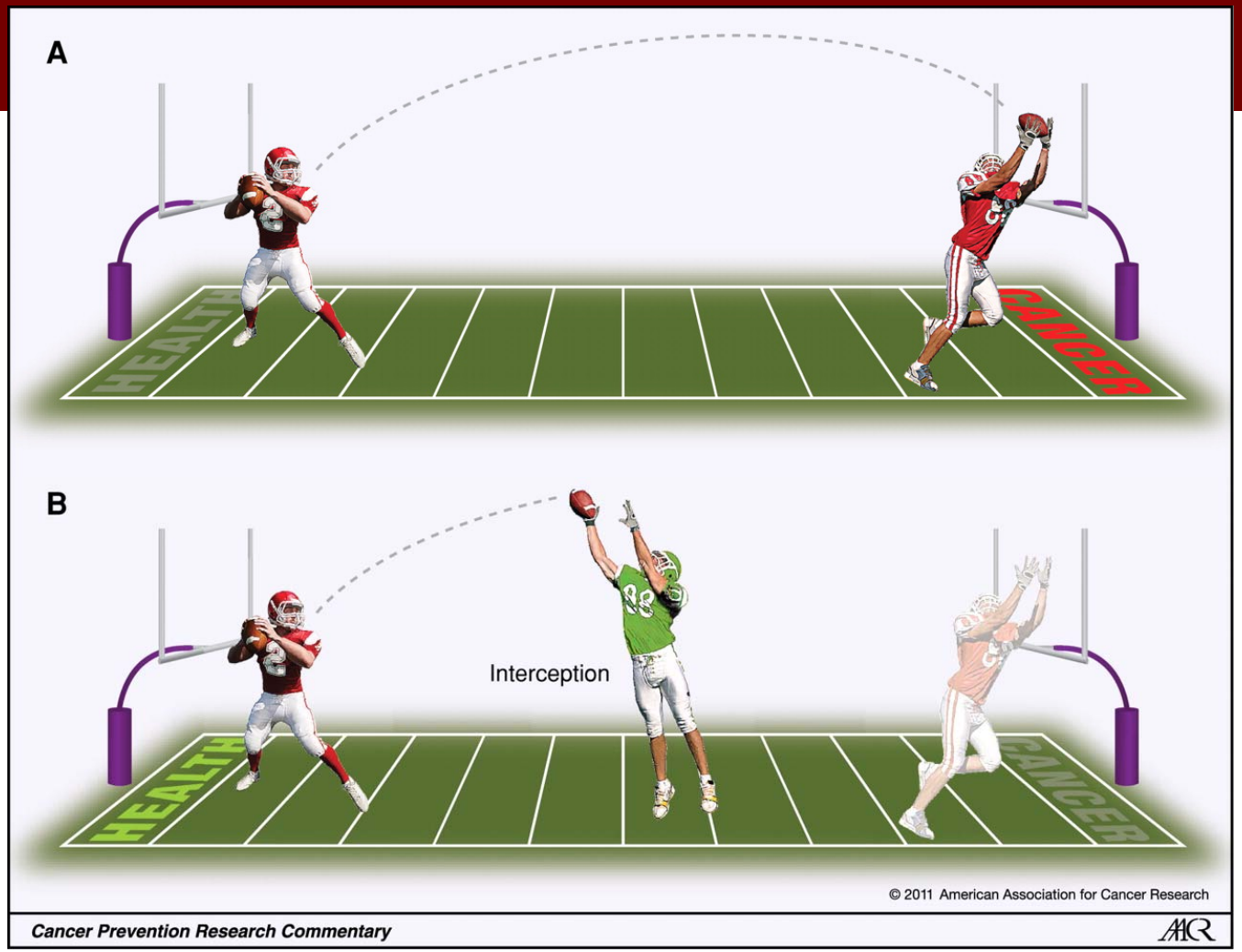
Cancer interception.

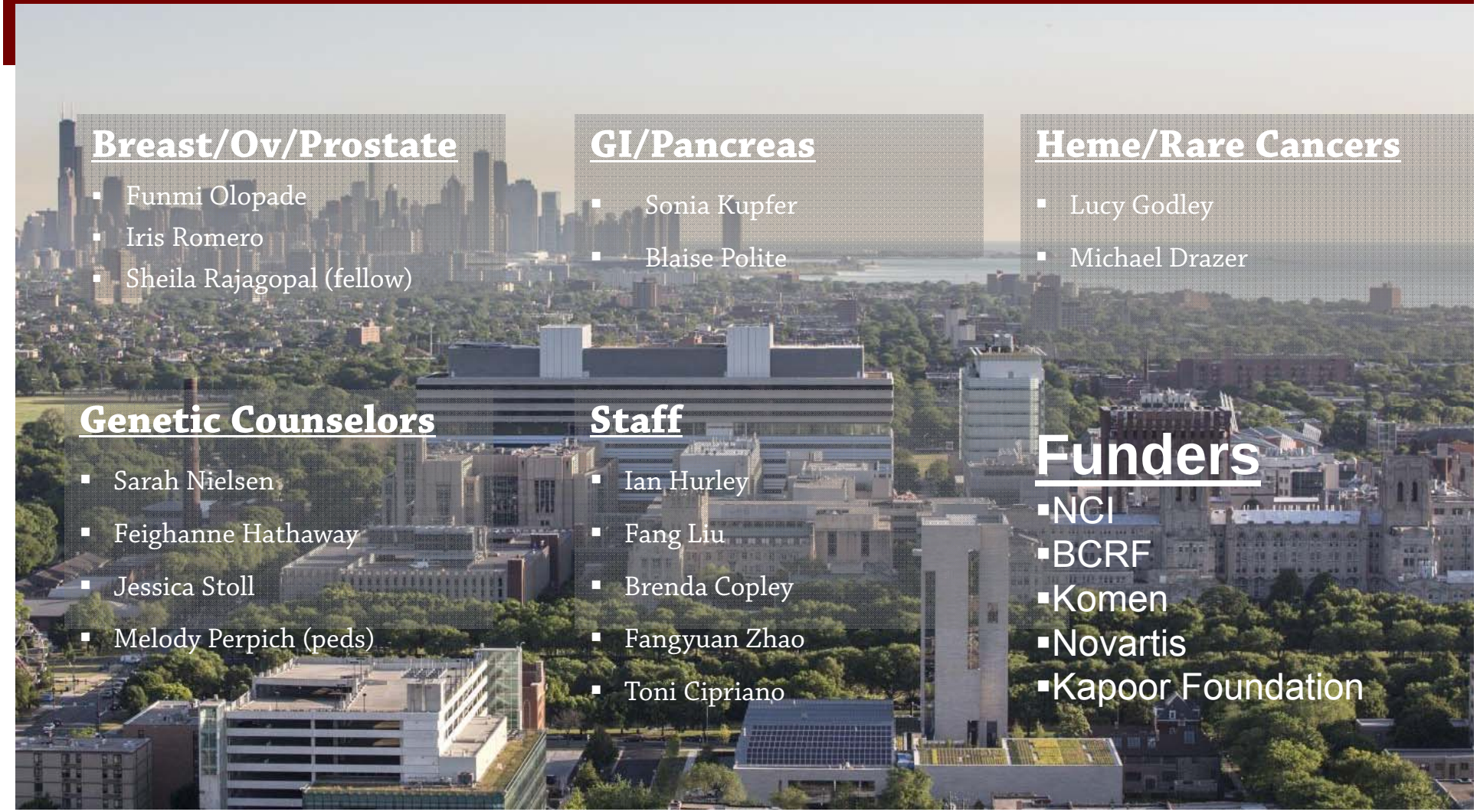


Elizabeth H. Blackburn Cancer Prev Res 2011;4:787-792

Summary

- After decades, genomic testing for population risk stratification happening everywhere
- Many unanswered questions remain
  - When to test?
  - How to test?
  - When to intervene?
  - Whether clinicians and genetic counselors will collaborate to provide quality cancer genetic risk assessment services?
- Future prevention and cancer interception trials will accelerate progress in the field

Thank you



Breast/Ov/Prostate

- Funmi Olopade
- Iris Romero
- Sheila Rajagopal (fellow)

GI/Pancreas

- Sonia Kupfer
- Blaise Polite

Heme/Rare Cancers

- Lucy Godley
- Michael Drazer

Genetic Counselors

- Sarah Nielsen
- Feighanne Hathaway
- Jessica Stoll
- Melody Perpich (peds)

Staff

- Ian Hurley
- Fang Liu
- Brenda Copley
- Fangyuan Zhao
- Toni Cipriano

Funders

- NCI
- BCRF
- Komen
- Novartis
- Kapoor Foundation

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