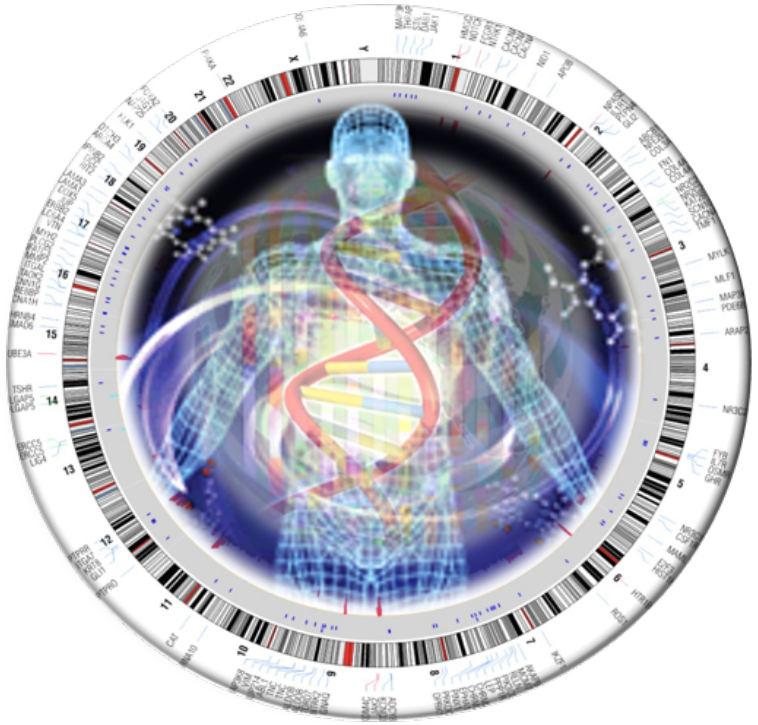
Genomics and Cancer Disparities

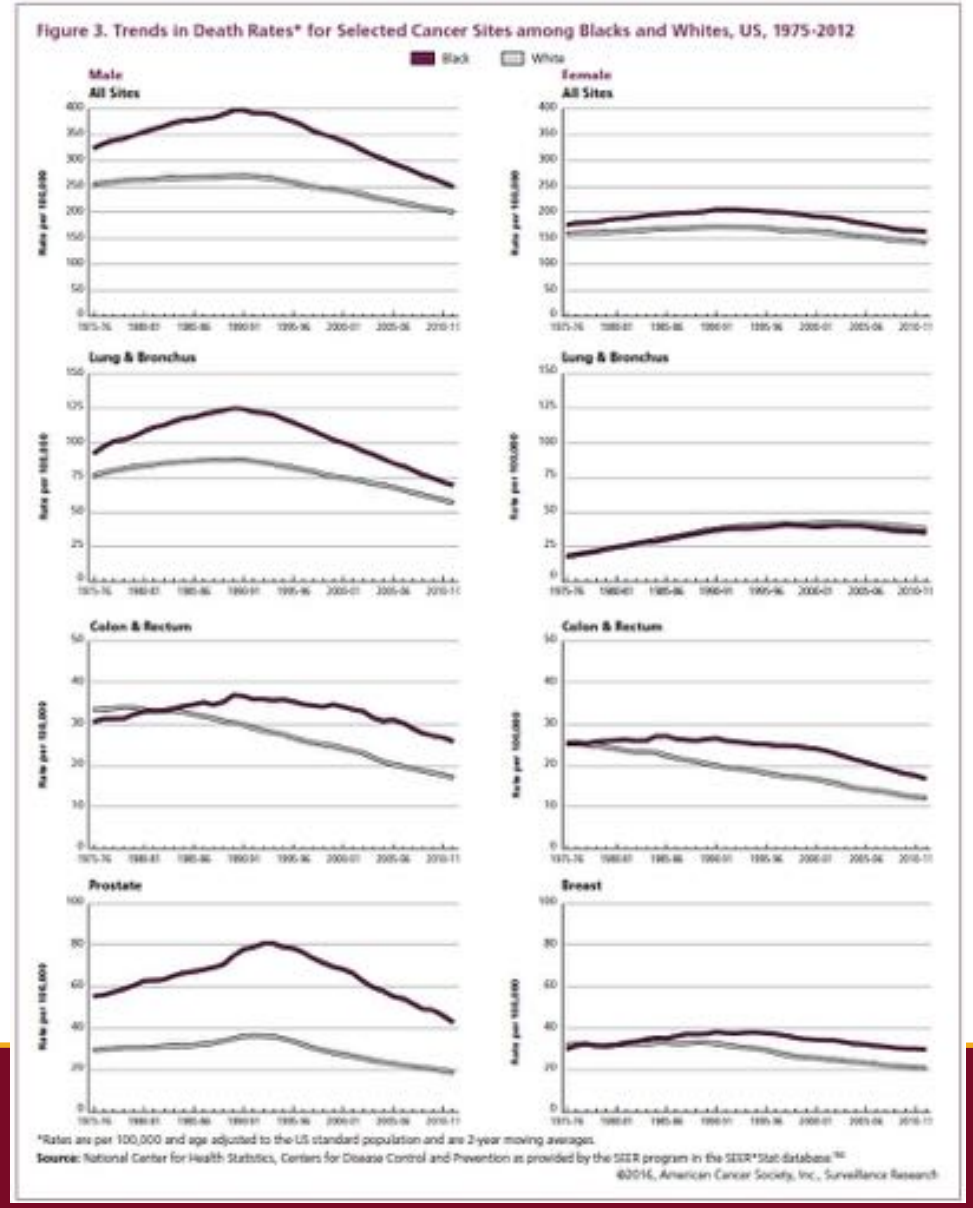


John D. Carpten, Ph.D.
Professor and Chair, Department of Translational Genomics

Disclosures

- Collaborative Research Agreement with 10X Genomics, Inc.
- Roche/Genentech Ad Board Honoraria
- Break Through Cancer Scientific Advisory Board
- Stand Up To Cancer (SU2C) Scientific Advisory Committee
- AACR Board of Directors
- Special Government Employee

Cancer Statistics and Cancer Disparities



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Cancer Statistics and Cancer Disparities

Table 6. Comparison of Cancer Death Rates between Non-Hispanic (NH) Blacks and Whites, US, 2008-2012

Male					Female				
Cancer	NH Black Rate*	NH White Rate*	Absolute Difference†	Rate Ratio‡	Cancer	NH Black Rate*	NH White Rate*	Absolute Difference†	Rate Ratio‡
Stomach	9.4	3.6	5.8	2.58	Stomach	4.5	1.8	2.7	2.48
Prostate	47.2	19.9	27.3	2.38	Myeloma	5.4	2.4	3.0	2.22
Larynx	3.7	1.8	1.9	2.02	Uterine cervix	4.1	2.0	2.1	2.00
Myeloma	7.8	4.0	3.8	1.95	Uterine corpus	7.8	4.1	3.7	1.92
Liver & intrahepatic bile duct	12.8	7.6	5.2	1.69	Liver & intrahepatic bile duct	4.4	3.1	1.3	1.43
Colon & rectum	27.6	18.2	9.4	1.52	Breast	31.0	21.9	9.1	1.42
Oral cavity & pharynx	5.2	3.8	1.4	1.36	Colon & rectum	18.2	12.9	5.3	1.41
Lung & bronchus	74.9	62.2	12.7	1.20	Pancreas	12.6	9.5	3.1	1.32
Pancreas	15.4	12.7	2.7	1.21	Esophagus	2.0	1.6	0.4	1.28
Kidney & renal pelvis	5.7	5.9	-0.2	0.97	Urinary bladder	2.6	2.3	0.3	1.12
Hodgkin lymphoma	0.4	0.5	-0.1	0.94	Kidney & renal pelvis	2.6	2.6	0.0	1.02
Esophagus	7.1	8.0	-0.9	0.89	Lung & bronchus	36.7	41.1	-4.4	0.89
Leukemia	8.1	9.9	-1.8	0.82	Leukemia	4.8	5.4	-0.6	0.89
Non-Hodgkin lymphoma	5.9	8.3	-2.4	0.71	Hodgkin lymphoma	0.3	0.3	0.0	0.89
Urinary bladder	5.4	8.4	-3.0	0.65	Ovary	6.8	8.2	-1.4	0.83
Brain & other nervous system	3.2	6.0	-2.8	0.53	Non-Hodgkin lymphoma	3.6	5.0	-1.4	0.71
Melanoma of the skin	0.5	5.0	-4.5	0.09	Brain & other nervous system	2.2	3.9	-1.7	0.55
					Melanoma of the skin	0.4	2.1	-1.7	0.18
All sites	**267.7**	**210.6**	**57.1**	**1.27**	**All sites**	**170.4**	**149.2**	**21.2**	**1.14**

Note: Sites listed in descending order by rate ratio. *Rates are per 100,000 and age adjusted to the 2000 US standard population. †Absolute difference is the rate in blacks minus the rate in whites. ‡Rate ratio is the unrounded rate in blacks divided by the unrounded rate in whites.

Source: National Center for Health Statistics, Centers for Disease Control and Prevention as provided by the SEER program in the SEER*Stat database.[36]

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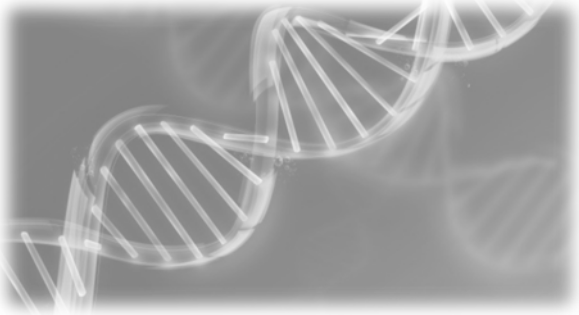
Race and Ancestry Represent Different but Related Factors

Social/Societal

vs

Biological/Genetic

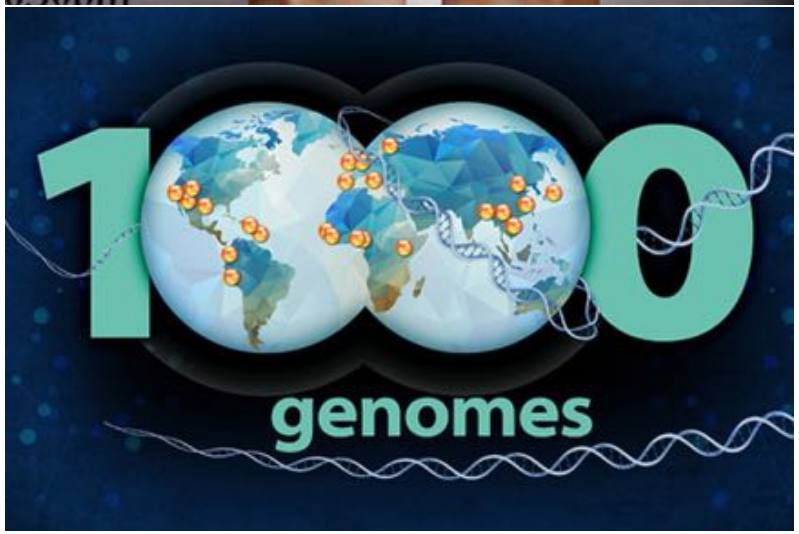


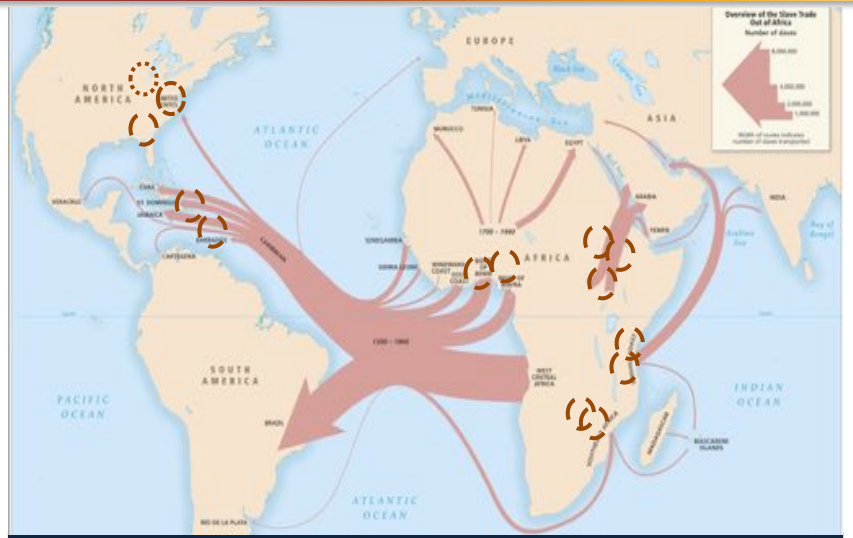
(SDOH)
Race/Ethnicity
(social)

Ancestry
(genetic)

Host/Tumor
Biology

Race and Ancestry Represent Different but Related Factors





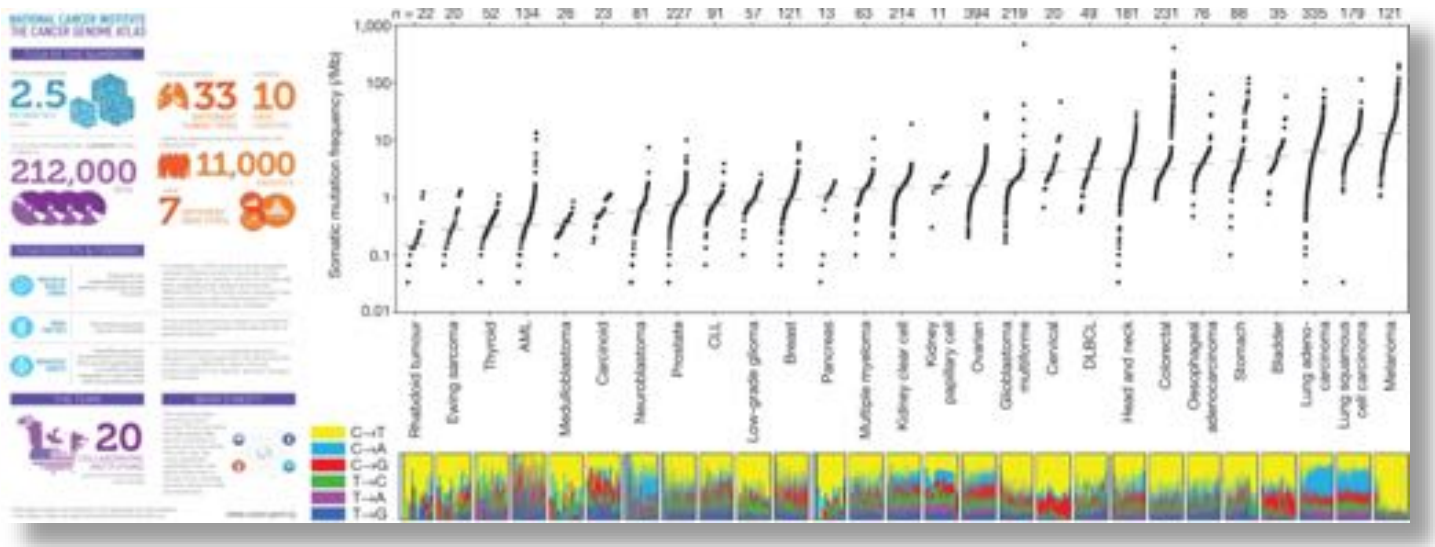

YRI ASW CEU MXL CHB
YRI
Yoruba in Ibadan, Nigeria
ASW
Americans of African Ancestry in SW USA
CHB
Han Chinese in Bejing, China
MXL
Mexican Ancestry from Los Angeles USA
CEU
Utah Residents (CEPH) with
Northern and Western Ancestry

A Rationale for Exploring the Role of Biology in Cancer Disparities

- Social factors such as financial toxicities and access influence these disparities.
- Issues related to the breakdown in the [Health Care:Patient Interface] influence these disparities.
- There is significant dearth of investigation into differences in tumor biology across racial/ethnic groups.
- Exploring the role of biological differences in tumors across populations will help to broaden our understanding of the complexity of cancer in a way to best approach disease management more effectively for all patients.

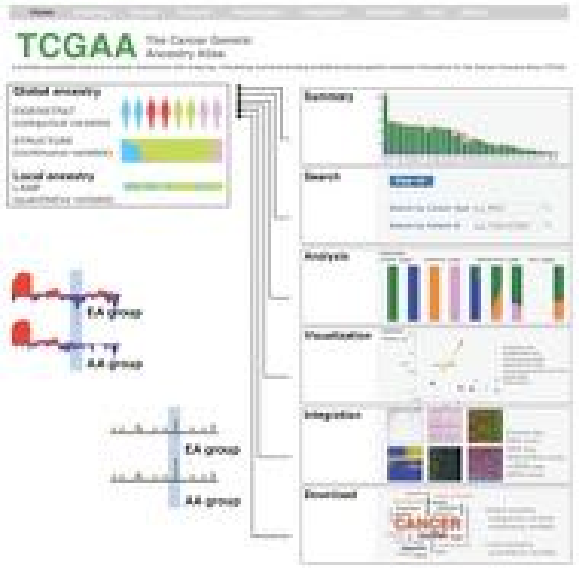
Cancer Genomics Studies in Diverse Populations

- Significantly limited diversity in TCGA (<10% in most tumor types), despite many tumor types demonstrating significant disparities in incidence and outcomes.
  - Prostate Cancer
  - Triple Negative Breast Cancer
  - Colorectal Cancer
  - Ovarian Cancer
  - Endometrial Cancer
  - Leukemia
  - Multiple Myeloma



- This remains an important unmet need in helping to determine if genomic differences are associated with differences in cancer incidence and outcomes displayed among underrepresented patients.

Cancer Genomics Studies in Diverse Populations



- **Breast, head and neck, and endometrial cancers derived from African Americans (AA) exhibit higher levels of chromosomal instability**; but lower levels of chromosomal instability for kidney cancers derived from AA.
- **TP53 mutations and amplification of CCNE1 were increased in AAs in the cancer types showing higher levels of chromosomal instability.**
- **Observed lower frequencies of genomic alterations affecting genes in the PI3K pathway in AA patients across cancers.**

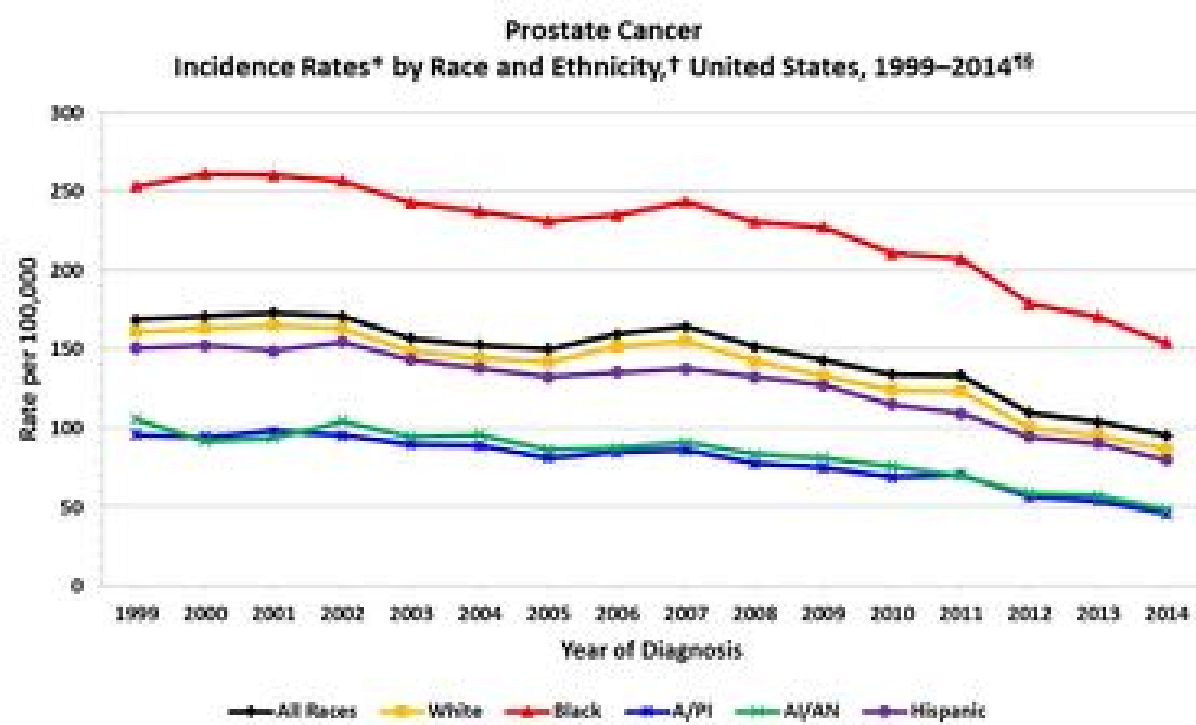
Yuan et al., (2018) *Cancer Cell*; 34(4):549-560.

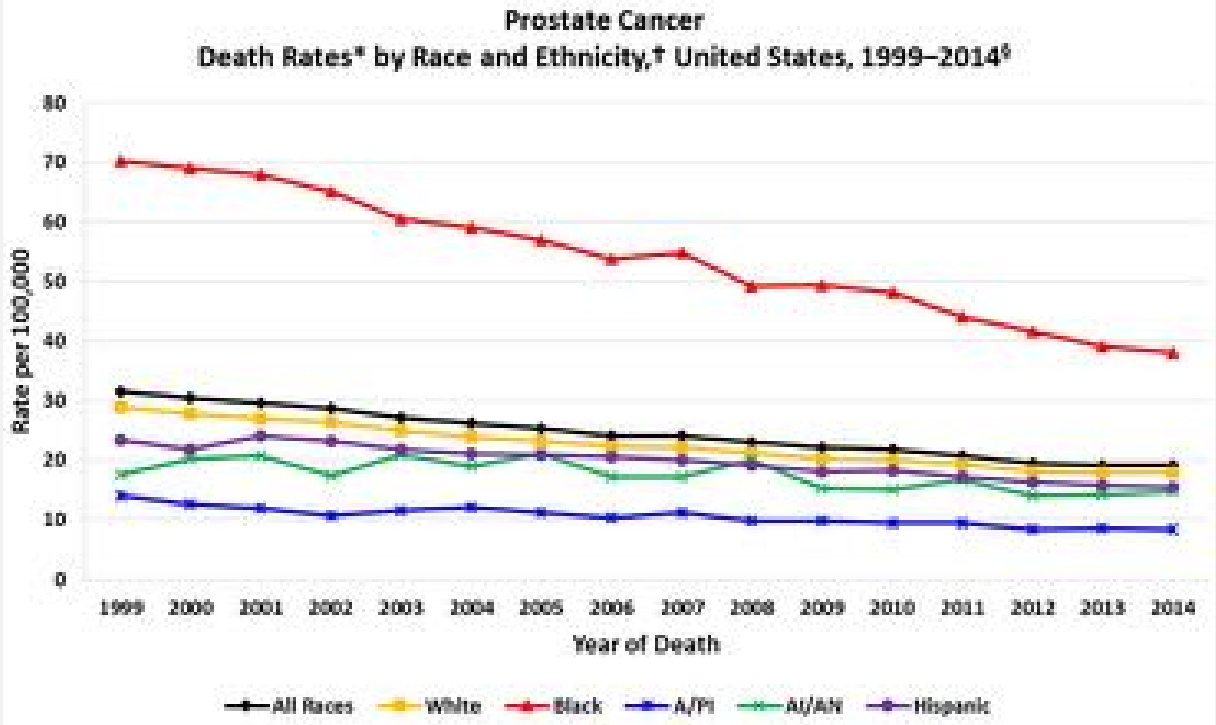
Prostate Cancer

Genomic Studies In Cancer Disparities – Prostate Cancer

The Cancer Genome Atlas Research Network

Prostate Cancer

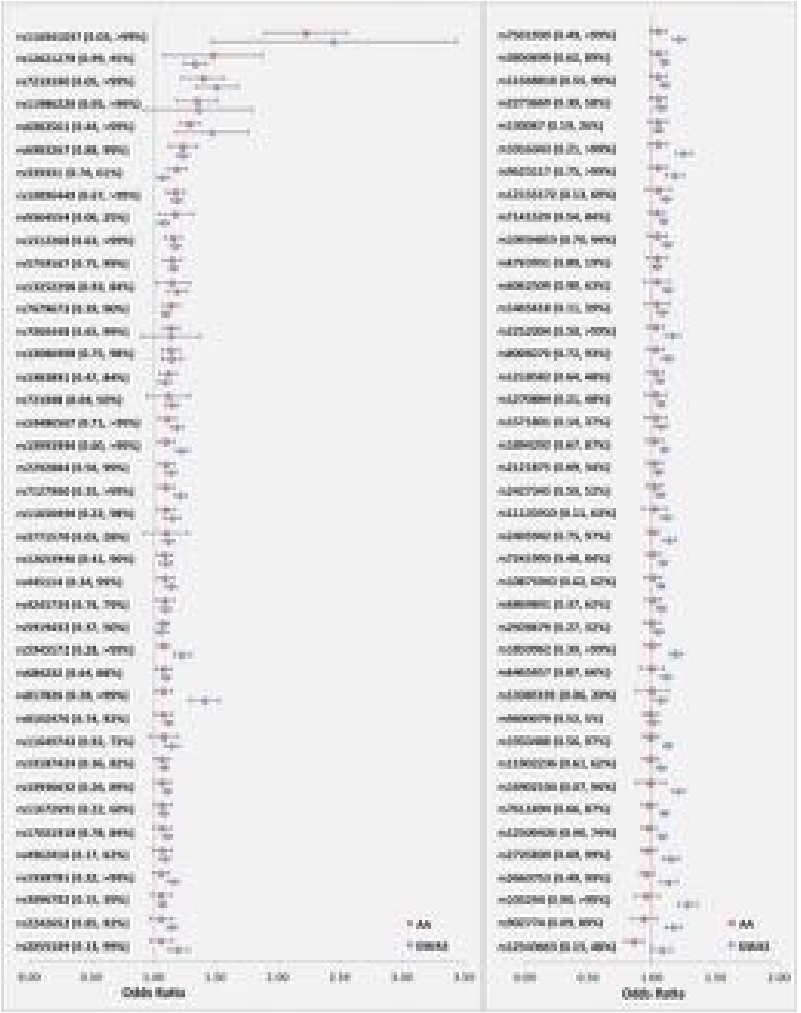




https://www.cdc.gov/

Genomic Studies In Cancer Disparities – Prostate Cancer

- Association study of 82 previously reported risk variants in 4,853 prostate cancer cases and 4,678 controls of African ancestry were examined.
- Of the 82 known risk variants, 68 (83%) had effects that were directionally consistent in their association with prostate cancer risk.
- 30 (37%) were significantly associated with risk at $p<0.05$, with the most statistically significant variants being rs116041037 ($p=3.7\times10^{-26}$) and rs6983561 ($p=1.1\times10^{-16}$) at 8q24, as well as rs7210100 ($p=5.4\times10^{-8}$) at 17q21.
- rs116041037 risk variant is highly enriched in African populations.
- By exploring each locus in search of better markers, the number of variants that captured risk in men of African ancestry ($p<0.05$) increased from 30 (37%) to 44 (54%).

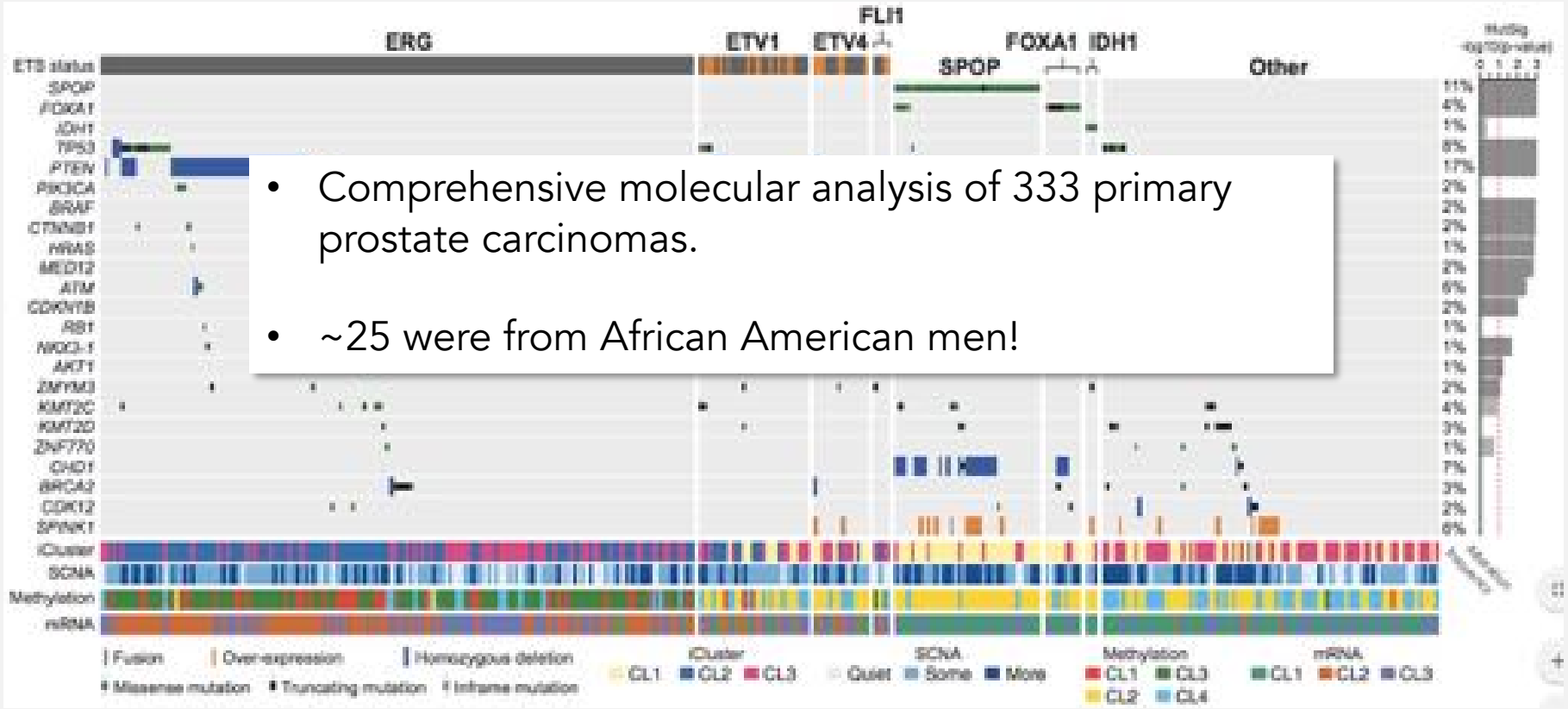


Han et al., Int. J. Cancer: 136, 1210–1217 (2015)

Genomic Studies In Cancer Disparities – Prostate Cancer

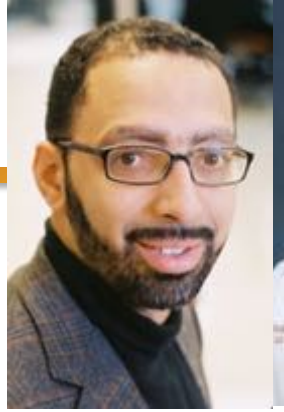
The Molecular Taxonomy of Primary Prostate Cancer

The Cancer Genome Atlas Research Network



- Comprehensive molecular analysis of 333 primary prostate carcinomas.
- ~25 were from African American men!

Genomic Studies In Cancer Disparities – Prostate Cancer



CANCER DISCOVERY

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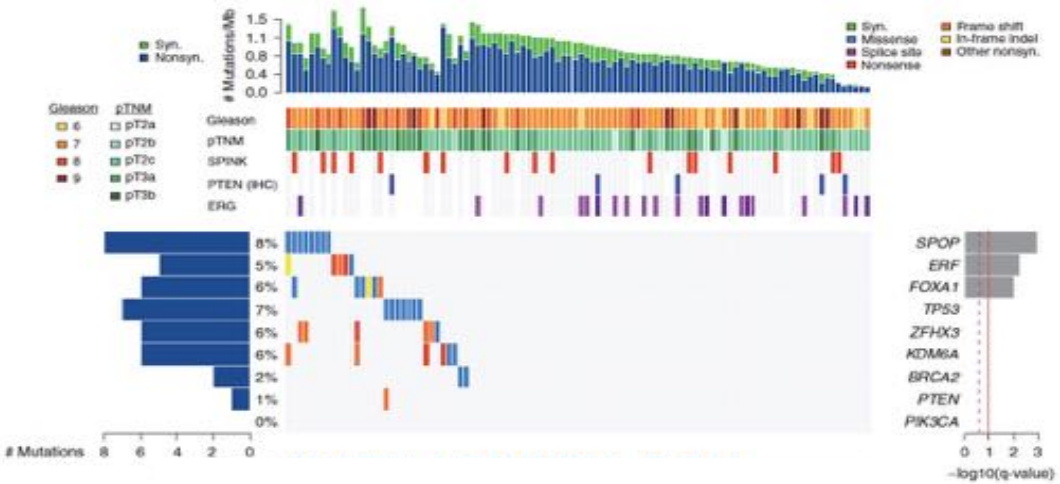
Research Briefs

Exome Sequencing of African-American Prostate Cancer Reveals Loss-of-Function *ERF* Mutations

Franklin W. Huang, Juan Miguel Mosquera, Andrea Garofalo, Coyin Oh, Maria Baco, Ali Amin-Mansour, Bokang Rabasha, Samira Bahl, Stephanie A. Mullane, Brian D. Robinson, Saud Aldubayan, Francesca Khani, Beerinder Kahr, Eejung Kim, Jeremy Chimene-Weiss, Matan Hofree, Alessandro Romanel, Joseph R. Osborne, Jong Wook Kim, Gissou Azabdaftari, Anna Woloszynska-Read, Karen Sfanos, Angelo M. De Marzo, Francesca Demichelis, Stacey Gabriel, Eliezer M. Van Allen, Jill Mesirov, Pablo Tamayo, Mark A. Rubin, Isaac J. Powell, and Levi A. Garraway



Huang et al., *Cancer Discovery*, 2017, 7(9):973-983.

nature

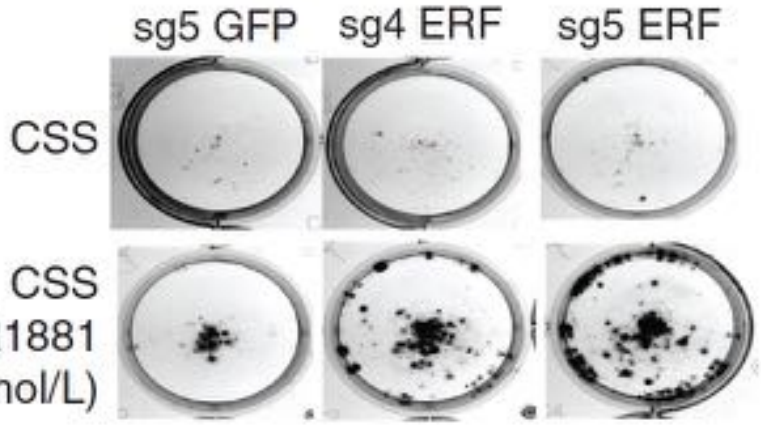
International journal of science

Letter | Published: 14 June 2017

ERF mutations reveal a balance of ETS factors controlling prostate oncogenesis

Rohit Bose, Wouter R. Karthaus, Joshua Armenia, Wassim Abida, Phillip J. Iaquinta, Zeda Zhang, John Wongvipat, Elizabeth V. Wasmuth, Neel Shah, Patrick S. Sullivan, Michael G. Doran, Ping Wang, Anna Patruno, Yilin Zhao, The International SU2C/PCF Prostate Cancer Dream Team, Deyou Zheng, Nikolaus Schultz & Charles L. Sawyers

Nature **546**, 671–675 (29 June 2017) | Download Citation



CRISPR-Cas9 knockout of ERF increases clonogenic growth in an androgen-dependent manner in LNCAP cells

Genomic Studies In Cancer Disparities – Prostate Cancer

A large, national, population-based cohort study, RESPOND, (Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Immunity and Access to Care) of 10,000 AA men with incident PCa identified through nine SEER and NPCR U.S. cancer registries from states that include 38% of all AA PCa cases in the U.S.

Multiple Myeloma

Cancer Statistics and Cancer Disparities

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Source: National Center for Health Statistics, Centers for Disease Control and Prevention as provided by the SEER program in the SEER*Stat database.[36]

www.cancer.org

Genomic Studies In Cancer Disparities – Multiple Myeloma

CoMMpass Enrollment

1,000+ patients enrolled from >90 sites worldwide, with over 850 samples molecularly profiled at baseline and >100 sequentially.

3


Zarko Manojlovic


Jonathan Keats


John Carpten

PLOS GENETICS

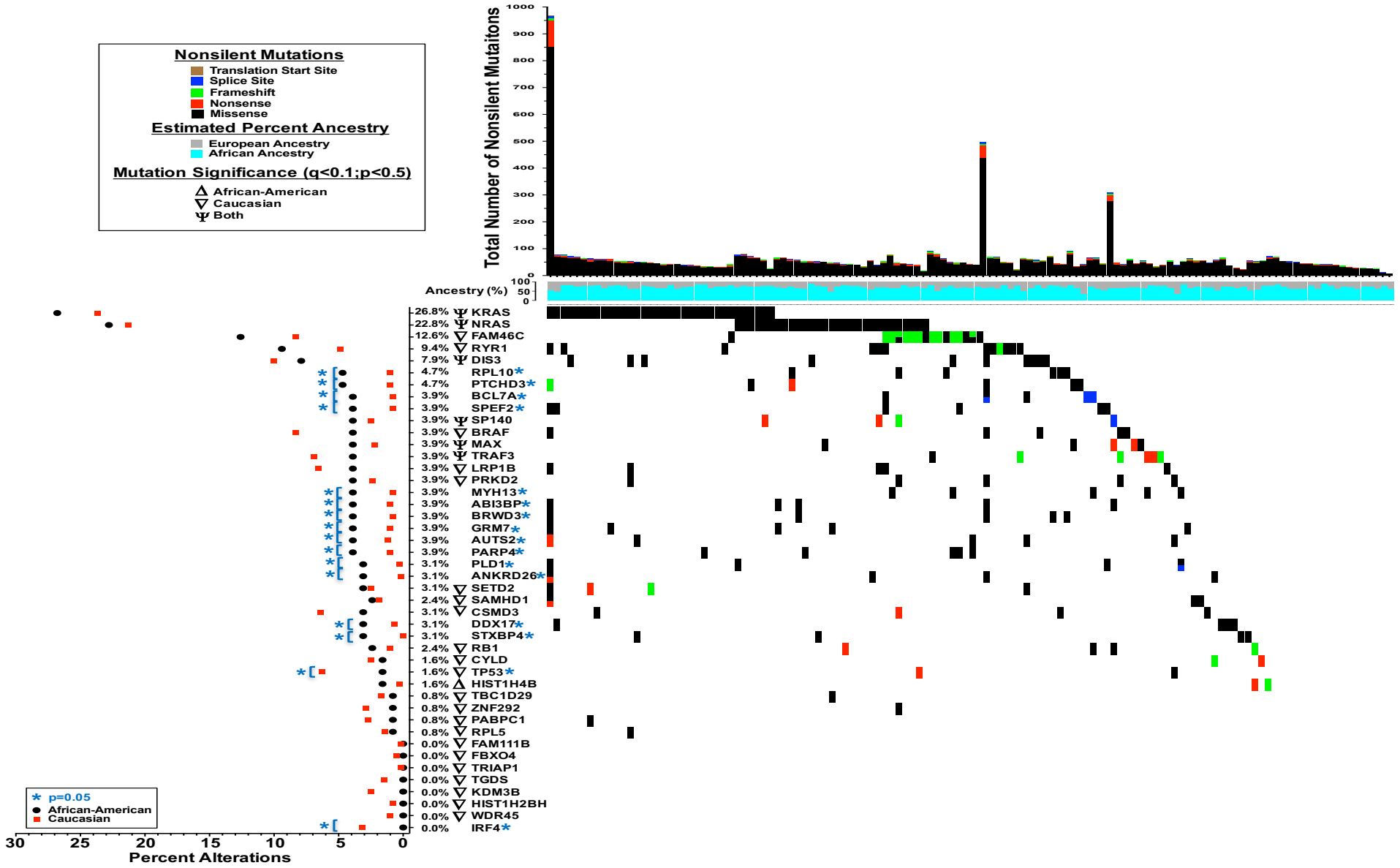
RESEARCH ARTICLE

Comprehensive molecular profiling of 718 Multiple Myelomas reveals significant differences in mutation frequencies between African and European descent cases

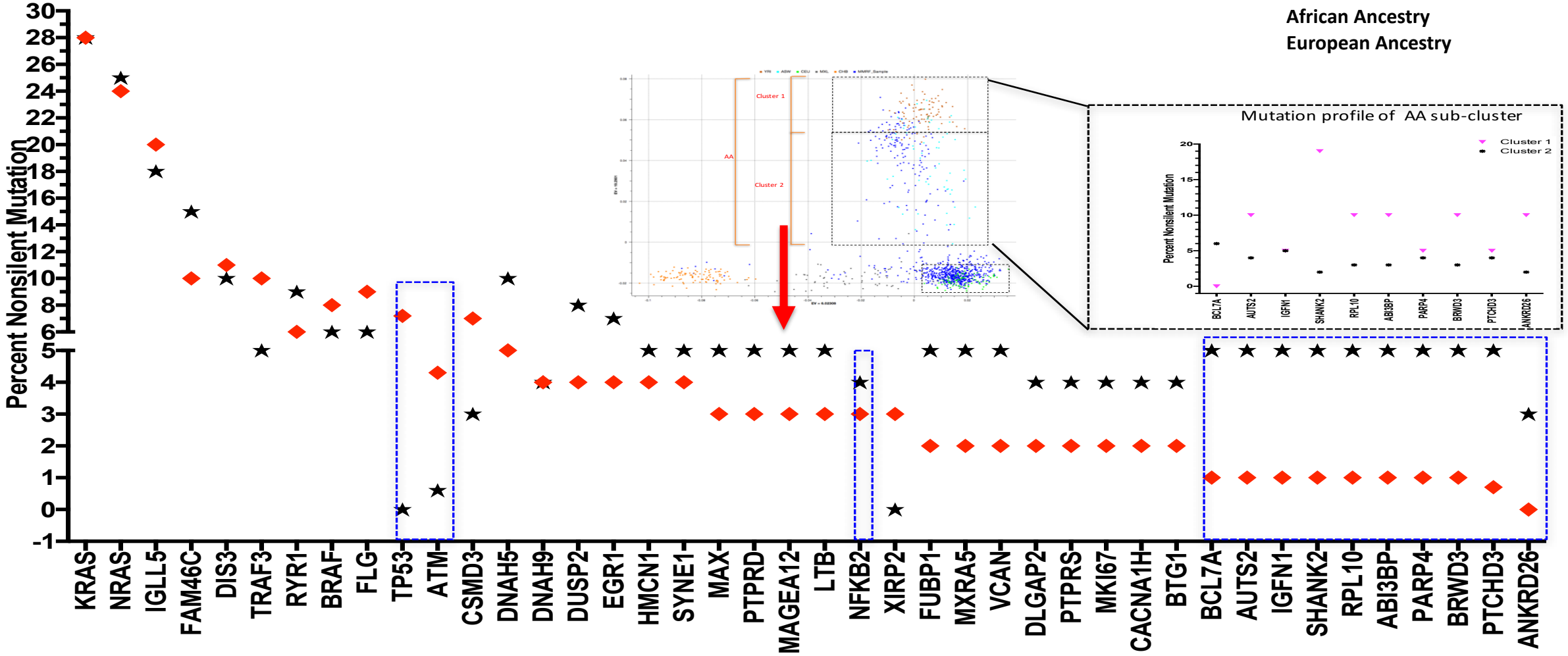
Zarko Manojlovic[1,2]*, Austin Christofferson[2], Winnie S. Liang[2], Jessica Aldrich[2], Megan Washington[2], Shukmei Wong[2], Daniel Rohrer[2], Scott Jewell[3], Rick A. Kittles[4], Mary Derome[5], Daniel Auclair[5], David Wesley Craig[1], Jonathan Keats[2], John D. Carpten[1,2]

1 Department of Translational Genomics, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States of America, 2 Translational Genomics Research Institute, Phoenix, AZ, United States of America, 3 Van Andel Research Institute, Grand Rapids, MI, United States of America, 4 Department of Surgery, Division of Population Genetics, University of Arizona, Tucson, AZ, United States of America, 5 Multiple Myeloma Research Foundation, Norwalk, CT, United States of America

Genomic Studies In Cancer Disparities – Multiple Myeloma

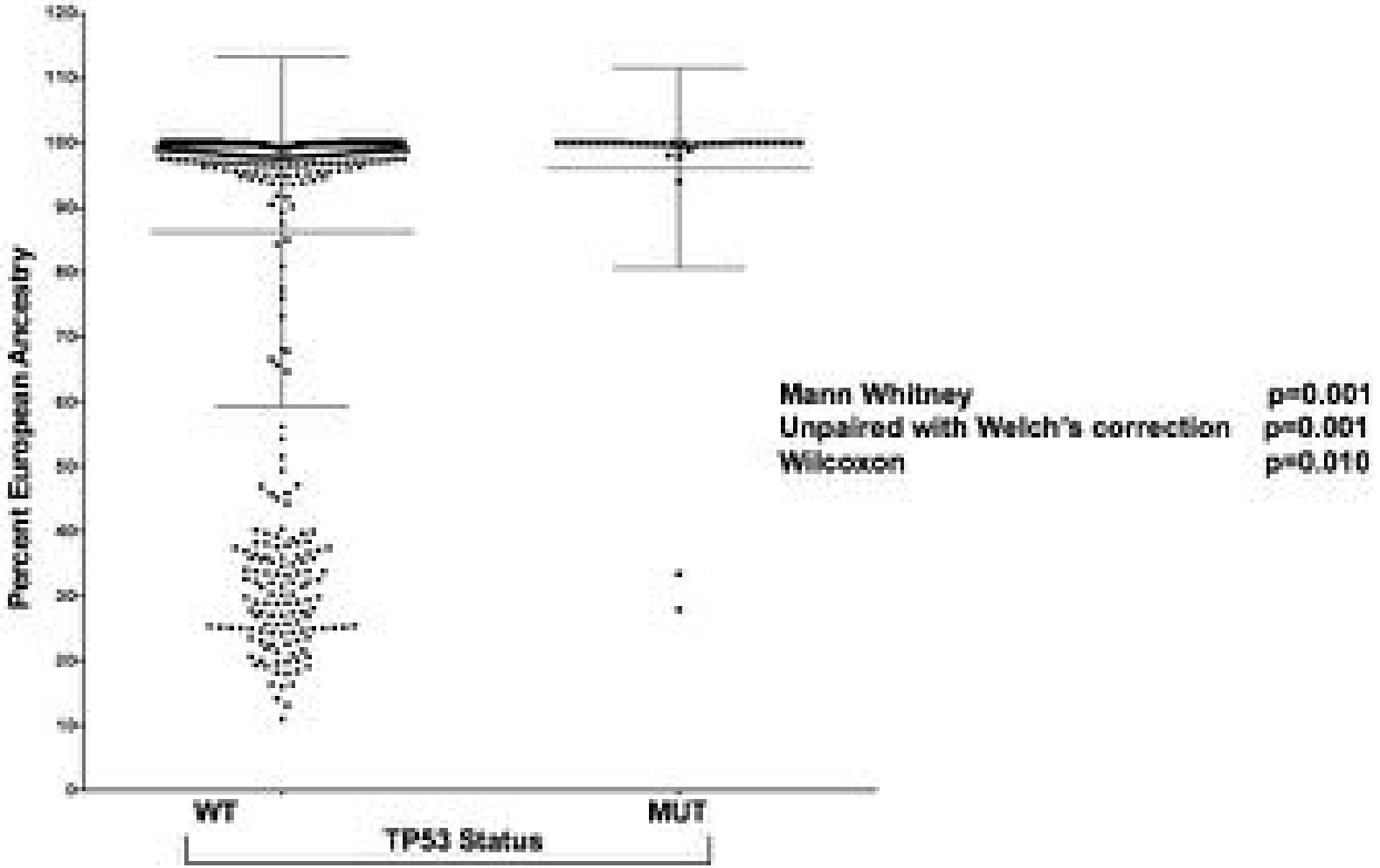


Genomic Studies In Cancer Disparities – Multiple Myeloma



African Ancestry AA (n=152)
European Ancestry EA (n=555)

Genomic Studies In Cancer Disparities – Multiple Myeloma



Genomic Studies In Cancer Disparities – Multiple Myeloma

- These data provide further evidence of differences in tumor profiles among AA and EA MM patients in a sufficiently powered tumor cohort.
- TP53 loss is associated with poor outcome, yet is enriched in tumors from EA cases.
- *These data suggest that AA MM patients may have tumors with molecular features associated with more favorable outcomes.*
- *Perhaps in MM, equal treatment could lead to similar or better outcomes in AA patients.*

Genomic Studies In Cancer Disparities – Multiple Myeloma


STIMULUS REPORT

blood advances

Survival of ethnic and racial minority patients with multiple myeloma treated with newer medications

E. Dianne Pulte, Lei Nie, Nicole Gormley, Kirsten B. Goldberg, Amy McKee, Ann Farrell, and Richard Pazdur

Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD

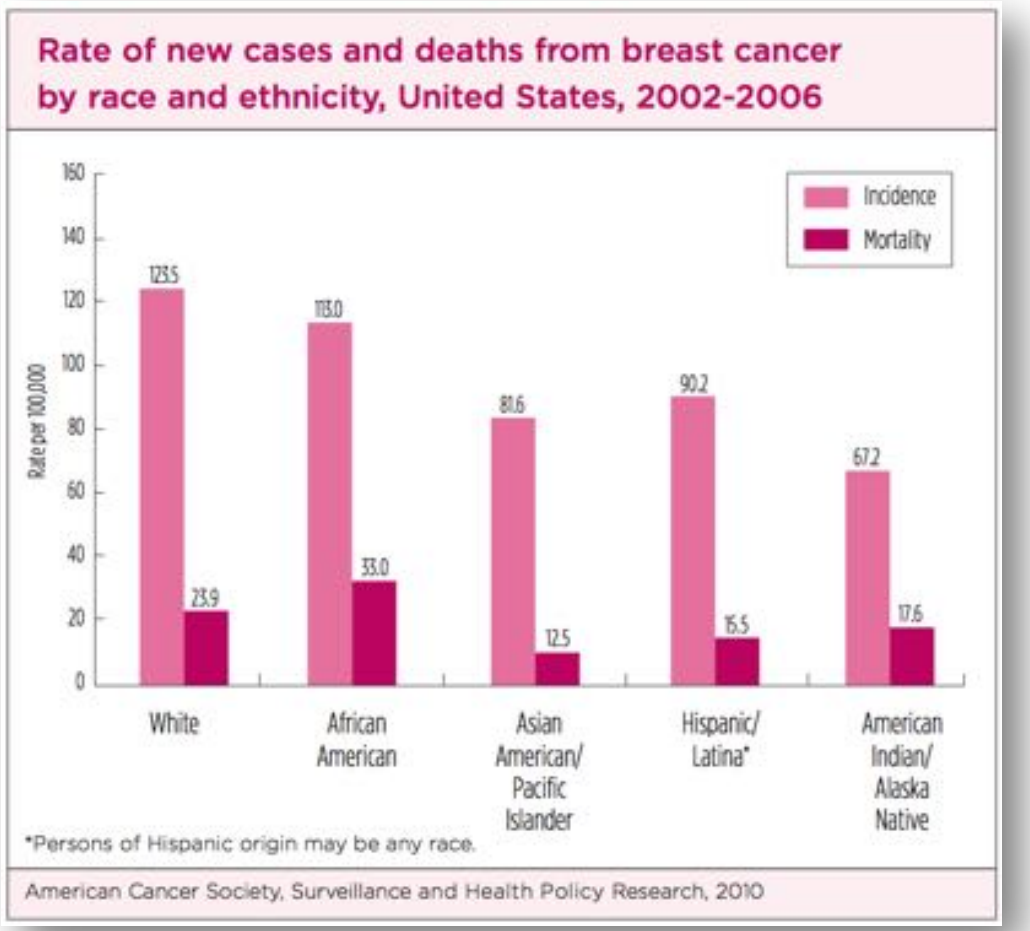
- Results show a low participation of minorities in MM clinical trials of newer agents.
- Despite this limitation, mortality was slightly lower in participants of other racial and ethnic groups.
- Observed that Imid- and PI-class drugs may be working better in minorities.
- Examination of survival in the current SEER data shows that overall 5-year survival from 2007 to 2013 increased to 52.3% for African Americans and 50.6% for whites, suggesting that the earlier observed disparities were likely related to a temporary phenomenon (ie, differences in treatment utilization, access).

Genomic Studies In Cancer Disparities – Multiple Myeloma

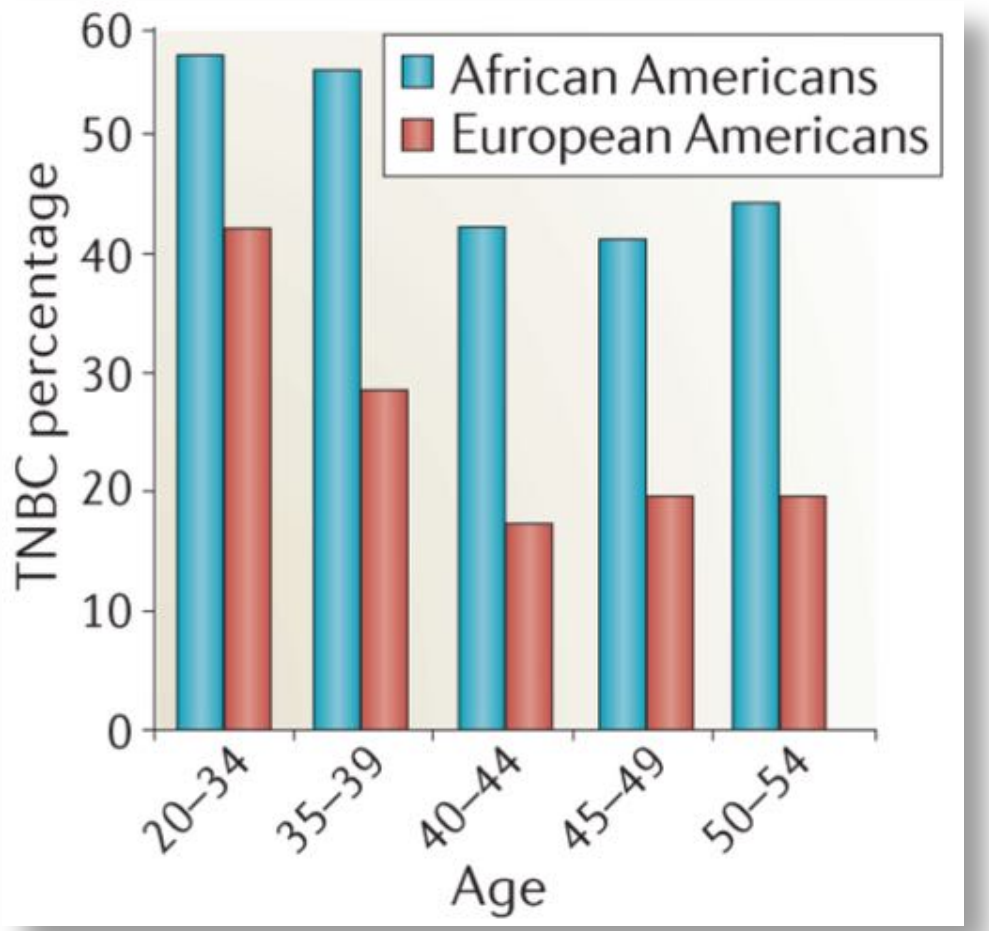
Although ours and other's data support a socio-economic/access issue related to the MM outcomes disparity, it does not explain the persisting difference in incidence rates.

Breast Cancer

Genomic Studies In Cancer Disparities – Breast Cancer

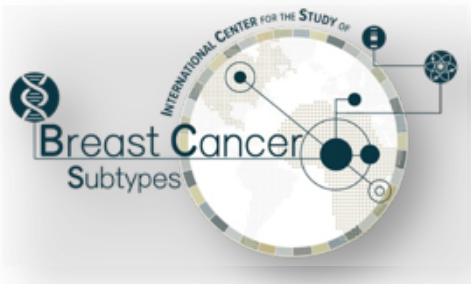


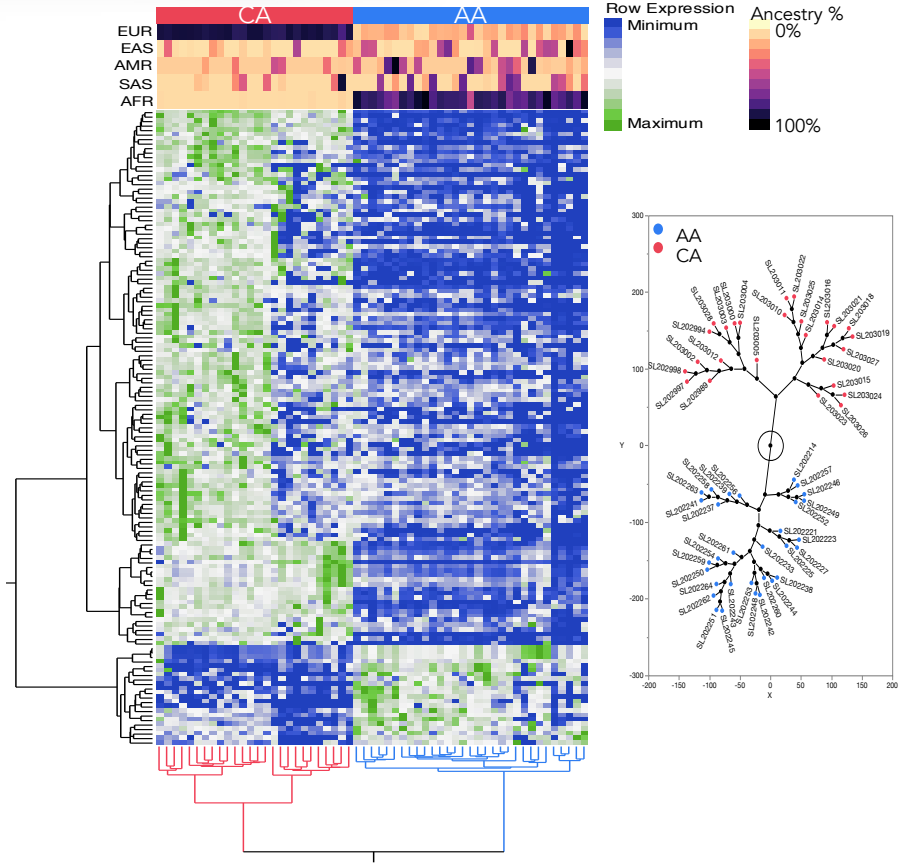
http://ww5.komen.org/



Dietze et al., *Nat Rev Cancer*. 2015 April ; 15(4): 248–254.

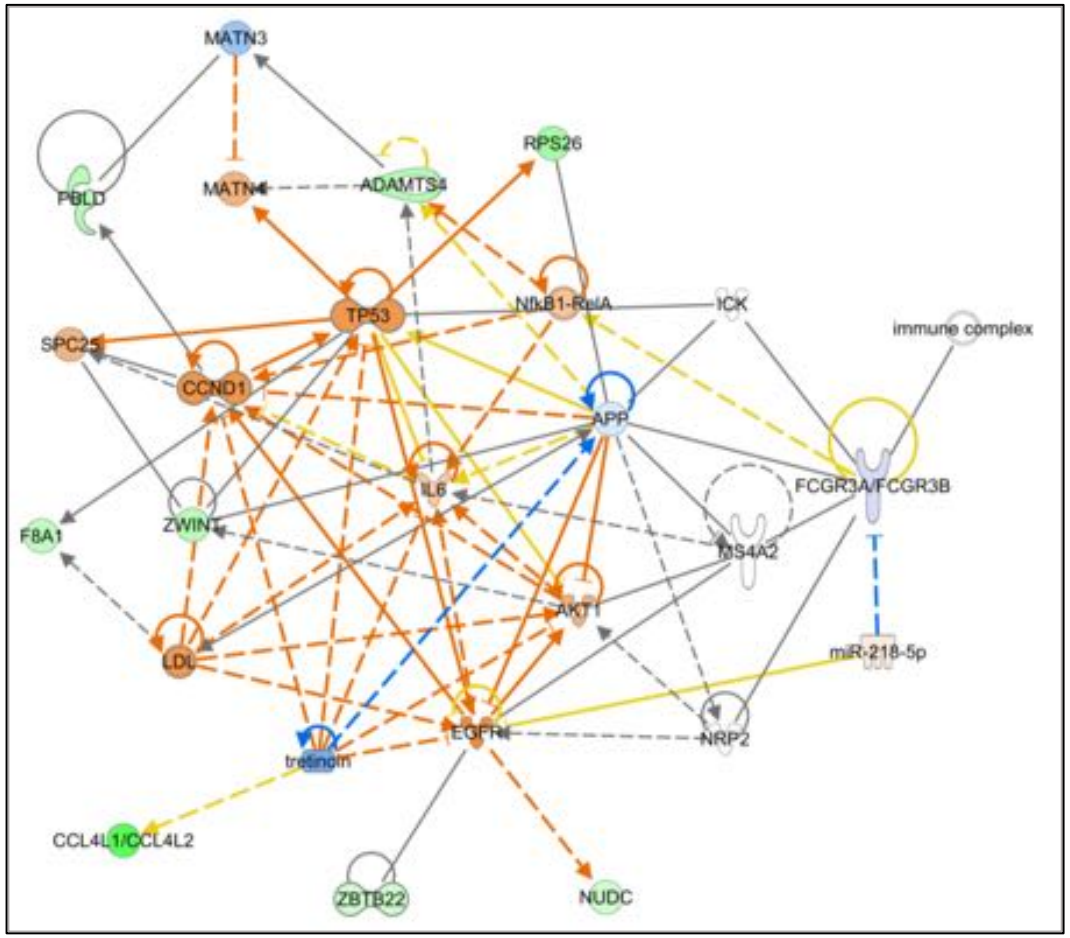
Biological mechanisms of Breast Cancer Disparities





Gene expression in TNBC associated with African Quantified Genetic Ancestry (QGA) – measured from RNAseq variants.

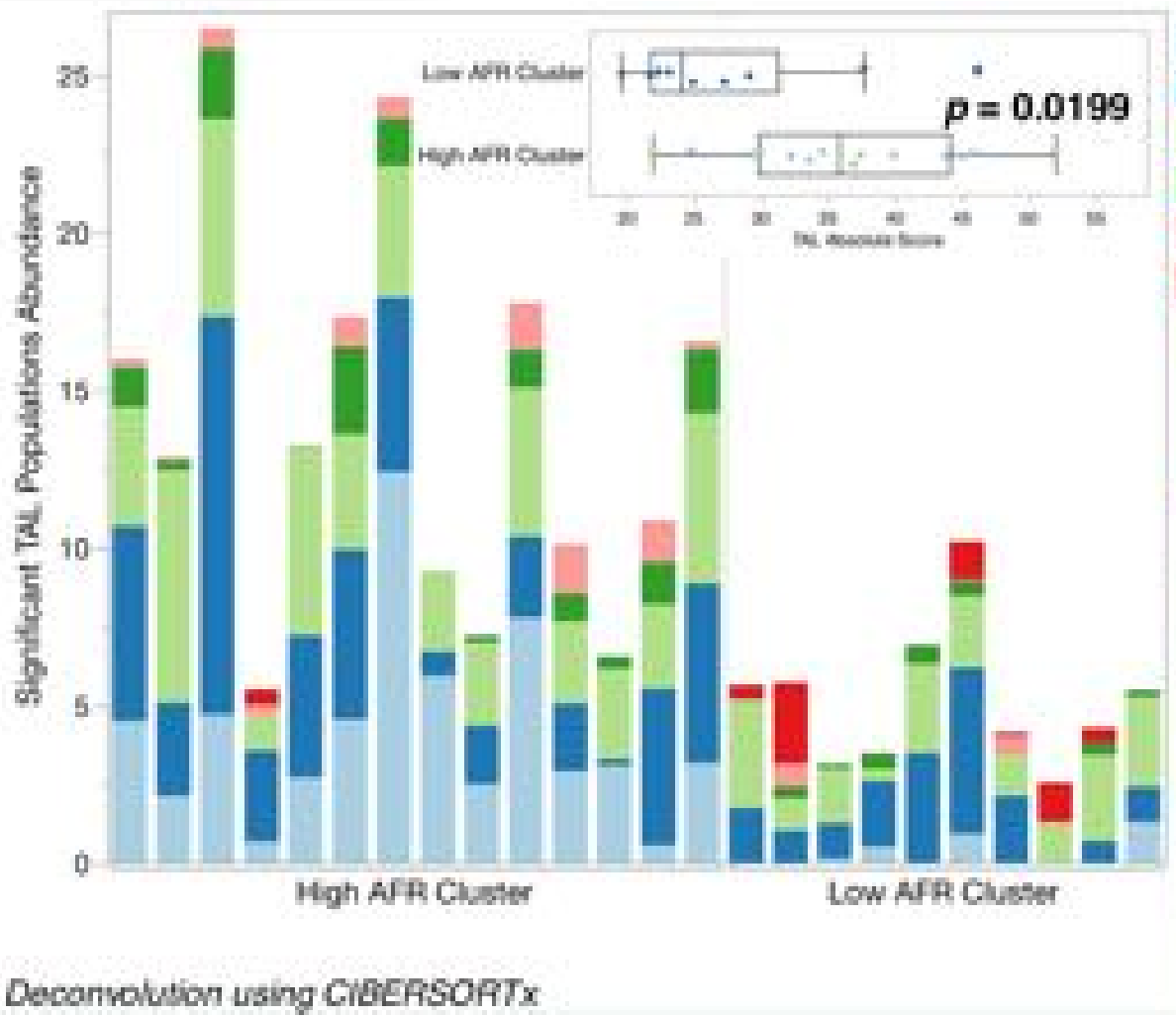
SYSTEMS BIOLOGY: African-associated gene upregulation in canonical cancer pathways reveal distinct functional interactions within previously defined networks.



CLINICAL IMPACT: African-associated genes include druggable targets with therapies already in clinic for other cancers, potentially new sources of precision TNBC treatment

Biological mechanisms of Breast Cancer Disparities

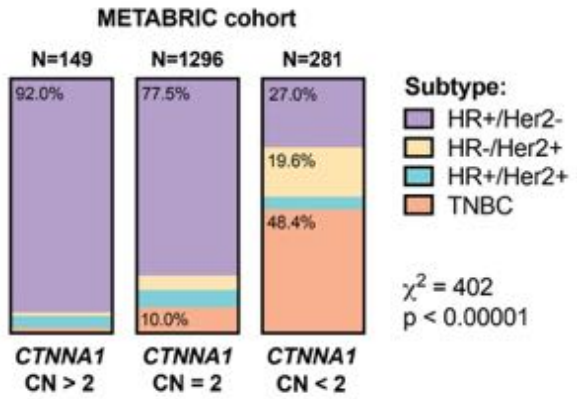
Abundance of tumor-associated leukocytes (TAL) significantly higher among High AFR cluster (Martini et al., 2020, *Cancer Research Supp*.

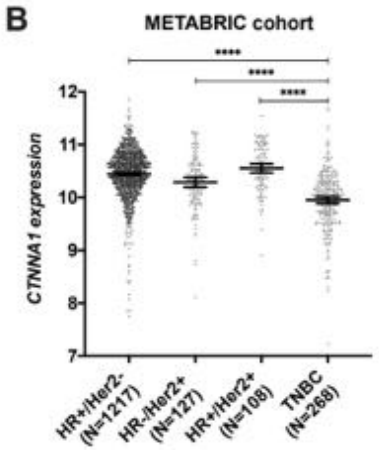


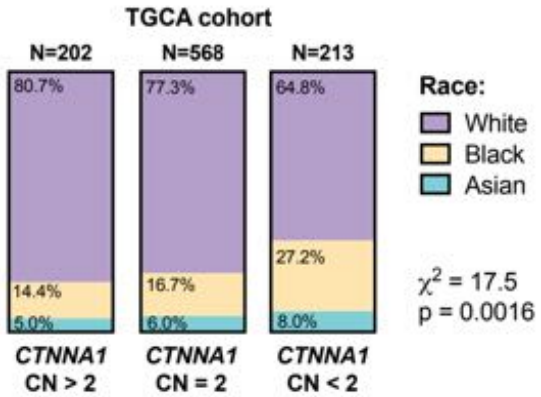
TAL population	High AFR cluster mean	Low AFR cluster mean	Student's t-test *p* value	ANOVA by SRR *p* value
B cells naive	**4.12**	0.29	0.0004	0.0016
T cells CD8	**4.16**	1.87	0.0268	0.0248
T cells follicular helper	**3.98**	1.98	0.0019	0.0037
NK cells activated	**1.01**	0.27	0.0103	0.0455
Monocytes	**0.55**	0.14	0.0291	0.0403
Mast cells activated	0.02	**0.61**	0.0613	0.0665

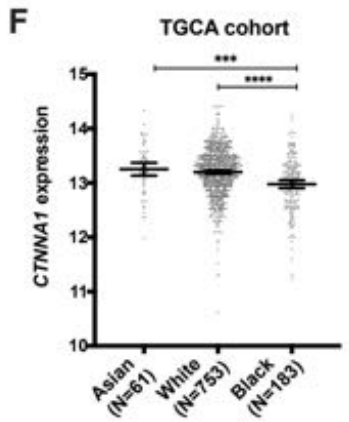
Genomic Studies In Cancer Disparities – Breast Cancer

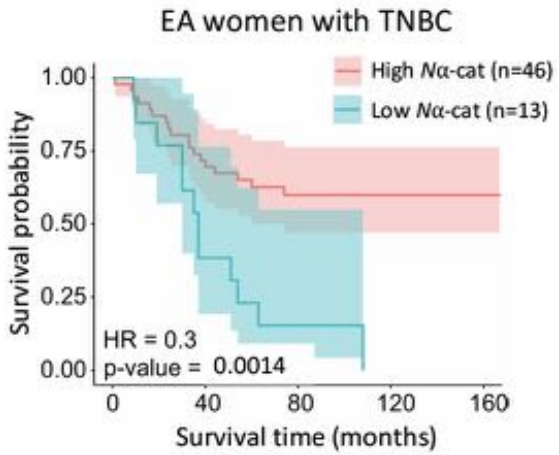
Role of nuclear α-catenin in TNBC among AA

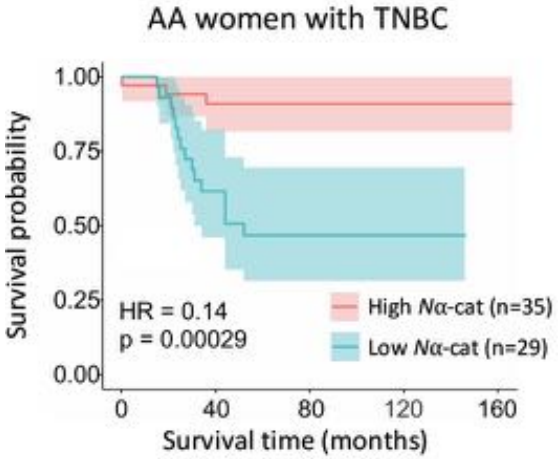


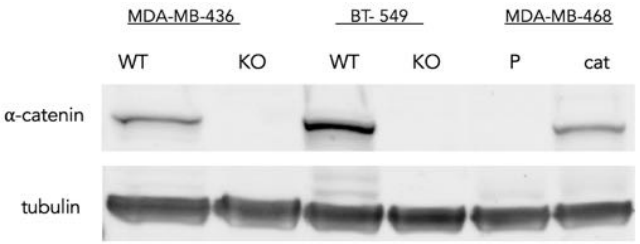


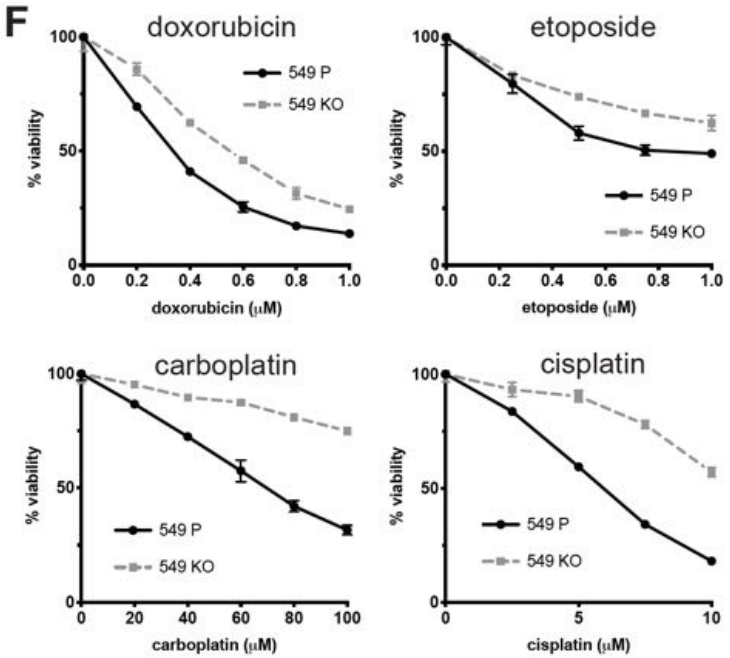




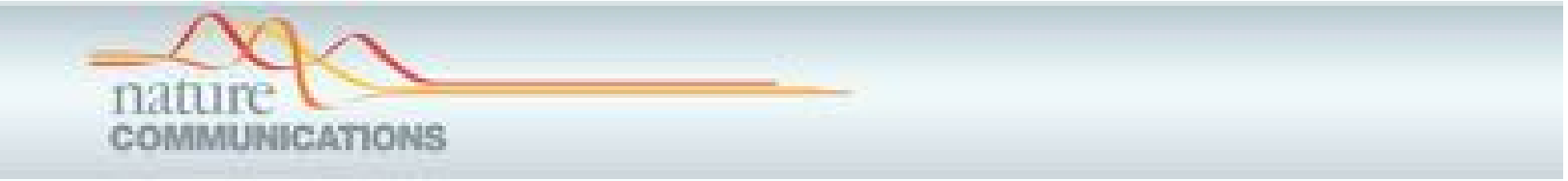








Genomic Studies In Cancer Disparities – Breast Cancer



ARTICLE

OPEN

Characterization of Nigerian breast cancer reveals prevalent homologous recombination deficiency and aggressive molecular features

Jason J. Pitt et al.

- 194 breast cancers from Nigerian women.
- "Relative to Black and White cohorts in TCGA, Nigerian HR+ /HER2 – tumors are characterized by increased homologous recombination deficiency signature, pervasive TP53 mutations, and greater structural variation—indicating aggressive biology."
- "GATA3 mutations are also more frequent in Nigerians regardless of subtype."

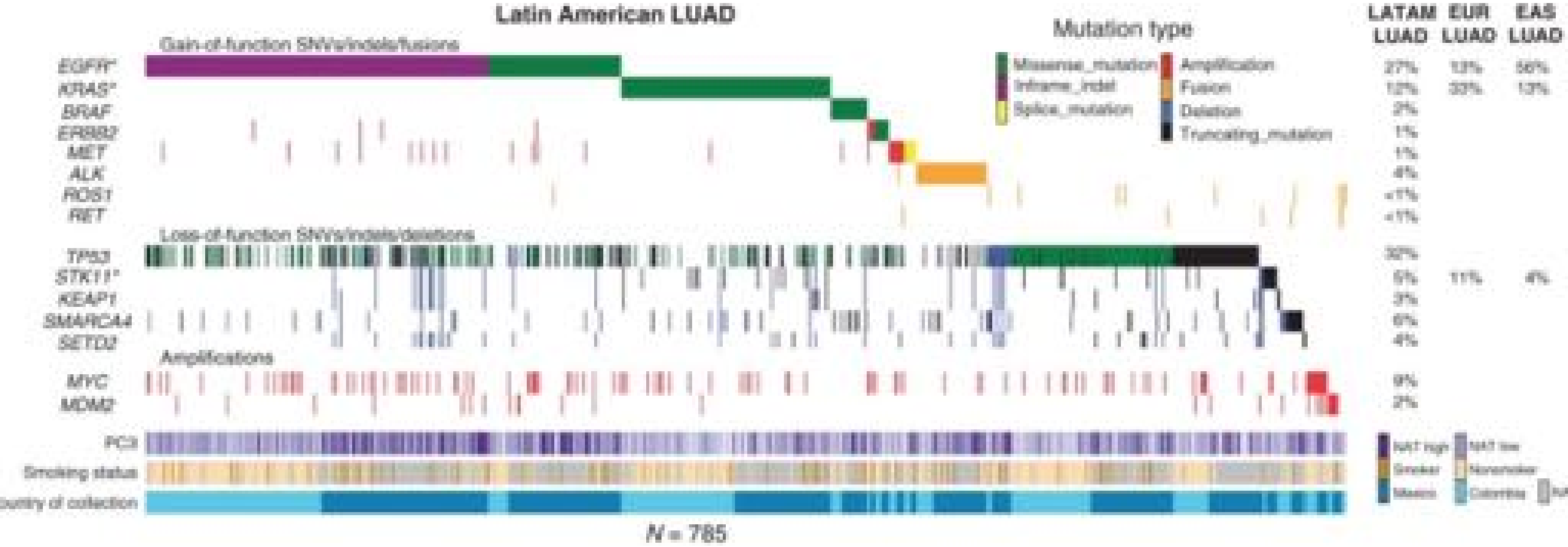
Pitt et al., (2018) *Nature Communications*; 9(1):4181.

Lung Cancer

Genomic Studies In Cancer Disparities – Lung Cancer

Carrot-Zhang et al., 2021. *Cancer Discov (2021) 11 (3): 591–598.*

Genomic Studies In Cancer Disparities – Lung Cancer



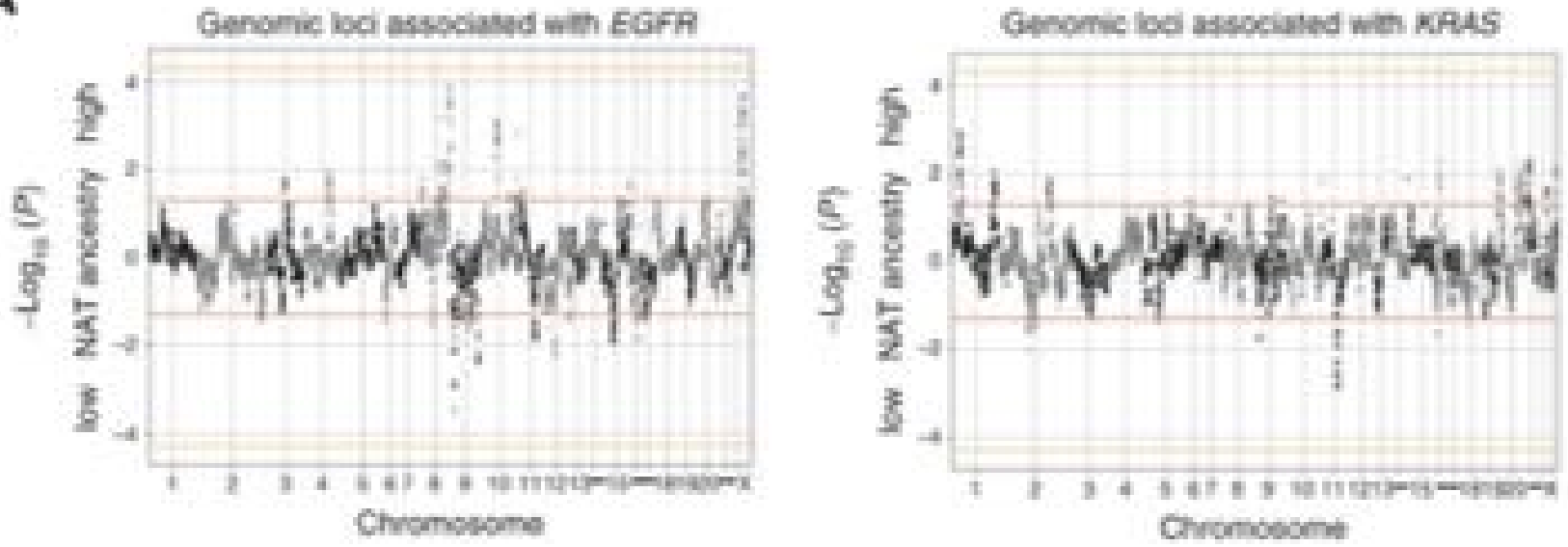
Carrot-Zhang et al., 2021. *Cancer Discov (2021) 11 (3): 591–598.*

Genomic Studies In Cancer Disparities – Lung Cancer

Carrot-Zhang et al., 2021. *Cancer Discov (2021) 11 (3): 591–598.*

Genomic Studies In Cancer Disparities – Lung Cancer

A



B

Gene – local ancestry risk score + global ancestry

		P val.	Coef.	95% CI
EGFR	Local ancestry risk score (cross-validated)	9e-08	0.53	0.35–0.71
	Global ancestry (NAT ancestry %)	0.31	0.11	−0.11–0.34
KRAS	Local ancestry risk score (cross-validated)	0.003	1.00	0.37–1.63
	Global ancestry (NAT ancestry %)	0.14	0.38	−0.12–0.89

Carrot-Zhang et al., 2021. *Cancer Discov (2021) 11 (3): 591–598.*

Summary

- Health disparities are real and are likely caused by a variety of factors, including socioeconomics.
- Differences in tumor biology are not well understood due to significant dearth in data derived from diverse patient populations.
- Mounting evidence from recent genomic studies demonstrating differences in genomic profiles from tumors derived from diverse patient cohorts. Profiles are not likely going to always be generalizable.
- Uncovering these factors may help us better understand disease etiology within different populations and could provide unique opportunities for improving disease management, potentially leading to decreases among certain known and validated cancer health disparities.
- WE MUST ENSURE PATIENT DIVERSITY IN DISCOVERY/VALIDATION STUDIES and in CLINICAL TRANSLATIONAL RESEARCH to increase our ability to be more thoughtful and impactful towards developing therapeutic approaches that are more personalized.

Towards Achieving Cancer Health Equity

https://www.chronicle.com