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Risk Prediction in non-EA Populations

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Center for Clinical Cancer Genetics & Global Health
The University of Chicago

May 6th, 2019

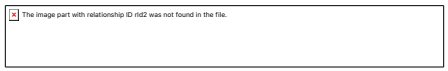
Disclosures

- Co-Founder: CancerIQ

I will discuss implementation of CancerIQ for POC testing

Overview

- Introduction
- Historical perspectives
- Panel Testing for Inherited Cancers
- Integrating germline and somatic testing
- Population Risk Stratification for cancer interception
- Future Directions



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Genetics in Oncology Care

Harvey M. Golomb, MD
Section Chief &
Program Director

Janet D Rowley, MD
1925-2013

The Original Dream Team circa 1997
ASCO Cancer Genetics Taskforce

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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.

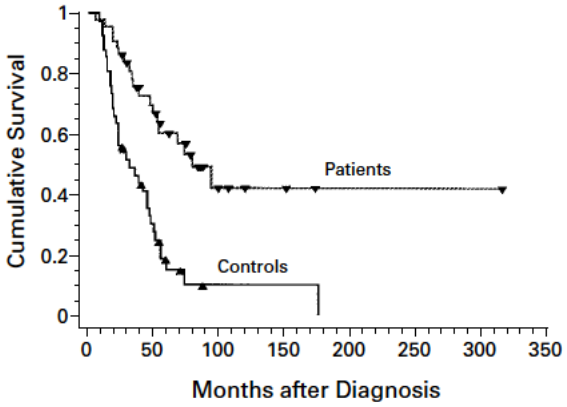

Figure 1. Actuarial Survival among 43 Patients with Advanced-Stage Ovarian Cancer and Germ-Line *BRCA1* Mutations, as Compared with Matched Controls without Such Mutations.
P<0.001 by the log-rank test. The triangles and inverted triangles indicate the durations of follow-up among surviving patients.

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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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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Heterogeneity in Breast Cancer

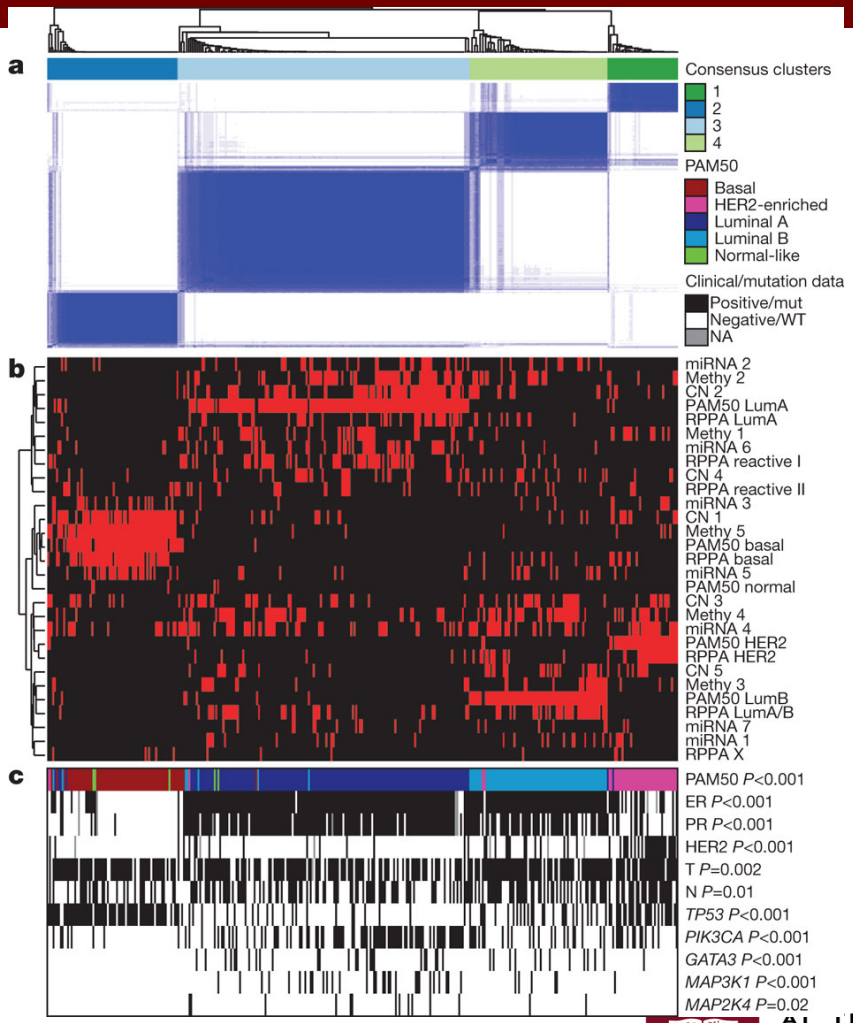
Are there population differences in phenotypes?

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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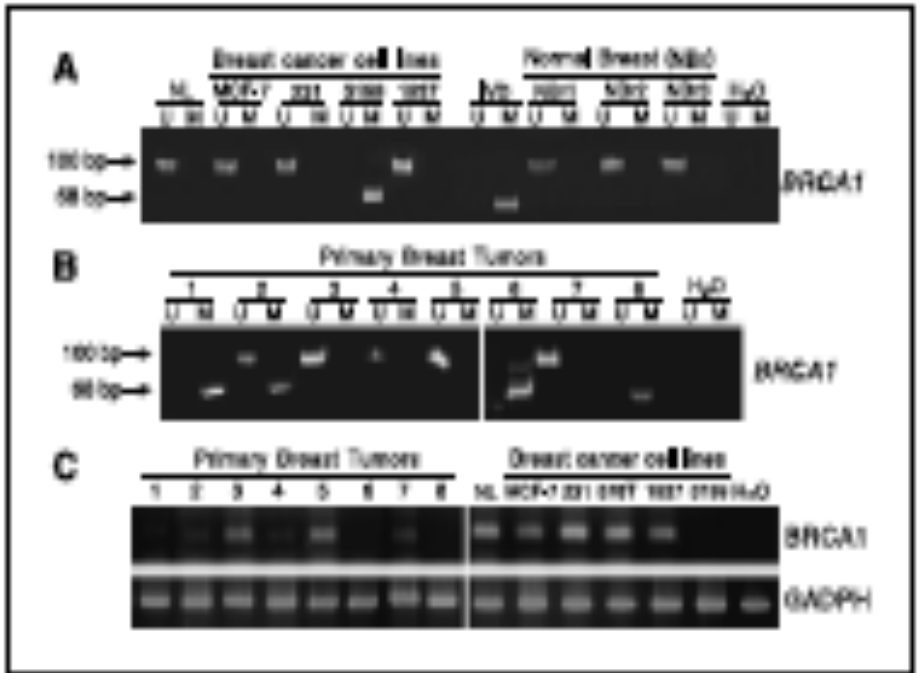
Research Article

BRCA1 Promoter Methylation in Sporadic Breast Cancer Is Associated with Reduced *BRCA1* Copy Number and Chromosome 17 Aneusomy

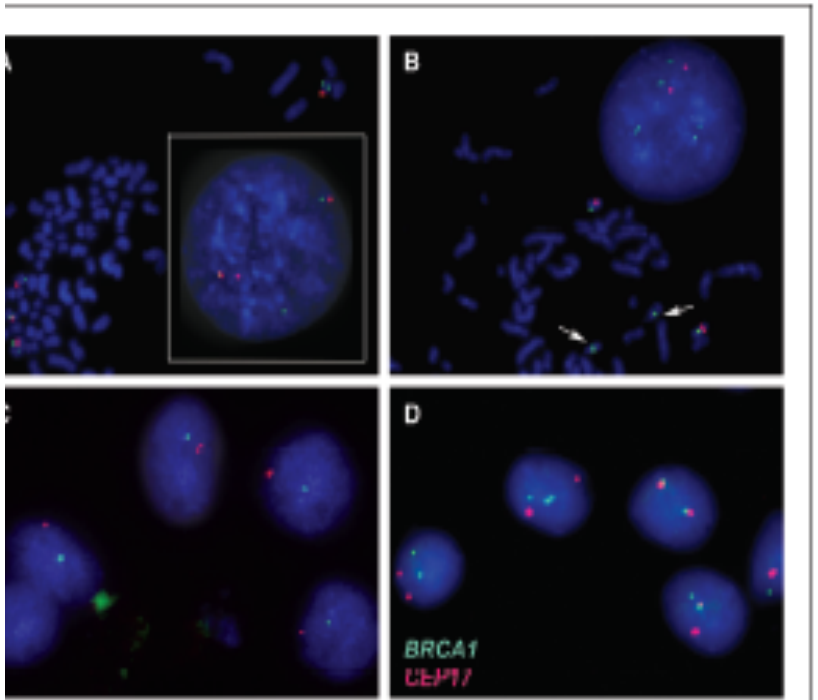
Minjie Wei,[1] Tatyana A. Grushko,[1] James Dignam,[2] Fitsum Hagos,[1] Rita Nanda,[1] Lise Sveen,[1] Jinhua Xu,[1] James Fackenthal,[1] Maria Tretiakova,[3] Soma Das,[4] and Olufunmilayo I. Olopade[1]

[1]Center for Clinical Cancer Genetics, Department of Medicine and Departments of [2]Health Studies, [3]Pathology, and [4]Human Genetics, University of Chicago, Chicago, Illinois

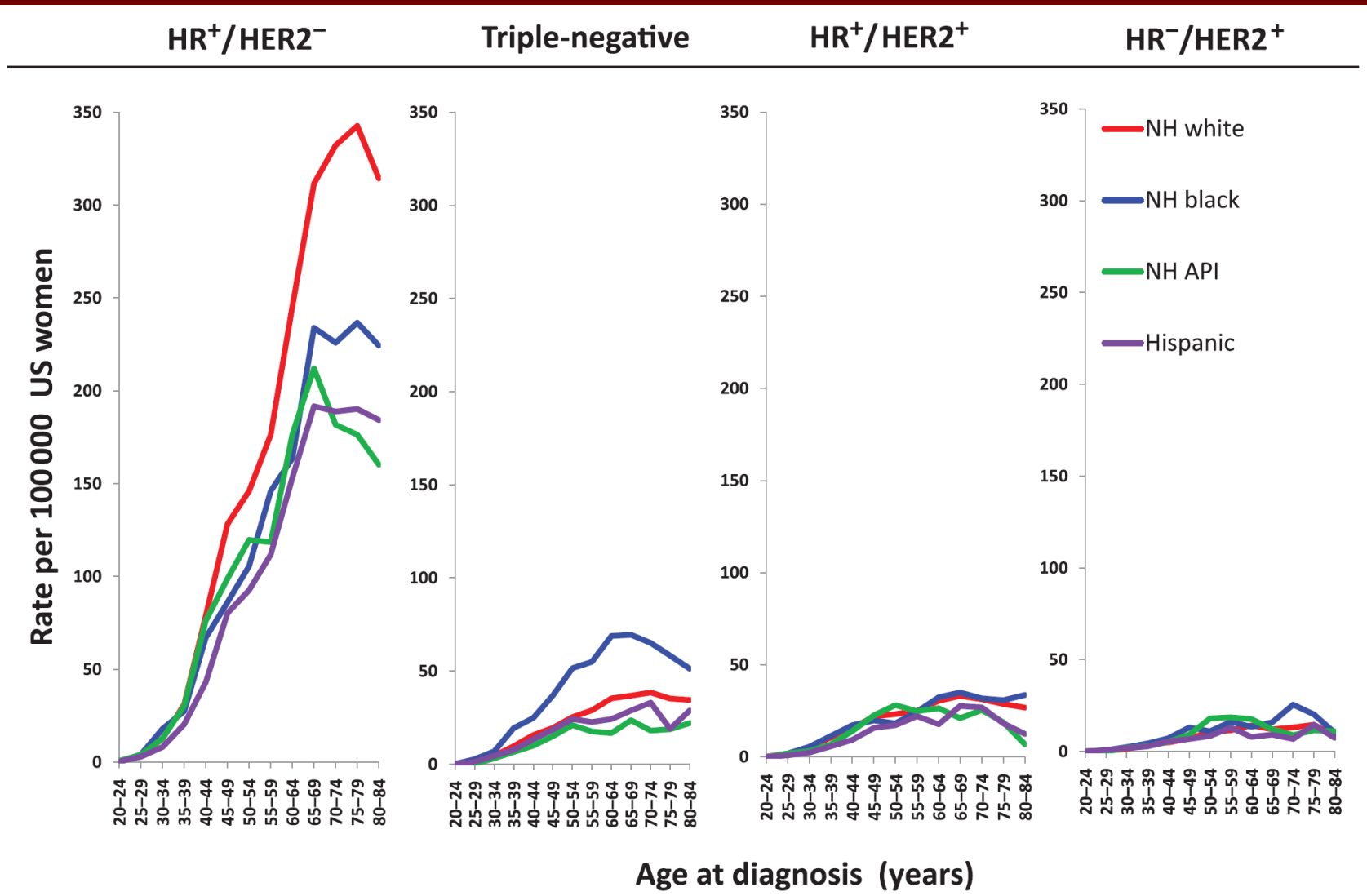
Methylation Assay & Expression



Fluorescent *in situ* Hybridization



Subtype-specific breast cancer incidence



Howlader et al. JNCI 2014

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Heterogeneity in Breast Cancer

Are there population differences in genotypes?

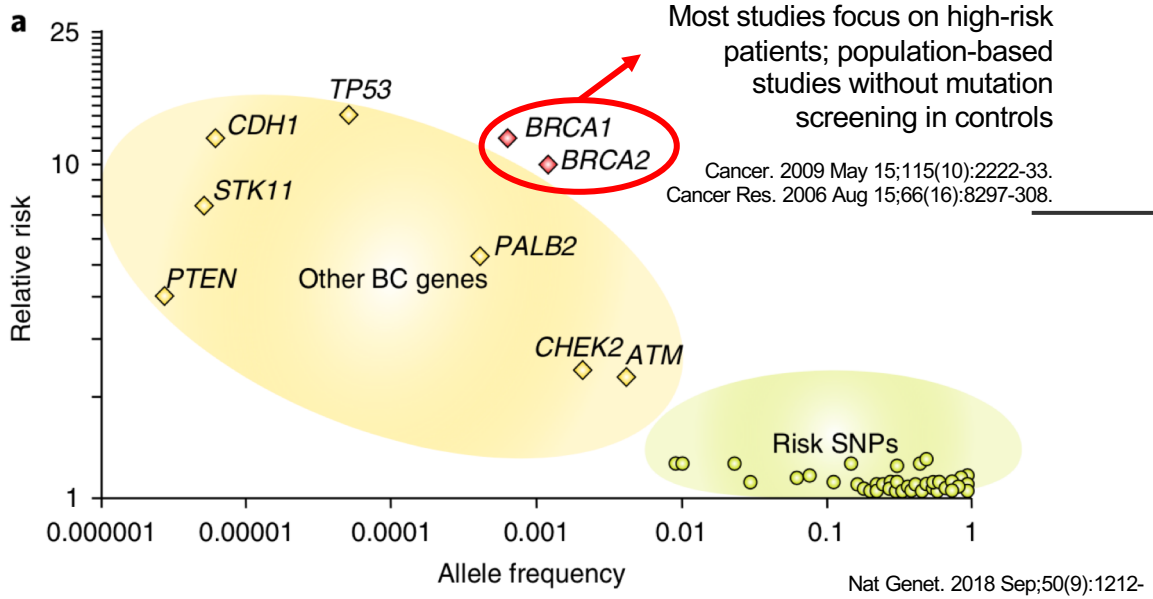
Why Genomic Testing?

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

Breast Cancer Susceptibility Genes



Most studies focus on high-risk patients; population-based studies without mutation screening in controls

Cancer. 2009 May 15;115(10):2222-33.
Cancer Res. 2006 Aug 15;66(16):8297-308.

Nat Genet. 2018 Sep;50(9):1212-1218.

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Nigerian Breast Cancer Study (NBCS) & African Breast Cancer Study (ABCS)

Selected epidemiologic risk factors in the NBCS

Risk factor	Ibadan 1998-2017		Lagos 2014-2017
	Case n=2487	Control n=2313	Case n=441
Age, mean±SD	48.1±11.8	42.5±13.0	49.2±12.7
Family history of breast cancer	4.5%	2.5%	5.4%
Age at menarche, mean±SD	15.3±2.1	15.3±2.2	15.1±1.6
Parity, mean±SD	4.2±2.1	4.1±2,3	3.1±1.7
Age at 1st live birth, mean±SD	23.5±4.9	23.1±4.6	25.6±4.9
Hormonal contraceptive use	46.8%	53.2%	27.9%
BMI in kg/m^2, mean±SD	26.0±5.6	26.3±5.7	27.1±4.0
Height in cm, mean±SD	161.6±7.3	158.9±6.5	161.6±7.2
Benign breast disease	7.8%	6.7%	3.0%
Alcohol consumption	8.8%	4.9%	12.2%

NBCS -- a case-control study of breast cancer in Ibadan, Nigeria, piloted in 1998 and extended to Lagos, Nigeria in 2014. ABCS – piloted in 2011, the standardized NBCS concept and design were extended to Cameroon (Yaounde) and Uganda (Kampala) sites.

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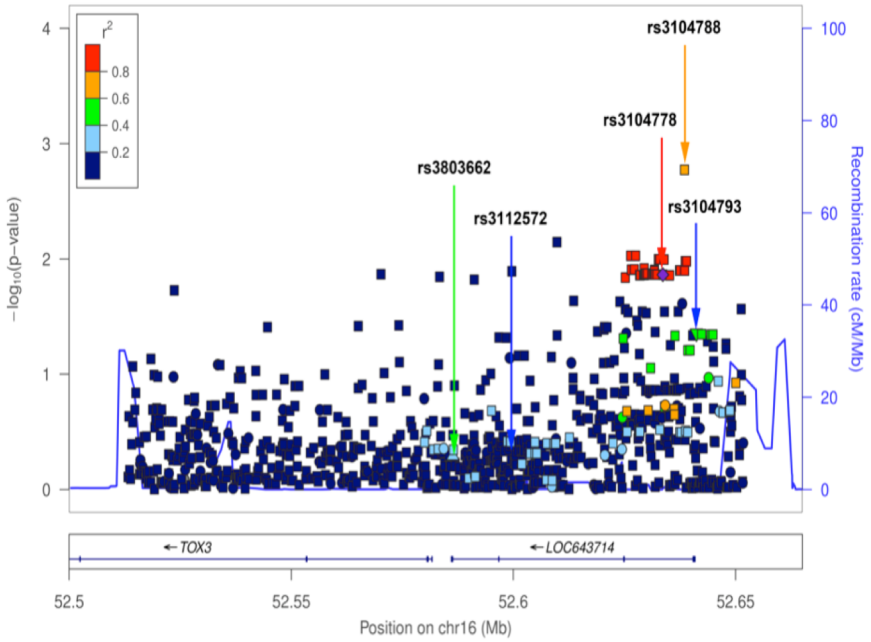
Reproducibility of Reported Breast Cancer GWAS

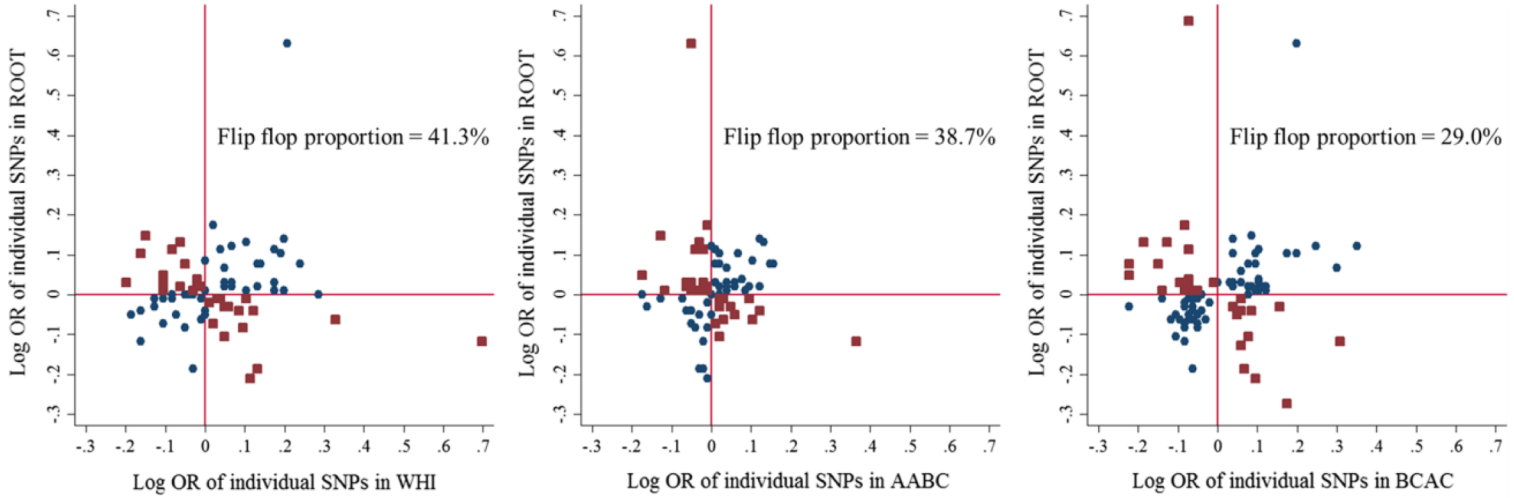


Replication is essential to control false positives and test generalizability of GWAS, especially in trans-ethnic populations.

Validation of GWAS-index variants found in Whites and Asians -- not quite successful. Fine-mapping identified better markers.

Carcinogenesis. 2012 Apr;33(4):835-40.
Carcinogenesis. 2013 Jul;34(7):1520-8.

Flip-flop Phenomenon is Common



Polygenic risk scores (PRSs) constructed from the published odds ratios (ORs) on GWAS-index variants in Whites and Asians did not provide a comparable degree of risk stratification for Blacks.

Breast Cancer Res Treat. 2018 Apr;168(3):703-712.

Breast Cancer GWAS in Women of African Ancestry

Root
1,657 cases
2,029 controls

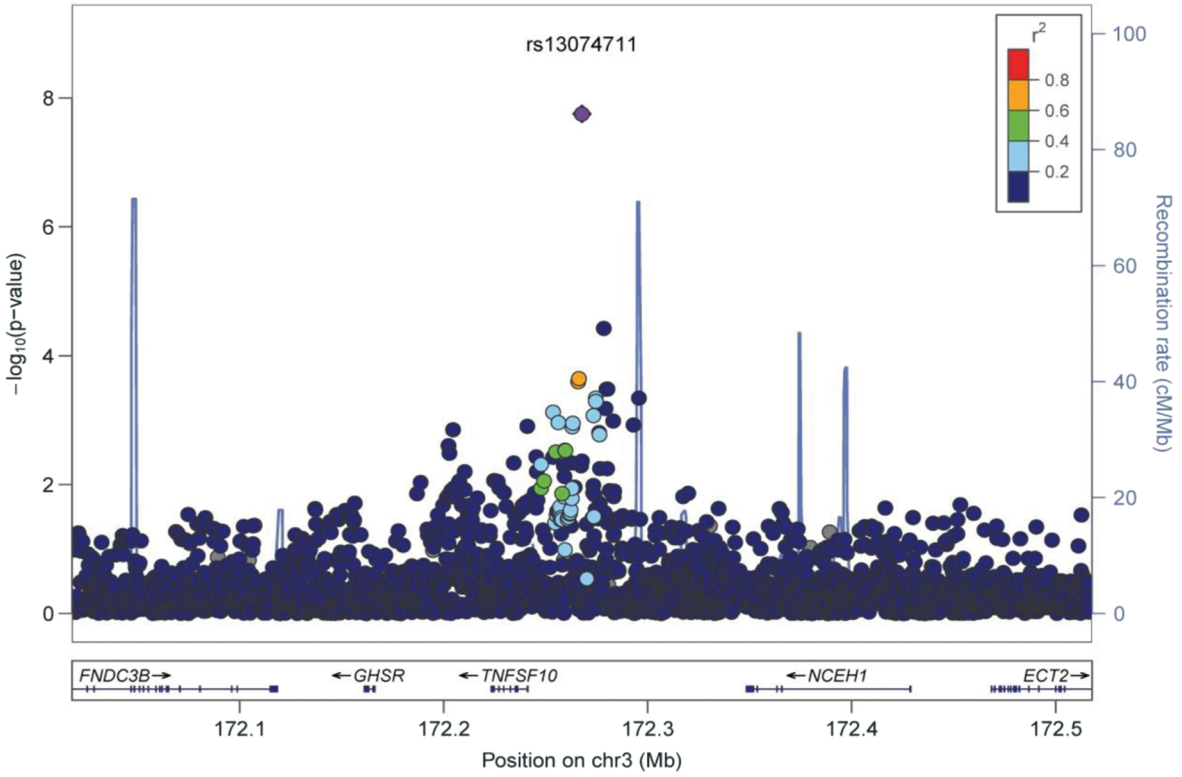
AABC
3,016 cases
2,745 controls

Meta-analysis

Top 18,376 SNPs for replication

AMBER
1,984 cases
2,939 controls

TNFSF10 --Tumor Necrosis Factor Ligand Superfamily Member 10



Hum Mol Genet. 2016 Nov 1;25(21):4835-4846.

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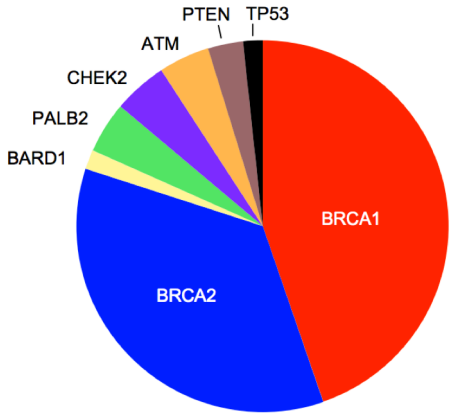
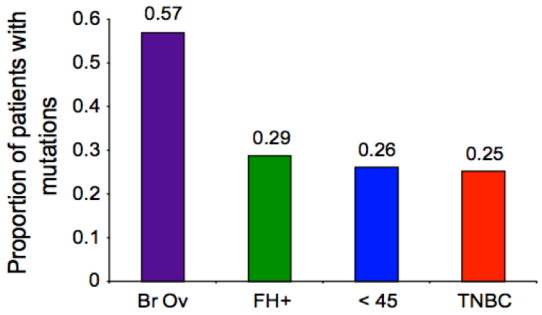
Genetic Testing in African American Patients with Breast Cancer at UChicago

- 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.

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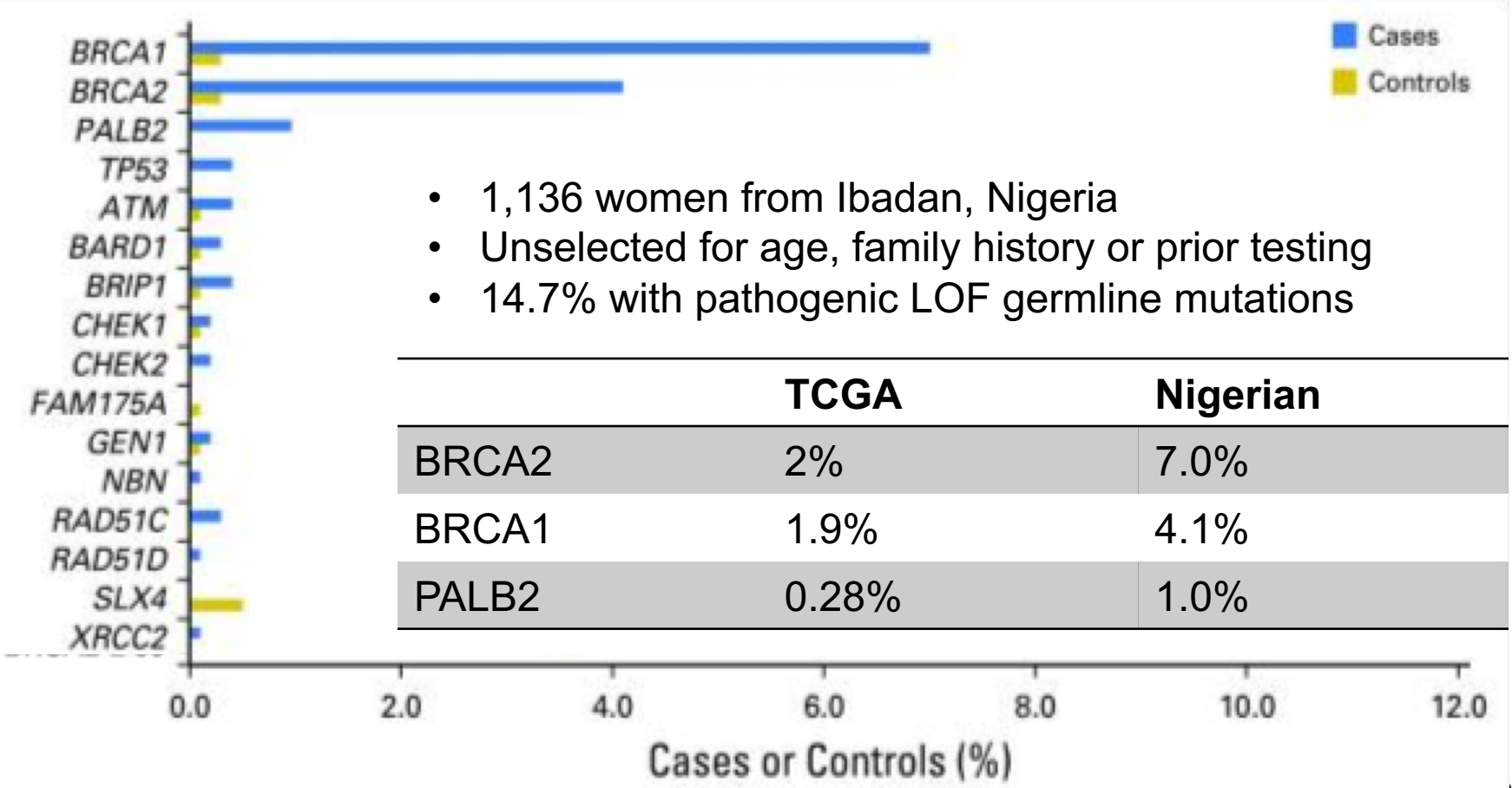
High rates of germline mutations in Nigerian breast cancer patients -- BROCA Panel and Tumor NGS



- 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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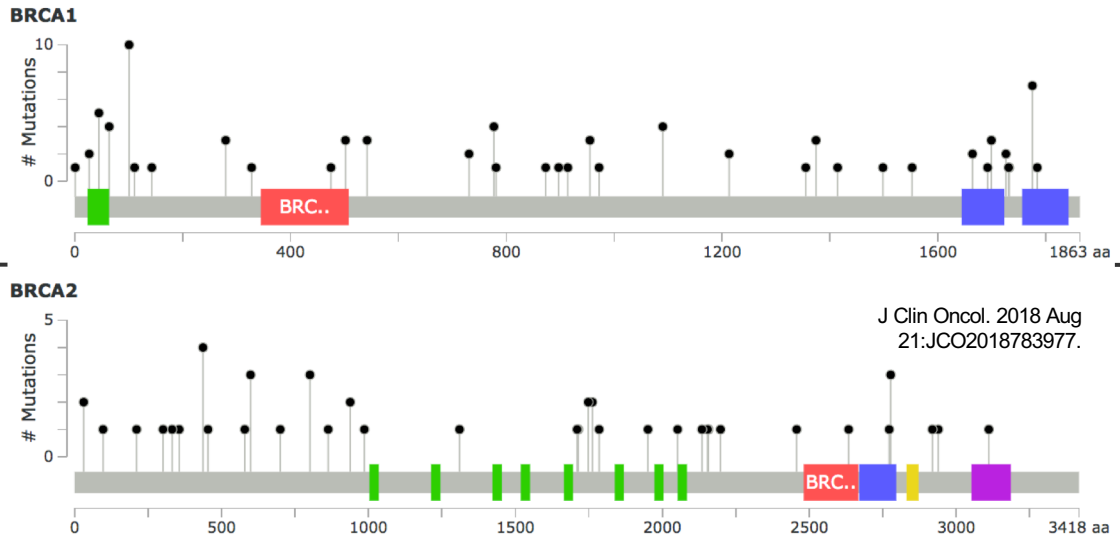
Highly Heterogeneous *BRCA1/2* Mutations in Nigerians



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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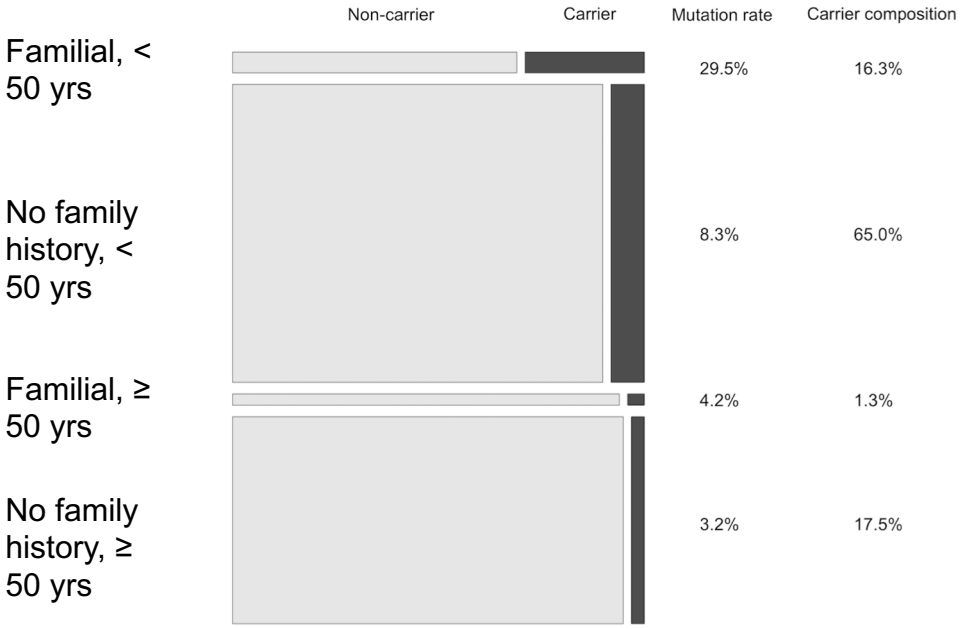
BRCA Mutations Stratified by Family History and Age in NBCS



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

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West African Breast Cancer Study

3-Way Partnership with Nigeria-Chicago-Boston

Can we use mutation signatures to decipher racial/ethnic disparities in breast cancer?

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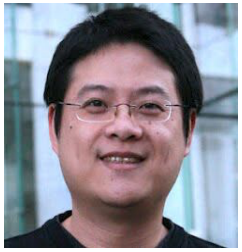
West African Breast Cancer Study

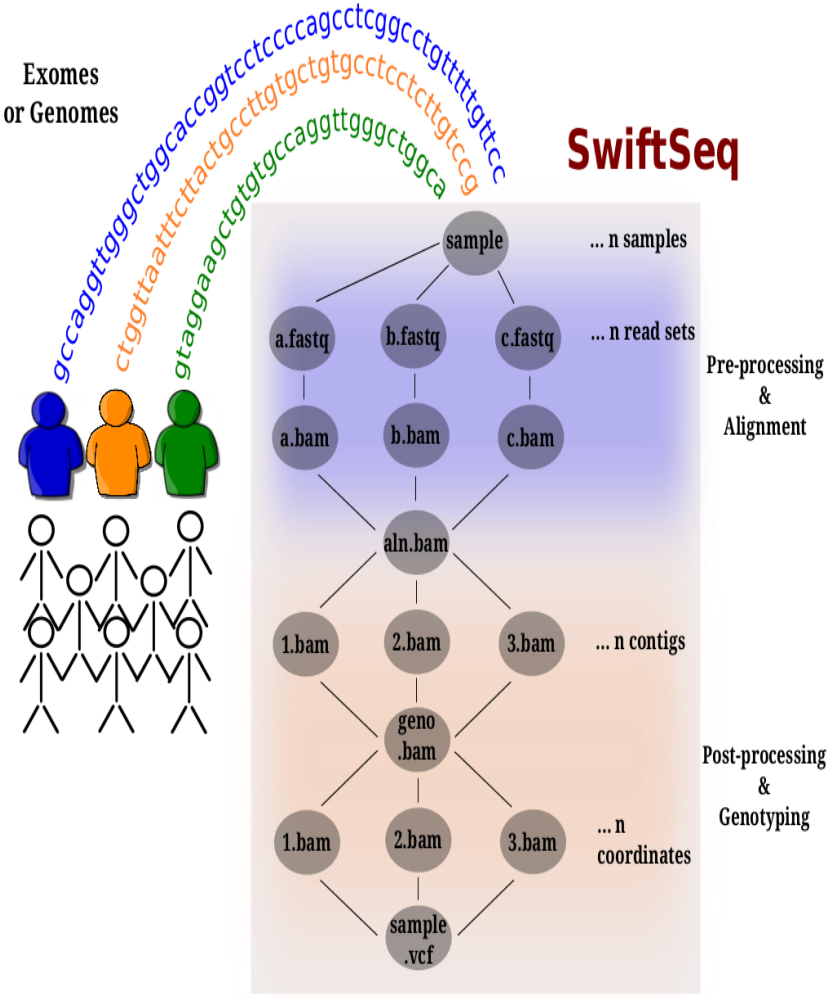
Data and comparisons

Jason J Pitt



Yonglan Zheng

Toshio F Yoshimatsu



Exomes

129 Nigerian TN pairs

1,035 TN pairs from TCGA

- 751 White
- 171 Black
- 114 Other

Genomes

98 Nigerian TN pairs

84 TN pairs from TCGA

- 46 White
- 30 Black
- 8 Other

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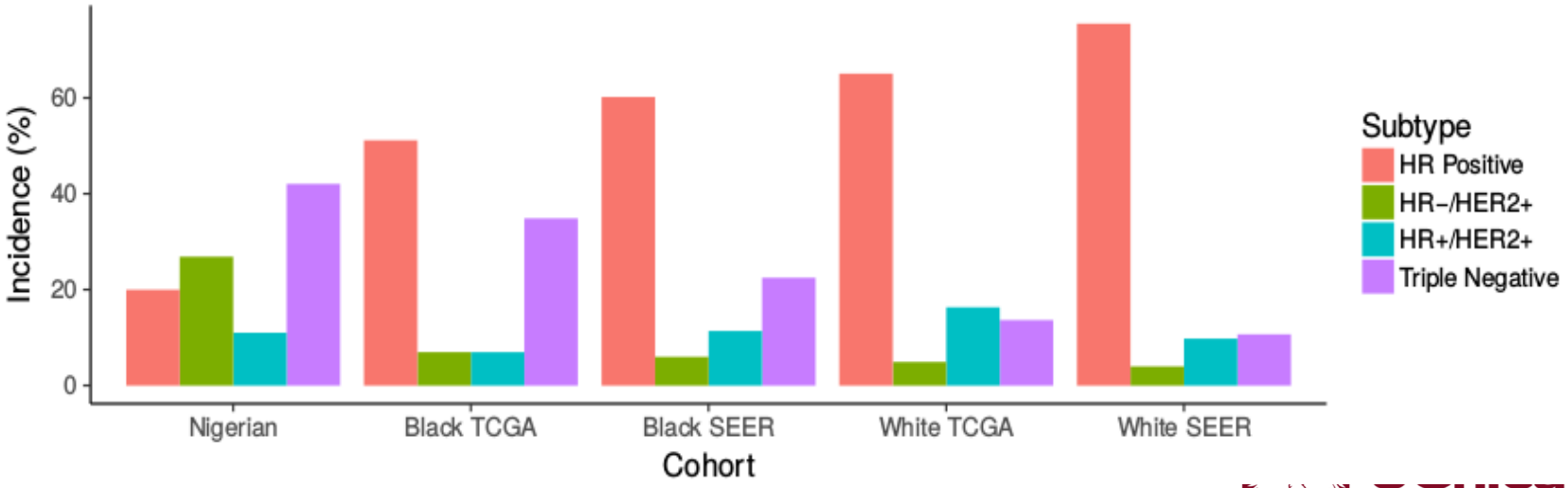
Subtype Incidence Rates
Nigerian cohort, TCGA, SEER comparison

Immunohistochemistry (IHC) for ER, PR, and HER2

Performed by clinical pathologist in Nigeria & laboratory pathologist at UChicago

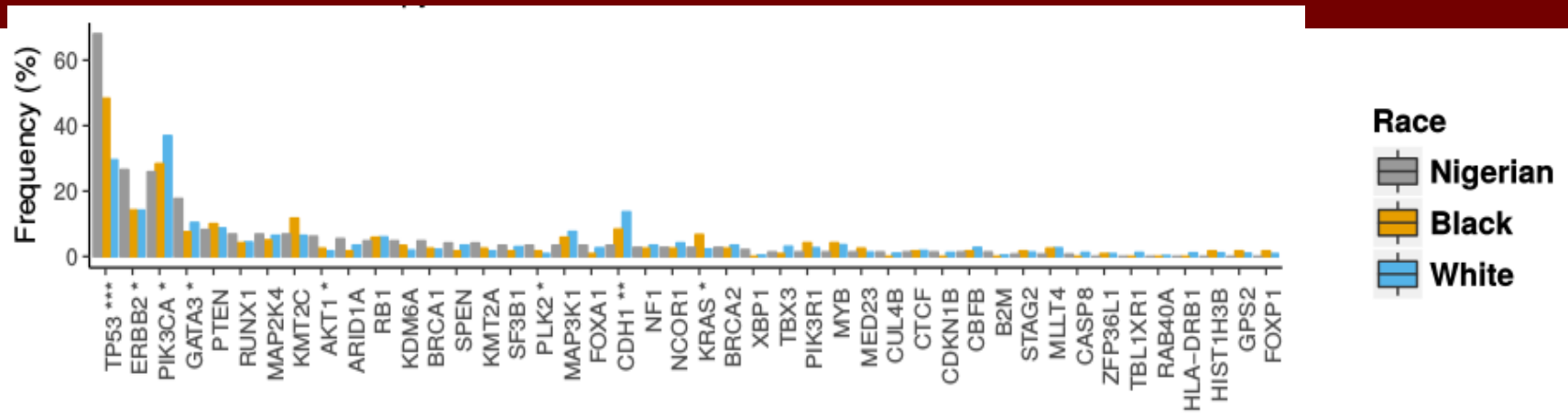
~80% concordance between ER and PR calls

~65-70% concordance between HER2+ calls
- Used copy number



Mutation Frequency Disparities

Mutation status by ancestry



Gene	Subtype	Pval	Qval	% mut White	% mut African-AA	% mut Nigerian
CDH1	HR+/HER2-	0.0031	0.025	20.9	12.0	0
TP53	HR+/HER2-	0.0026	0.025	18.1	22.9	48.1
GATA3	HR+/HER2-	0.0048	0.025	10.0	16.9	25.9
PIK3CA	HR+/HER2-	0.0083	0.033	42.0	26.5	29.6
TP53	HER2+	0.013	0.042	37.3	48.0	63.0

Nat Commun. 2018 Oct 16;9(1):4181.

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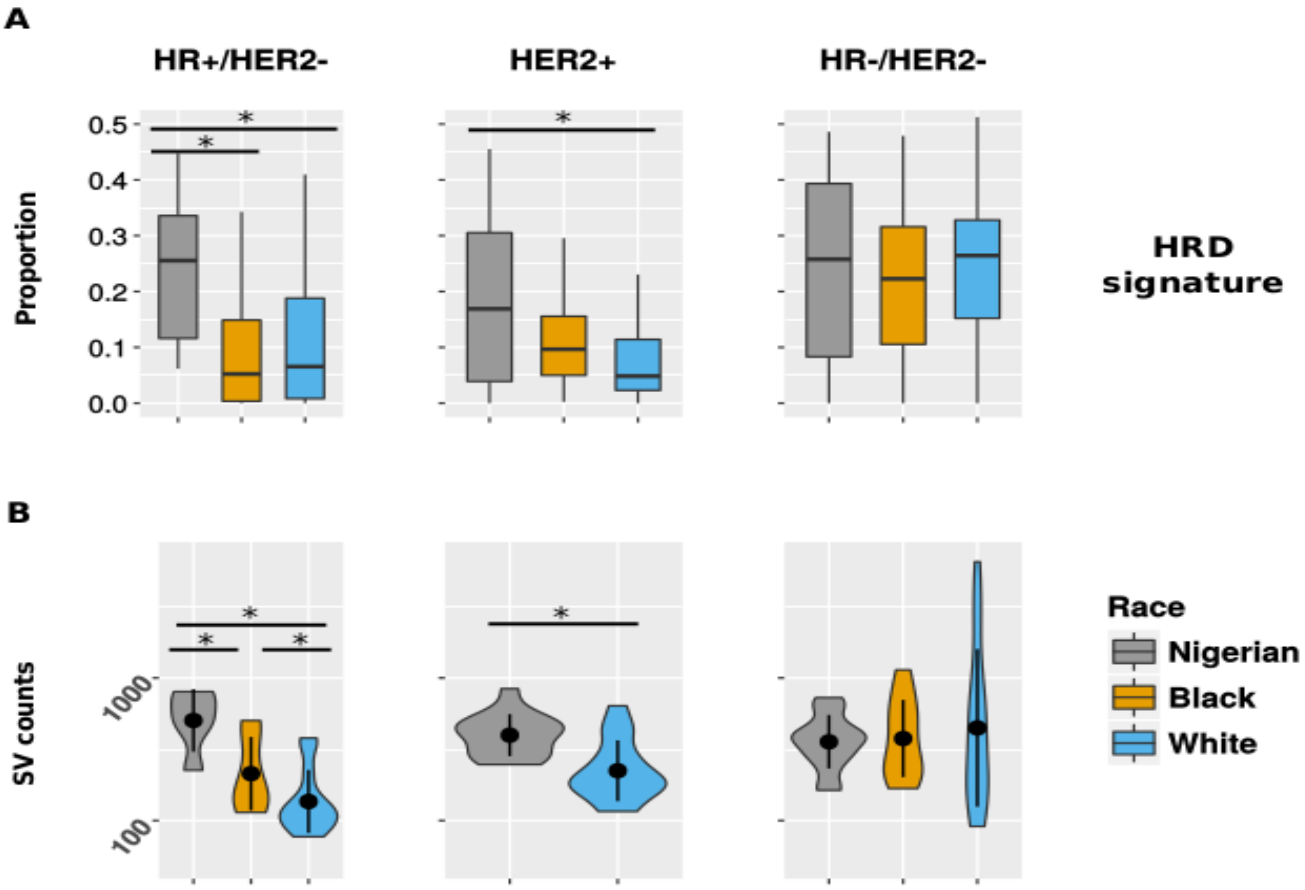
Mutation Signature Disparities

HRD signature – exomes & SVs



HR+/HER2- effect Remains when correcting for...

- *TP53*, *CHD1*, & *PIK3CA* status
- Histology
- Age

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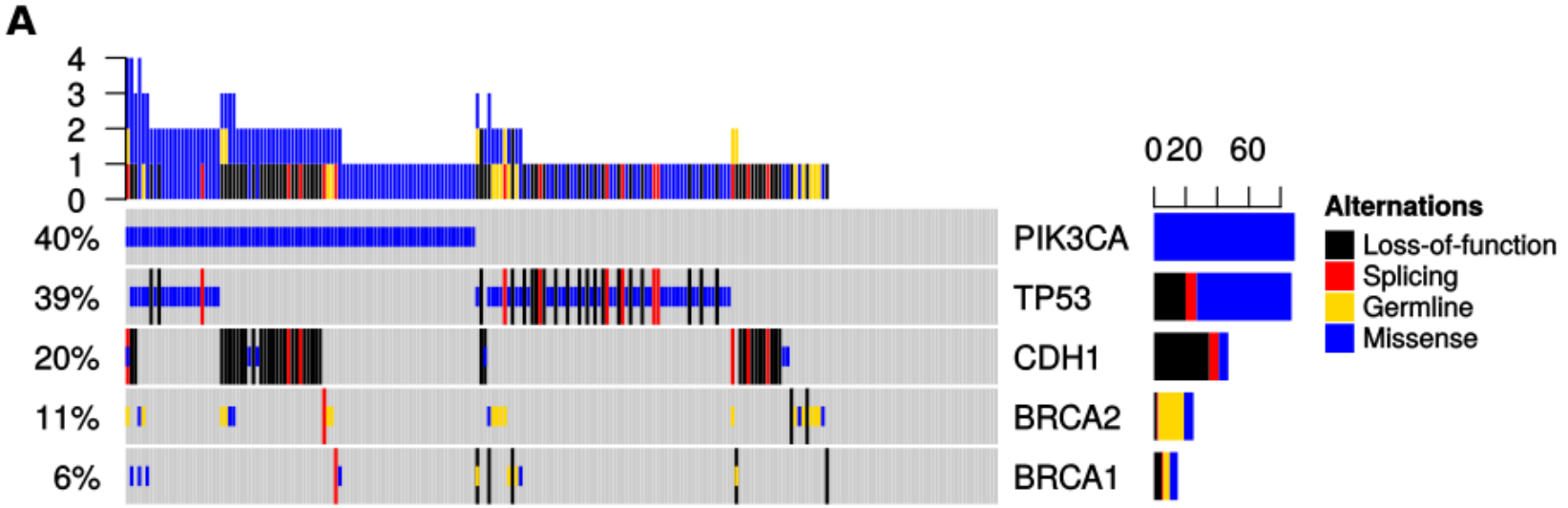
APOBEC & HRD Signature Balance?

HR+/HER2- samples

- Racial mutation rate differences in *TP53*, *CDH1*, & *PIK3CA*
- Mutations in these genes were strongly associated with APOBEC and HRD signatures
  - *BRCA1/2* mutations associated with increased HRD
- Nigerians have increased HRD
- Nigerian and Black cohorts have lower APOBEC C>T than Whites



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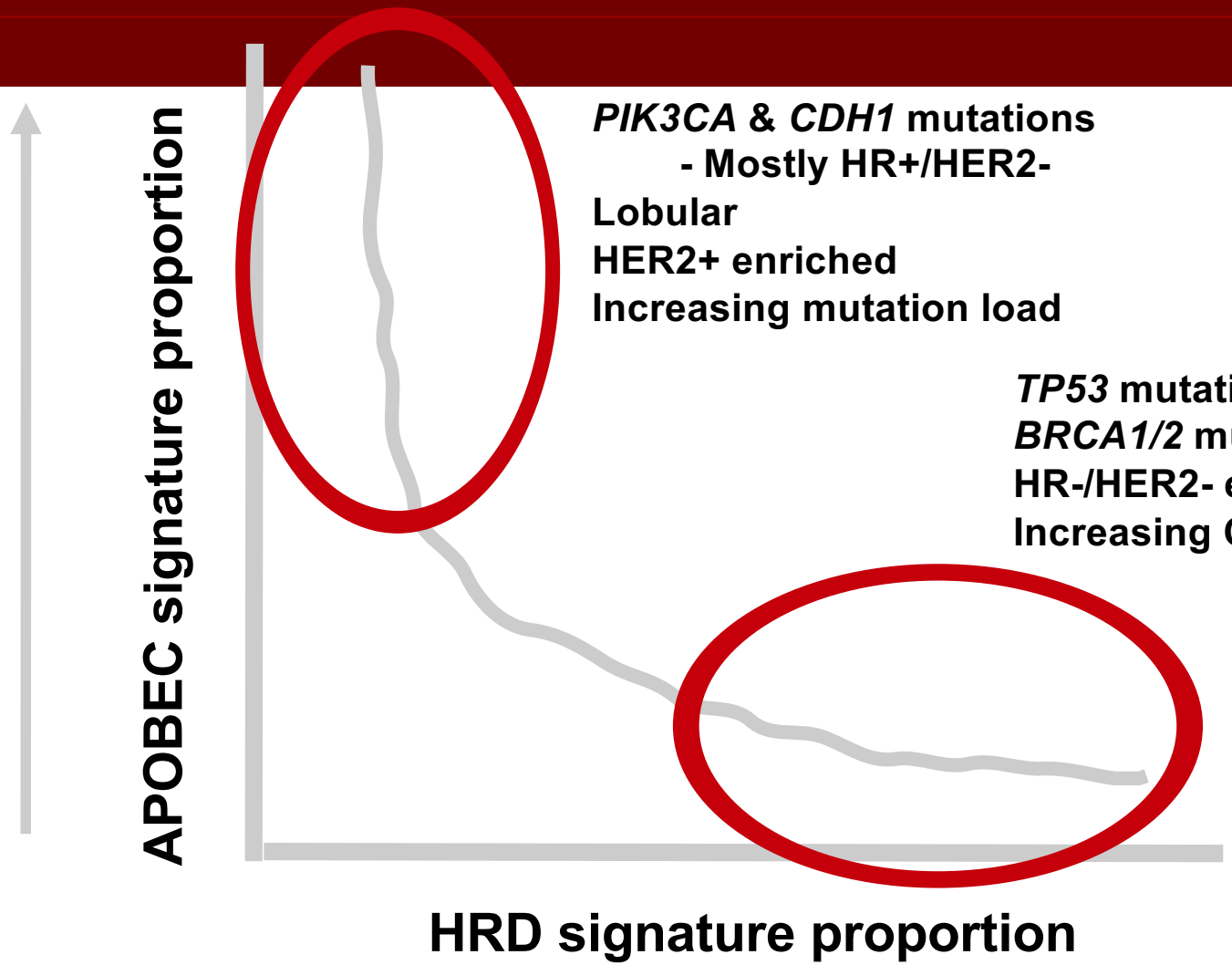
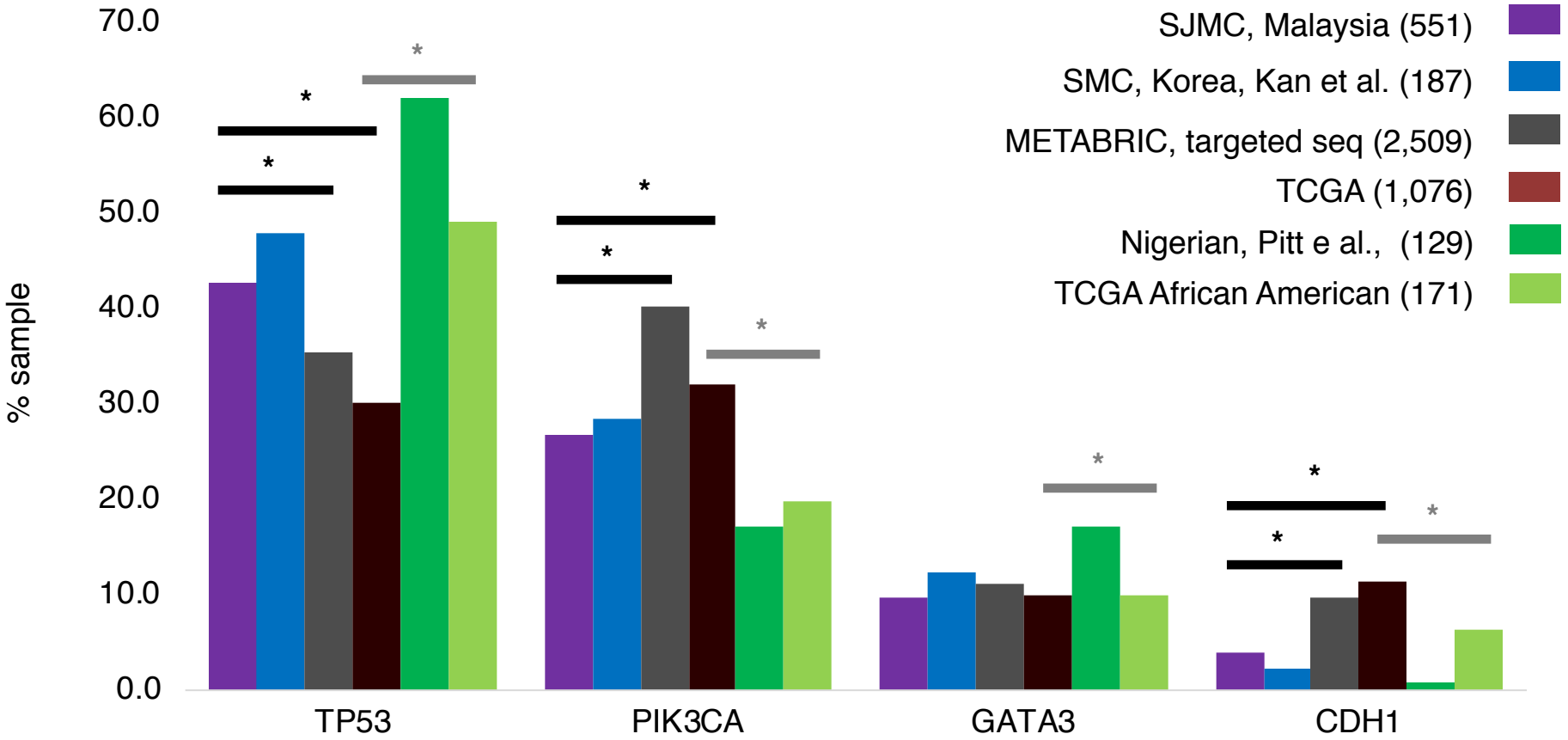
Overview of Findings



Top Breast Cancer Genes Across 6 Studies



**P<=0.05 Fisher's exact test, SJMC vs METABRIC or TCGA*

*Pitt et al 2018: *P<=0.05 Fisher's exact test, Nigeria vs TCGA non-AA vs TCGA AA*

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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.

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

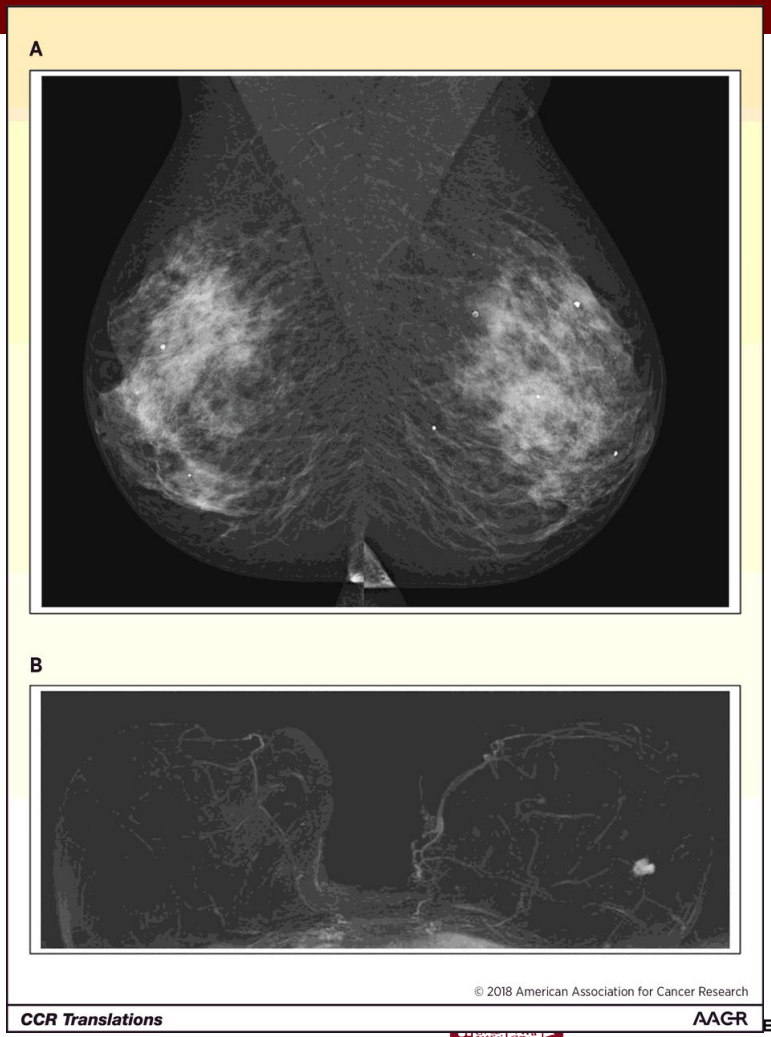
Clinical Cancer Research

CCR Translations

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

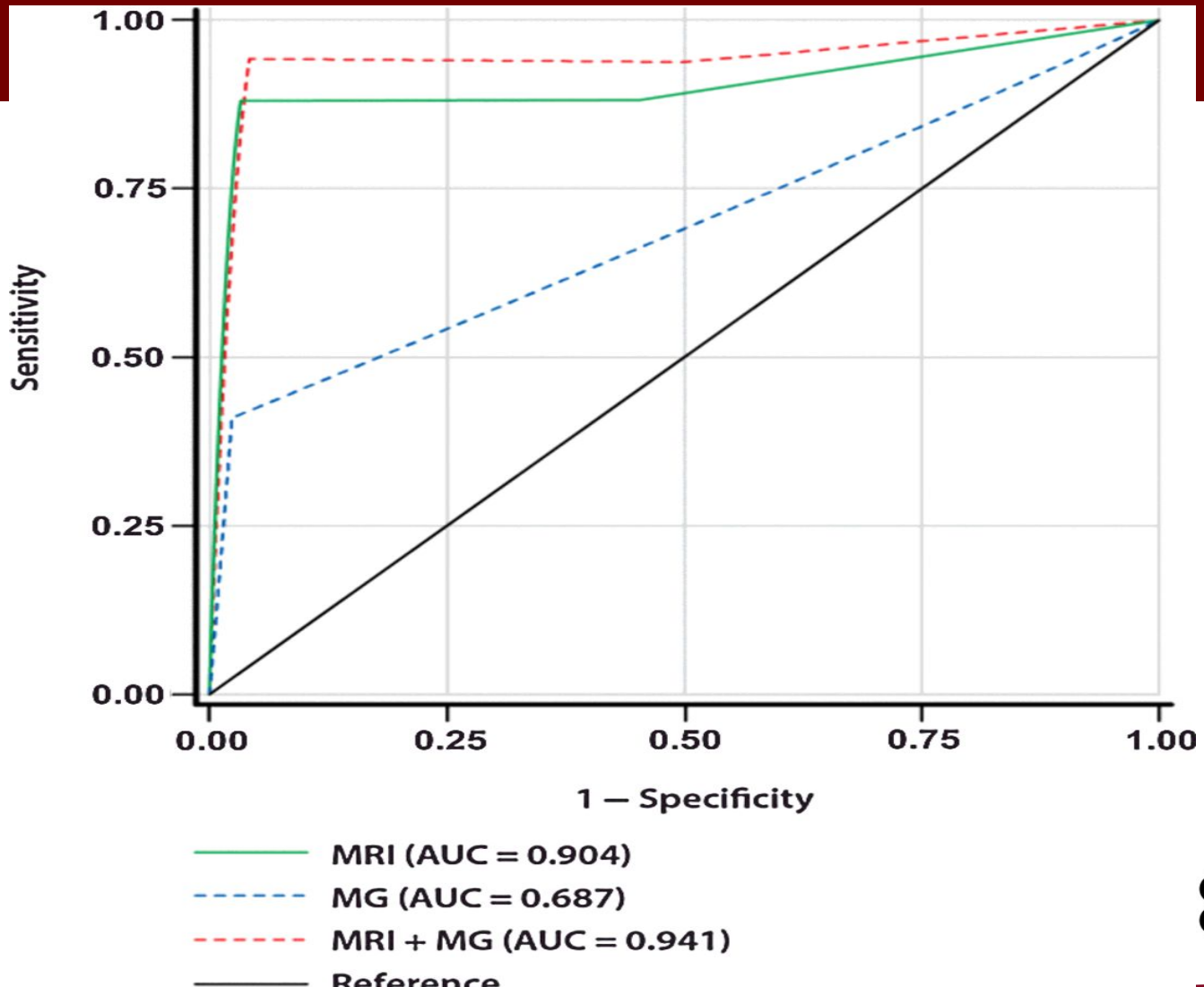
Christiane K. Kuhl and Simone Schrading

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

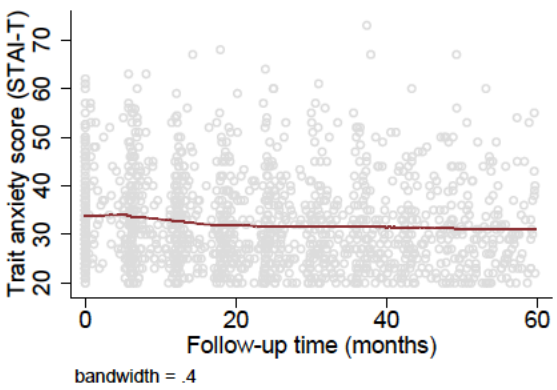
ROC curves for MRI and MG. The difference of the diagnostic performance employing ROC analysis between MRI (AUC = 0.904) and MG + MRI (AUC = 0.941) was not statistically significant (P = 0.53).

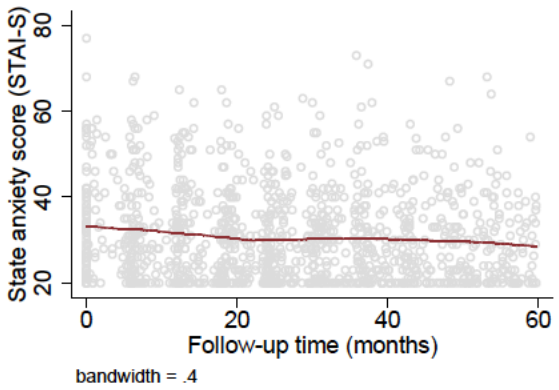


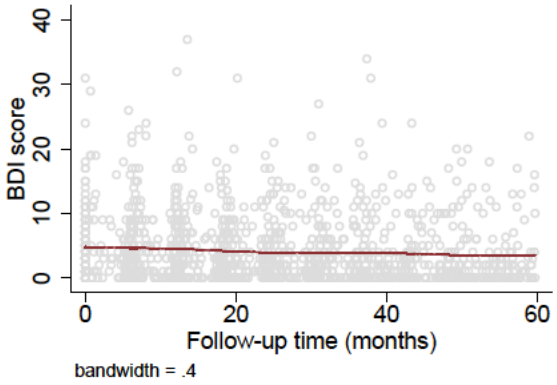
Rodrigo Santa Cruz Guindalini et al. Clin Cancer Res 2019;25:1786-1794

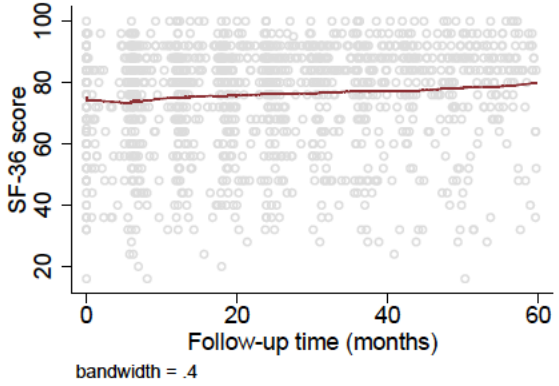
Clinical Cancer Research
AACR American Association for Cancer Research

Psychosocial Outcomes









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Cancer Outcomes

- Study Closed to Accrual in December 31st 2016
  - Median follow up 3.6 months
- **Seventeen cancers diagnosed**
  - Four DCIS and 13 early stage breast cancers were diagnosed; all but one screen detected
  - 15 occurred in subjects with pathogenic mutations(11 *BRCA1*, 3 *BRCA2*, 1 *CDH1*)
  - Mean size 6.1 mm
  - No lymph node involvement
  - Majority of mutation carriers healthy
  - Recall rate low

Guindalini et al. Clinical Cancer Research 2018

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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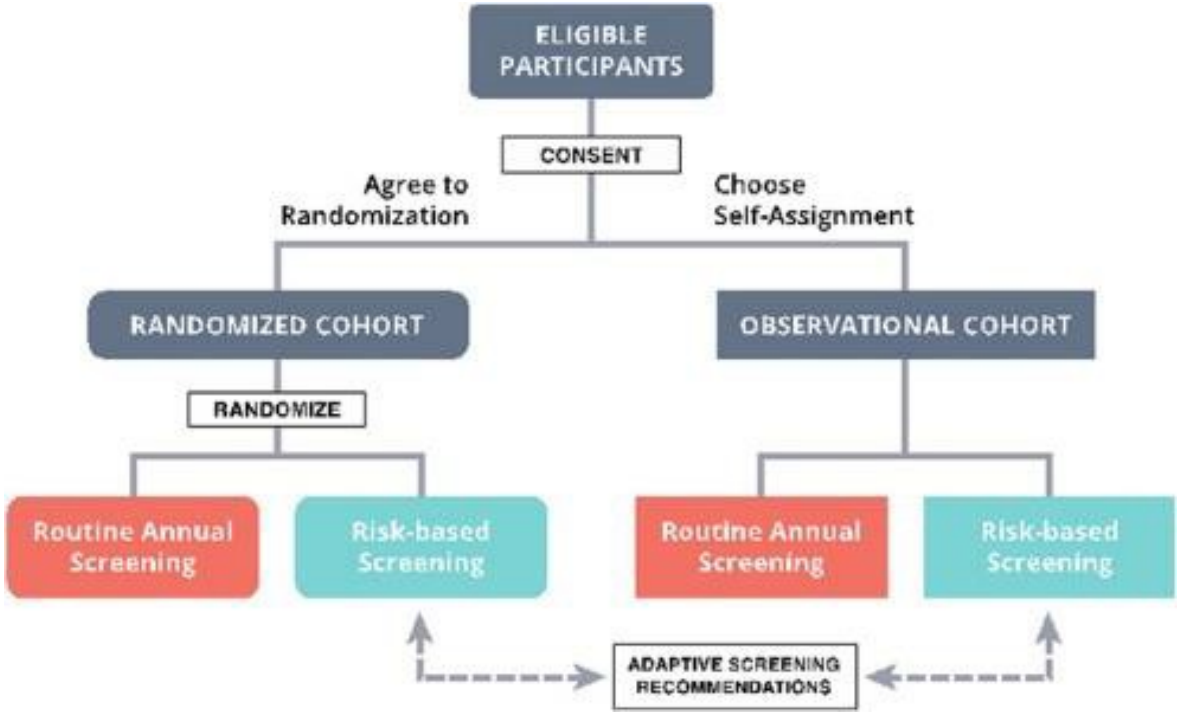
WISDOM study design

- Endpoint: Comparative rate of stage IIb breast cancer diagnosed in annual vs. risk based screening arms



Streamlined Point of Care Testing

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

Point B: Genetic Specialists in Every practice

CancerIQ Inc

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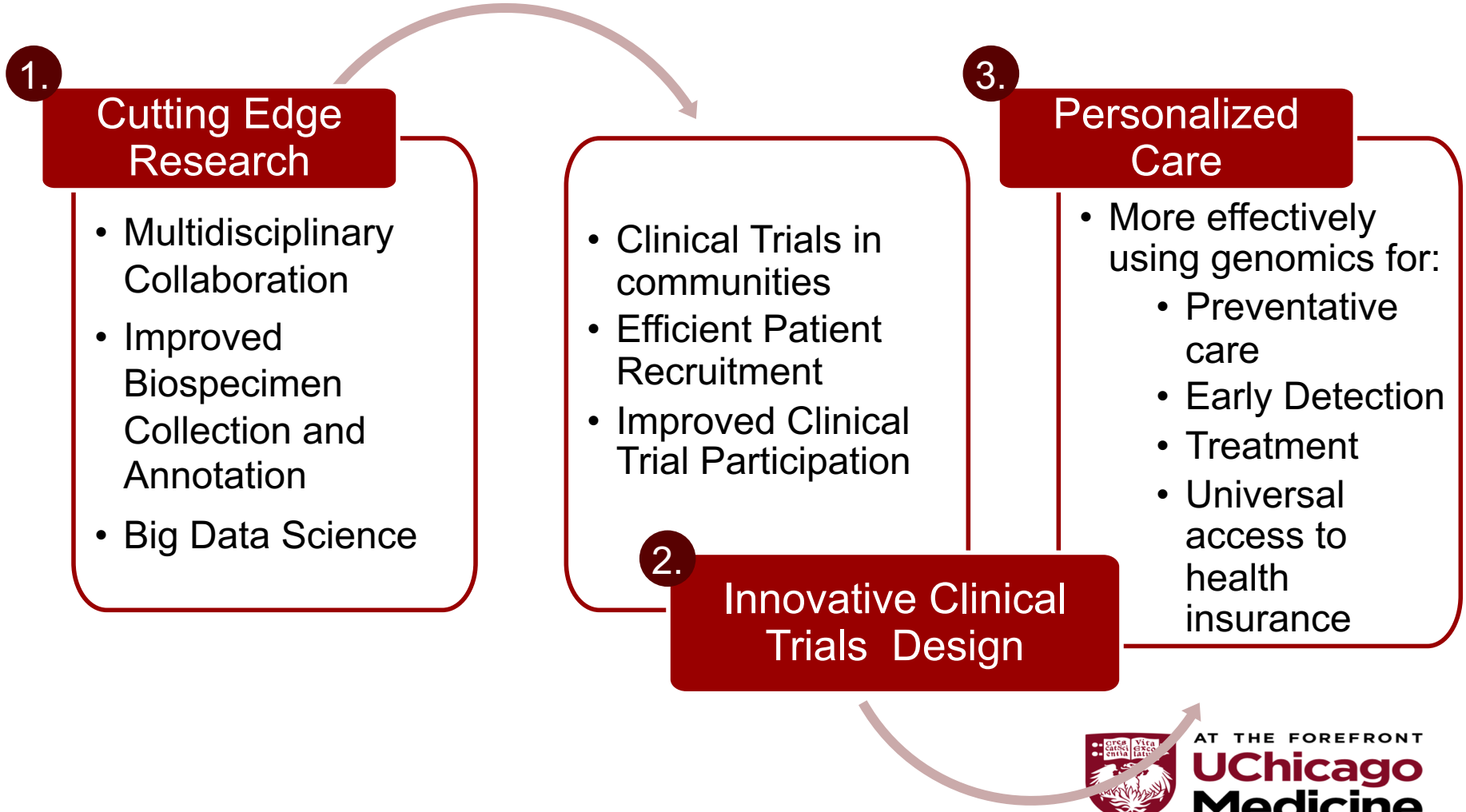
Clinical Trials for "All of Us"

Accelerating progress to promote health and well being in all populations



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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

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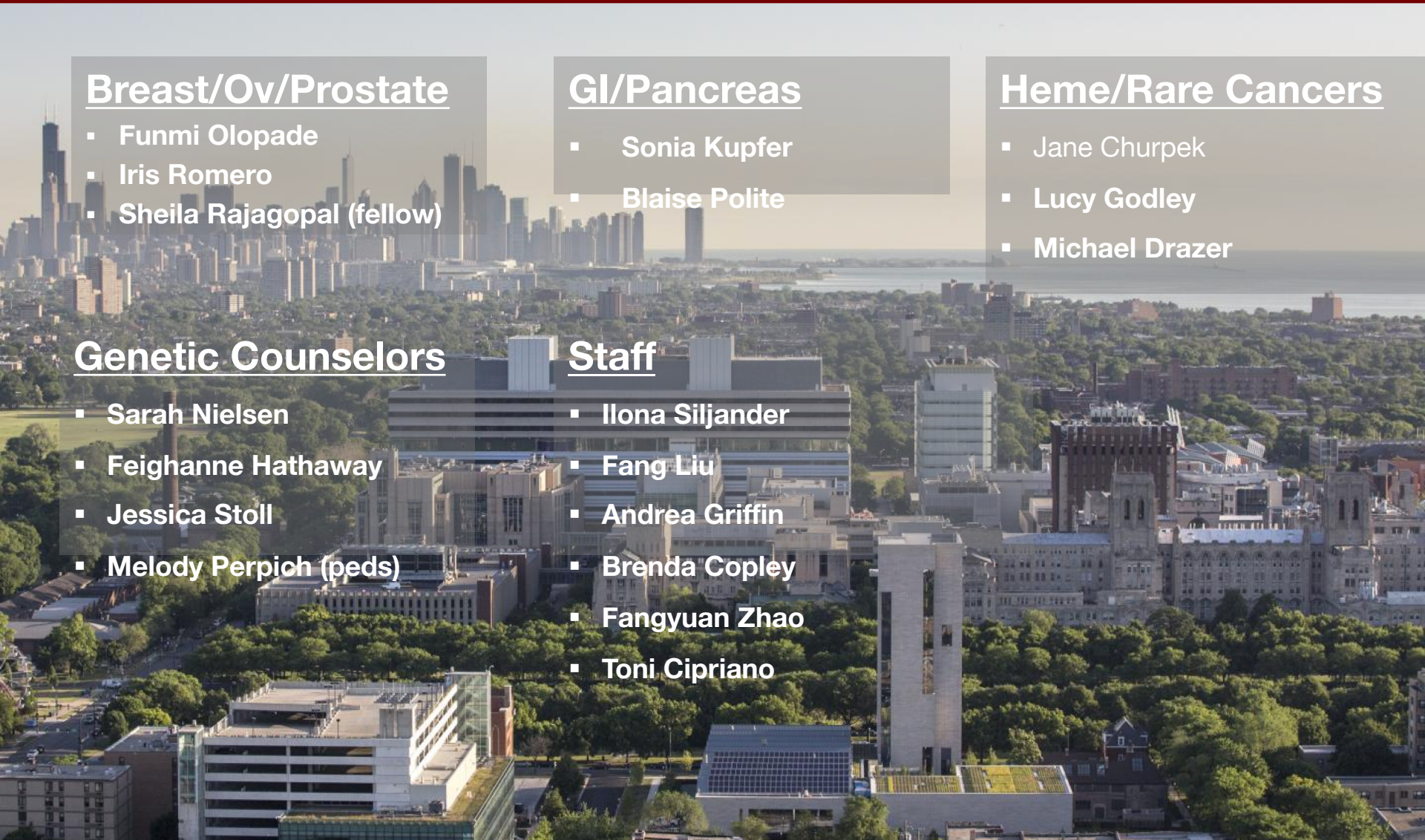
Thank you



Breast/Ov/Prostate

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

GI/Pancreas

- Sonia Kupfer
- Blaise Polite

Heme/Rare Cancers

- Jane Churpek
- Lucy Godley
- Michael Drazer

Genetic Counselors

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

Staff

- Ilona Siljander
- Fang Liu
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- Toni Cipriano