GLOBAL NETWORKS APPROACH TO REDUCE CANCER DISPARITY

Biological Effectors of Social Determinants of Health in Cancer: Identification and Mitigation
A National Cancer Policy Forum Workshop
March 20th 2024

Clayton Yates PhD
John R. Lewis Endowed Professor of Pathology
Director of Translational Health Disparities and Global Health Equity Research
Department of Pathology, Oncology, and Urology
Co-Leader Genomics and Epigenomics Core
Sidney Kimmel Comprehensive Cancer Center

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Disclosure Summary

Relationships:	
Consulting Fee	• Riptide Biosciences • PreludeDX
Honoraria	• QED Therapeutics • Amgen • Regeneron
Editorial	• Associate Editor Cancer Research Communication (AACR) • Scientific Reports (Nature)

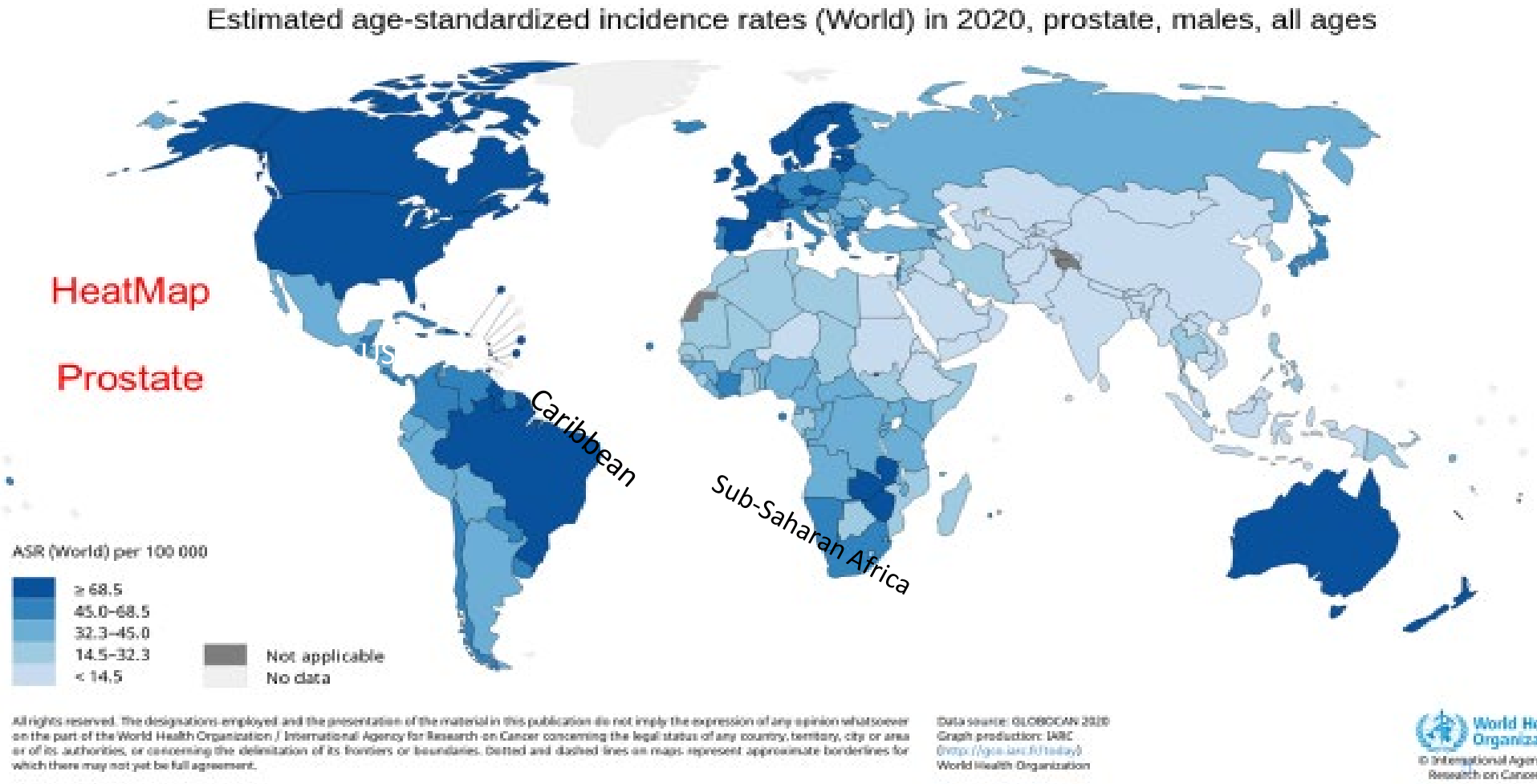
Off-label Disclosure

This activity may include presentations on drugs or devices, or use of drugs or devices, that have not been approved by the Food and Drug Administration (FDA) or have been approved by the FDA for specific uses only. The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or device he or she wishes to use in clinical practice.

CaPTC: Closing the CaP Gap

HeatMap

Prostate



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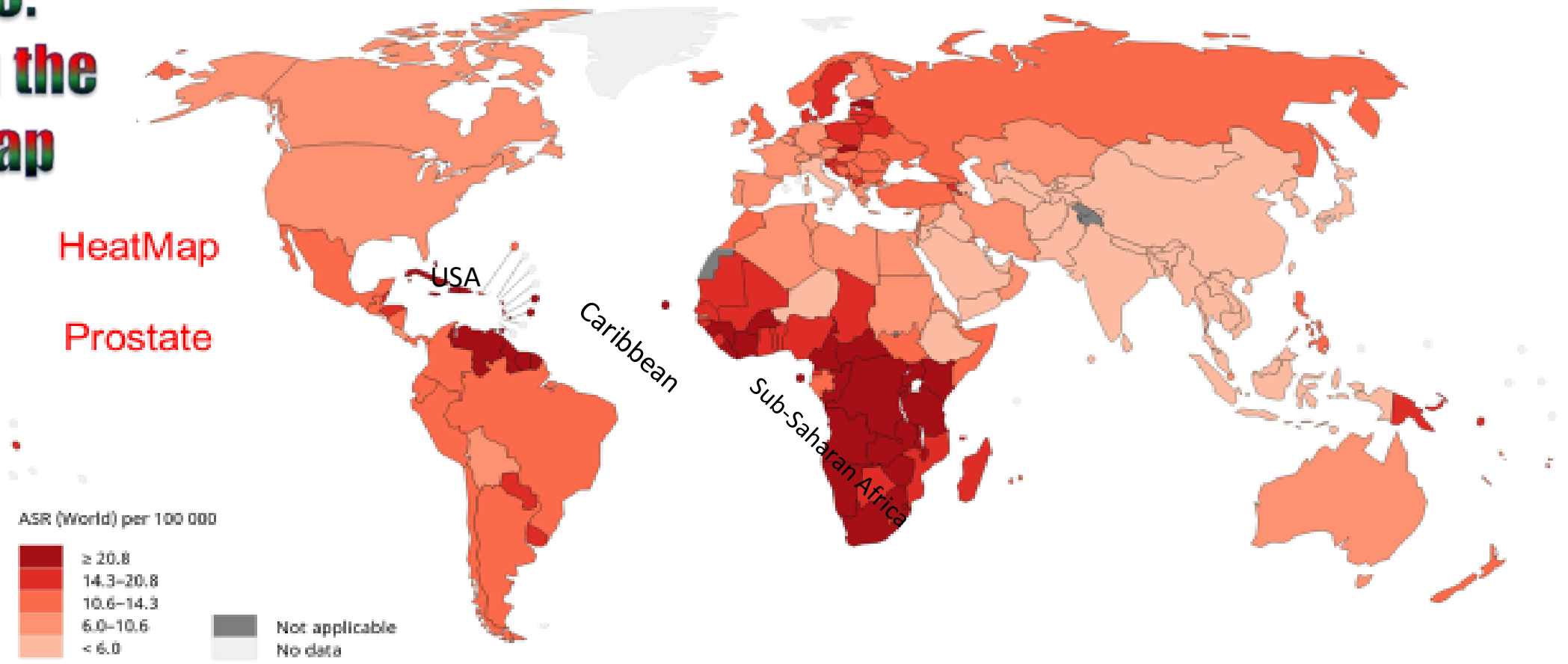
CaPTC: Closing the CaP Gap

HeatMap

Prostate



Data source: GLOBOCAN 2020
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

World Health Organization

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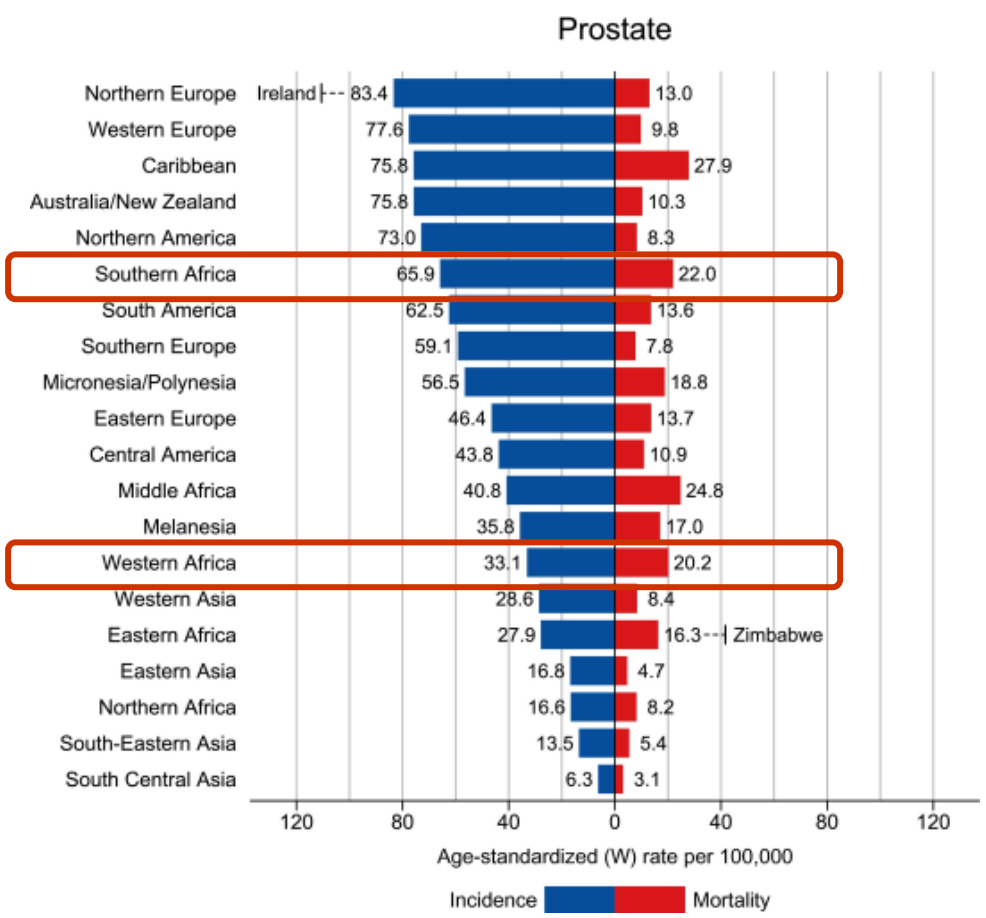
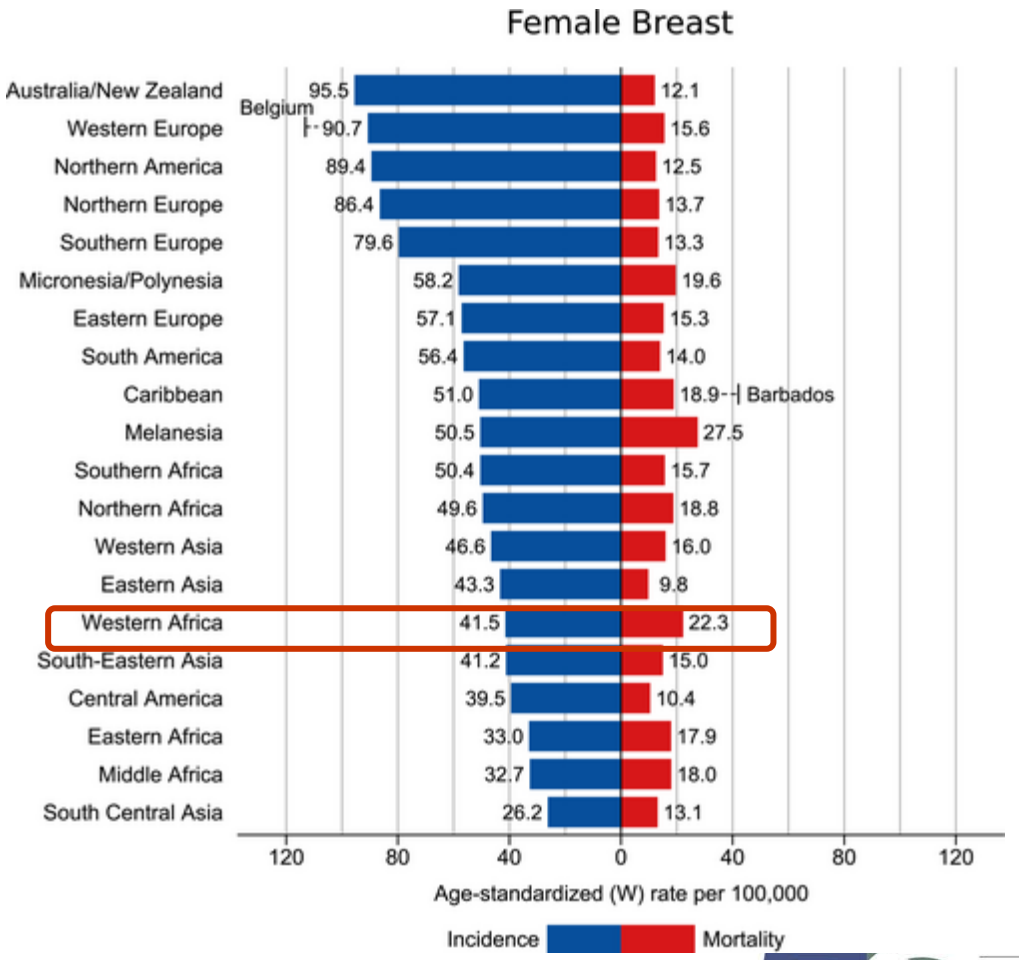
Global Prostate and Breast Cancer Rates





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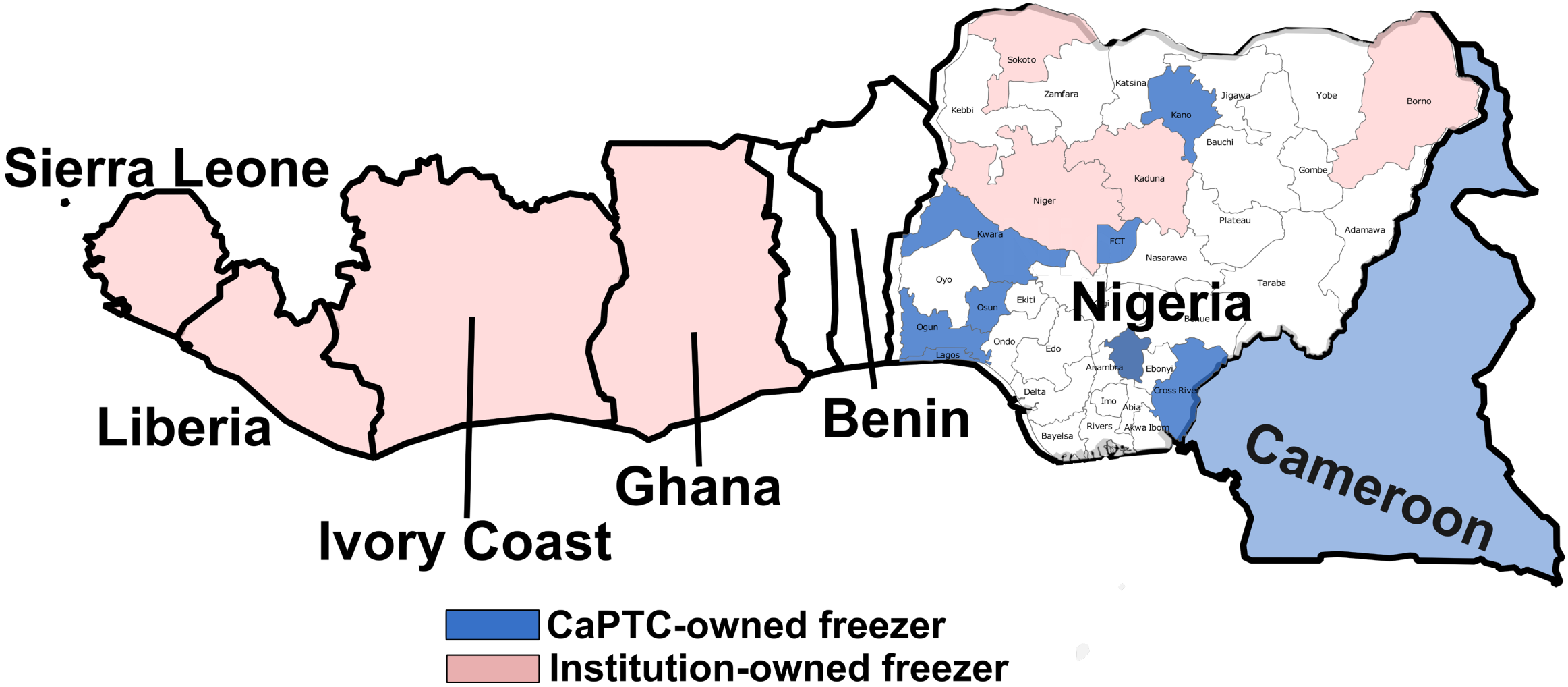
PROSTATE CANCER TRANSATLANTIC CONSORTIUM PROGRAM

Folakemi Odedina, PhD
Consortium co-PI & Director

Solomon Rotimi PhD
Consortium co-PI & Director

Clayton Yates PhD
Consortium co-PI & Director

CaPTC Sites and Biorepository Locations in Africa



Social and Behavioral Studies Led by CaPTC Investigators

CaPTC: Closing the CaP Gap

J Immigrant Minority Health (2009) 11:258–267
DOI 10.1007/s10903-008-9212-9

ORIGINAL PAPER

Prostate Cancer Cognitive-Behavioral Factors in a West African Population

Folakemi T. Odedina · Daohai Yu · Titilola O. Akinremi · R. Renee Reams · Matthew L. Freedman · Nagi Kumar

J Immigrant Minority Health (2009) 11:391–399
DOI 10.1007/s10903-009-9231-1

ORIGINAL PAPER

Comparing Dietary and Other Lifestyle Factors Among Immigrant Nigerian Men Living in the US and Indigenous Men from Nigeria: Potential Implications for Prostate Cancer Risk Reduction

Nagi B. Kumar · Daohai Yu · Titilola O. Akinremi · Folakemi T. Odedina

J Immigrant Minority Health
DOI 10.1007/s10903-011-9471-8

ORIGINAL PAPER

Within-Group Differences Between Native-Born and Foreign-Born Black Men on Prostate Cancer Risk Reduction and Early Detection Practices

Folakemi T. Odedina · Getachew Dagne · Margareth LaRose-Pierre · John Scrivens · Frank Emanuel · Angela Adams · Shannon Pressey · Oladapo Odedina

Cancer Health Disparities Journal Special Series, 2019

RESEARCH

Risk factors for prostate cancer in West African Men: The Familial Cohort Study

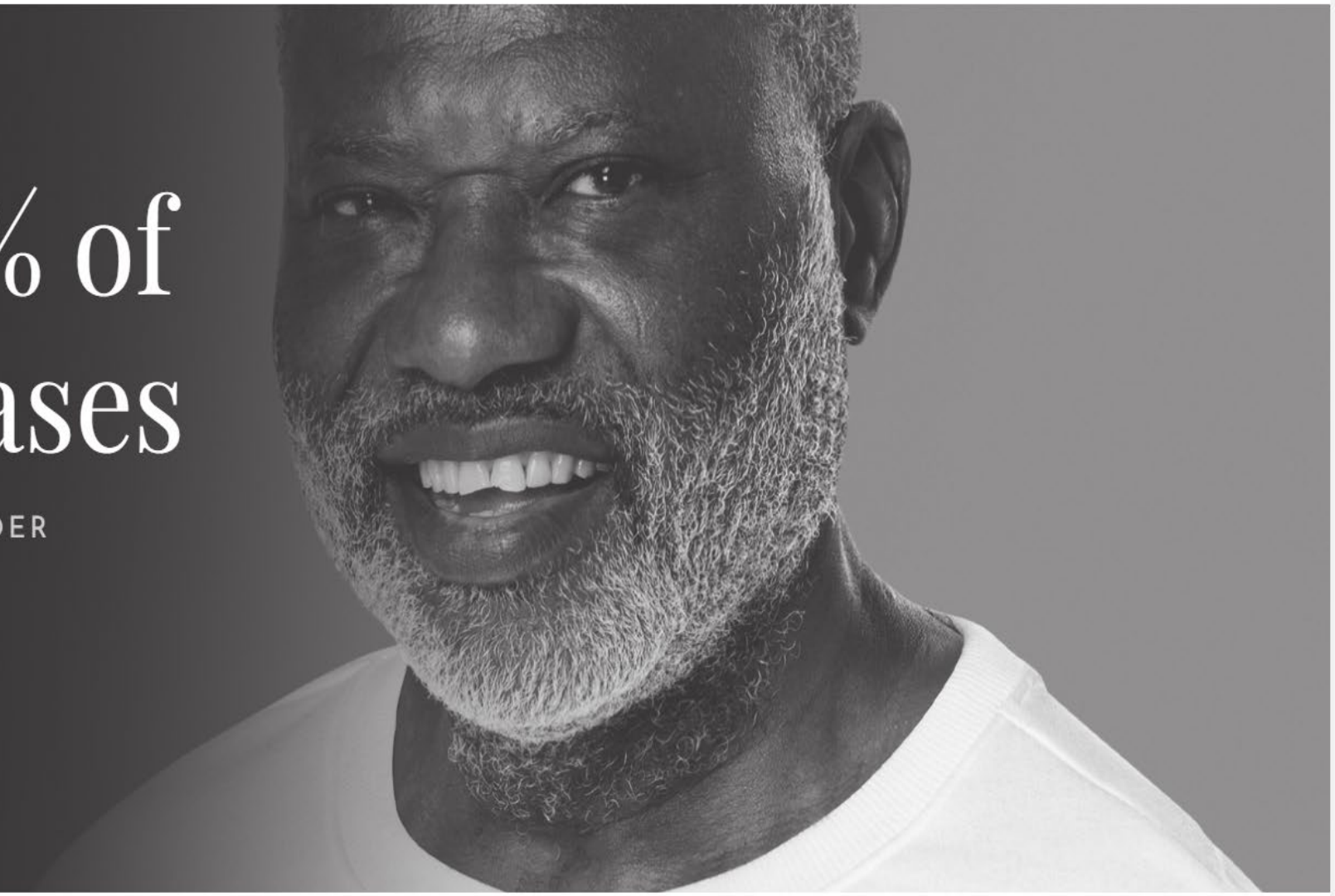
Catherine A. Oladoyinbo [1,7]*, Oluwafunke O. Akinbule[1,7], Opeyemi O. Bolajoko [1,7], Justice Moses K. Aheto[2,7], Getachew Dagne [3,7], Faruk Mohamed [4,7], Iya Eze Bassey[5,7], Folakemi T. Odedina[6,7], Ruth Agaba [7], Nissa Askins [6,7], Olubanke O. Ogunlana[8,7], Motolani E. Ogunsanya [9,7], Aishat M. Suleiman [4,7], Stanley O. Anyanwu [5,7], Rebecca M. Gali [10,7], Ernest Kaninjing [11,7], Blaise Nkegoum [12,7], Abidemi Omonisi[13,7], Anthonia C. Sowunmi [14,7], Paul Jibrin [15,7], Emeka E. Iweala[8,7], Omolara A. Fatiregun[16,7] and Ademola A. Popoola[17,7]

What is prostate cancer?

Globally, 60% of diagnosed cases

ARE MEN WHO ARE 65 YEARS OR OLDER

REQUEST DATA



Clinical Networks

Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men With Advanced Prostate Cancer (IRONMAN)

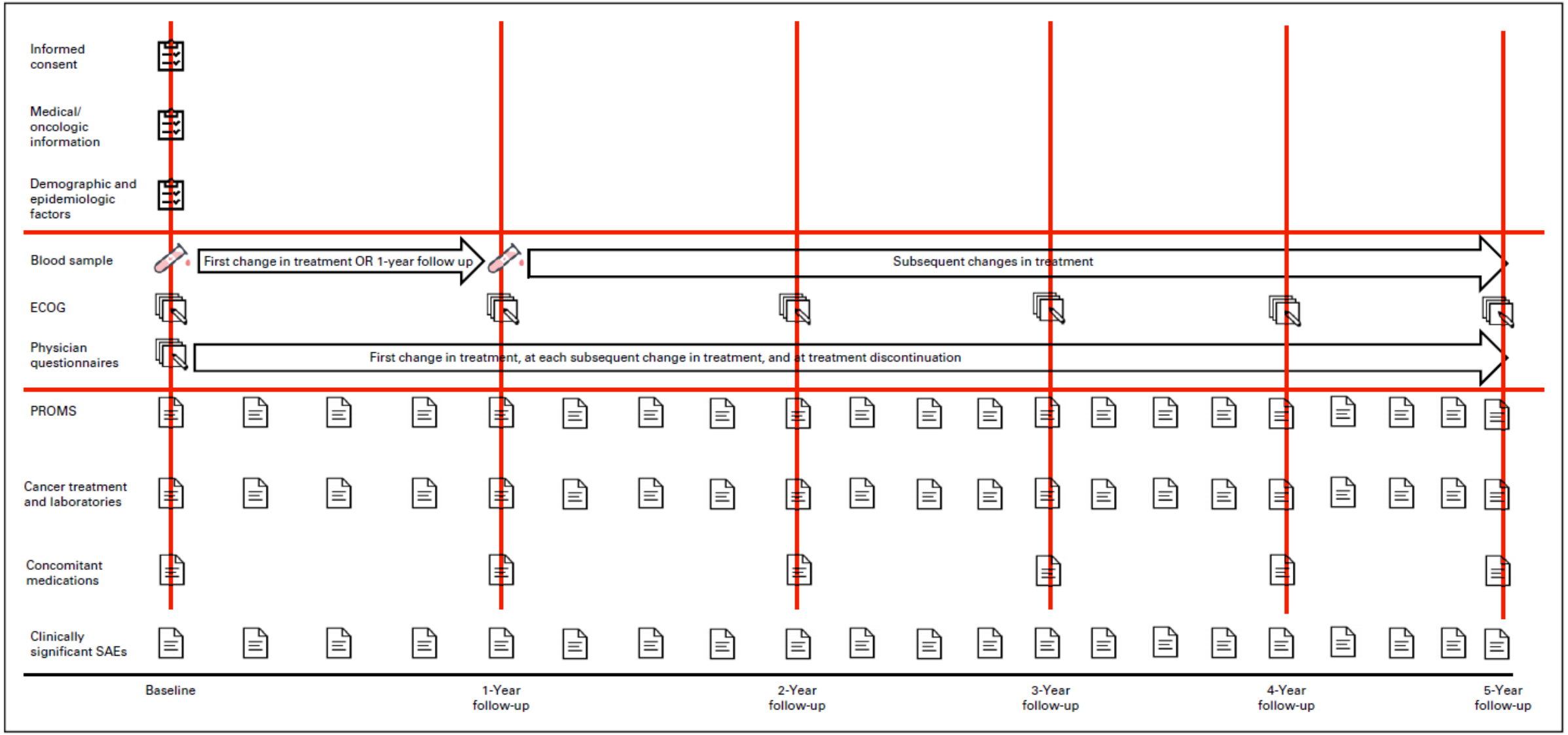
GENITOURINARY CANCER

Tackling Diversity in Prostate Cancer Clinical Trials: A Report From the Diversity Working Group of the IRONMAN Registry

Rana R. McKay, MD[1]; Theresa Gold, BS, MS[2]; Jelani C. Zarif, PhD[3]; Ilkania M. Chowdhury-Paulino, MPH[4]; Adam Friedant, BS, MS[2]; Travis Gerke, ScD[5]; Marie Grant, BA[2]; Kelly Hawthorne, MS[6]; Elisabeth Heath, MS[7]; Franklin W. Huang, MD, PhD[8]; Maria D. Jackson, PhD[9]; Brandon Mahal, MD[10]; Osarenren Ogbeide, MD[11]; Kellie Paich, MA, MPH[6]; Camille Ragin, PhD, MPH[12,13]; Emily M. Rencsok, BS[4]; Stacey Simmons, MD[14]; Clayton Yates, PhD[15,16]; Jake Vinson, MHA[2]; Philip W. Kantoff, MD[17]; Daniel J. George, MD[18]; and Lorelei A. Mucci, ScD[5]

https://clinicaltrials.gov/ct2/show/NCT03151629

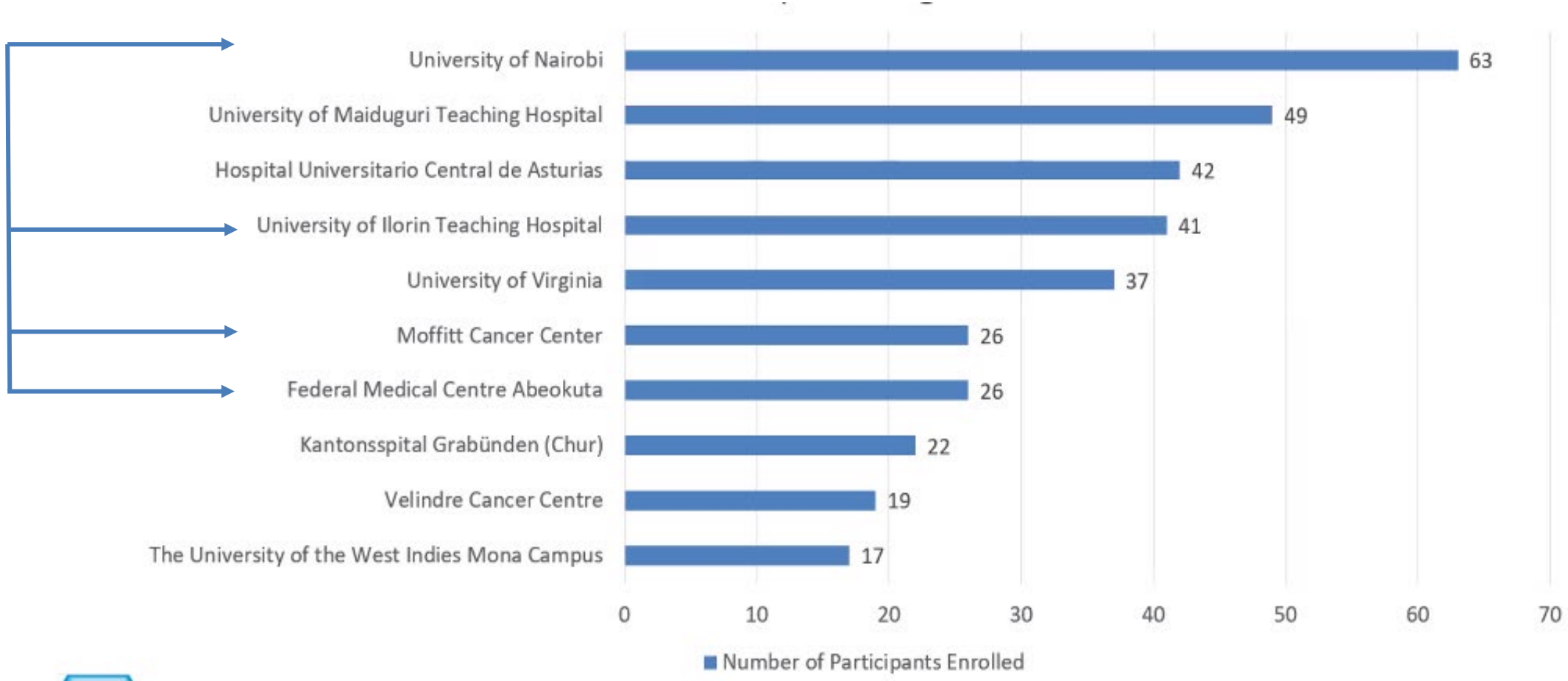
Overview of the IRONMAN Study



Mucci et al 2022 JCO Global

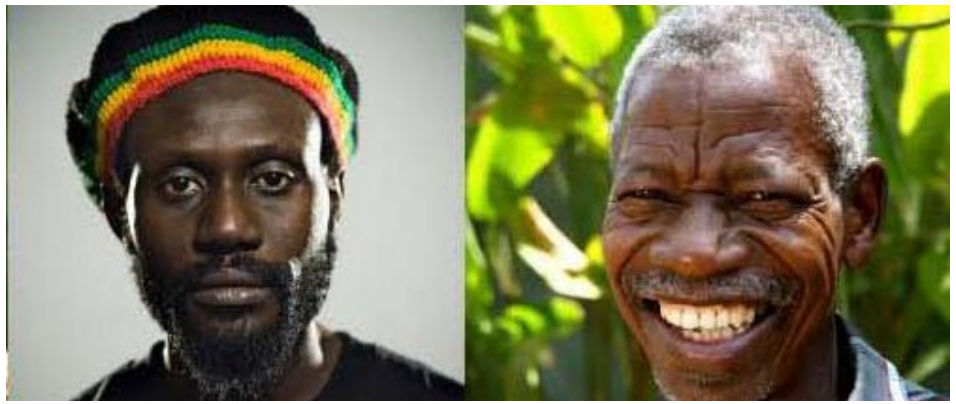
IRONMAN TOP Enrolling Site 2023

AC3/CaPTC Consortium



The Prostate Cancer Clinical Trials Consortium

CaPTC: Closing the CaP Gap



What ?

Prostate Cancer Disparities in Men of African Ancestry

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Infectious Agents and Cancer

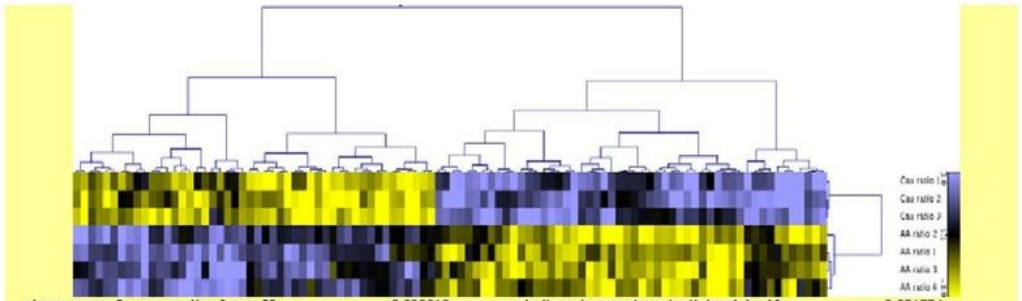
BioMed Central

Proceedings

Open Access

Microarray comparison of prostate tumor gene expression in African-American and Caucasian American males: a pilot project study

R Renee Reams*[1], Deepak Agrawal[†2], Melissa B Davis[†3], Sean Yoder[†2], Folakemi T Odedina[†2], Nagi Kumar[†2], Joseph M Higginbotham[†1], Titilola Akinremi[†4], Sandra Suther[†5] and Karam FA Soliman[†1]



chromosome 9 open reading frame 93	-5.288819	cholinergic receptor, nicotinic, alpha 10	-2.851774
helicase (DNA) B	4.651818	paired-like homeodomain transcription factor 1	3.531298
cholinergic receptor, muscarinic 3	-5.047906	chromosome 9 open reading frame 62	-3.983288
zyg-11 homolog A (C. elegans)	-5.491622	chromosome 21 open reading frame 88	2.890642
ring finger protein 187	-5.379997	tubulin tyrosine ligase-like family, member 5	4.073312
histone deacetylase 11	-4.487602	transcription factor 12 (HTF4, helix-loop-helix transcri	-2.795597
hypothetical protein LOC440295	4.920586	progesterone receptor	-2.783023
interferon regulatory factor 4	-4.214245	myeloid/lymphoid or mixed-lineage leukemia 4	-3.80314
paired box gene 5 (B-cell lineage specific activator)	3.166453	NSFL1 (p97) cofactor (p47)	-4.411559
homeobox D4	-3.859365	ring finger protein 168	4.556035
alanine-glyoxylate aminotransferase	-4.773391	hypothetical protein FLJ32658	-3.835421
contactin 4	4.053437	glypican 5	-3.178348
transcription factor 3 (E2A immunoglobulin enhancer	-3.119406	Friend leukemia virus integration 1	2.434884
potassium voltage-gated channel, KQT-like subfamily	-5.316092	heterogeneous nuclear ribonucleoprotein D (AU-rich	3.095944
zinc finger protein 650	-4.522508	ADAM metallopeptidase with thrombospondin type 1	3.204275
WD repeat domain 32	-4.752269	myelin-associated oligodendrocyte basic protein	2.572629
insculeable homolog (Drosophila)	-3.820665	Ran GTPase activating protein 1	-3.898153
chromosome 15 open reading frame 26	-4.805246	delta-like 3 (Drosophila)	2.556212
WD repeat domain 60	-4.202883	chemokine (C-X-C motif) ligand 2	-4.644899
transient receptor potential cation channel, subfamily	4.572568	G protein-coupled receptor 98	-3.110733
DEAD (Asp-Glu-Ala-As) box polypeptide 19B	4.220601	BUB3 budding uninhibited by benzimidazoles 3 homo	-3.065752
		doublecortin and CaM kinase-like 3	2.960531

Renee Reams PhD
Florida A&M Univ.

Stefan Ambs PhD
NCI

Research Article

Tumor Immunobiological Differences in Prostate Cancer between African-American and European-American Men

Tiffany A. Wallace,[1] Robyn L. Prueitt,[1] Ming Yi,[3] Tiffany M. Howe,[1] John W. Gillespie,[2] Harris G. Yfantis,[4] Robert M. Stephens,[3] Neil E. Caporaso,[5] Christopher A. Loffredo,[6] and Stefan Ambs[1]

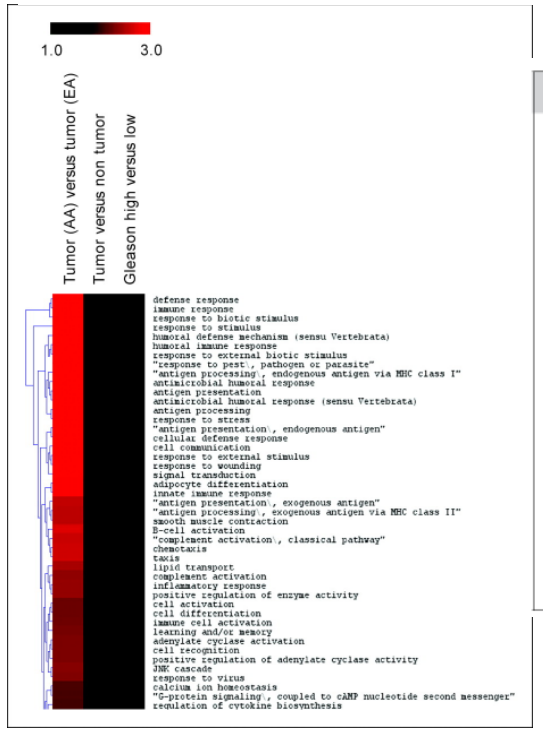


Table 2. Twenty highest-ranked GOBP terms enriched for differently expressed genes comparing tumors from African-American and European-American patients

GOBP term	Term hits*	All genes†	Annotated genes for term‡	All annotated genes§	*P* (Fisher's exact test)
Immune response	66	217	944	16,762	5.66E-31
Defense response	68	217	1,045	16,762	4.38E-30
Response to biotic stimulus	70	217	1,190	16,762	2.44e−28
Organismal physiologic process	74	217	2,111	16,762	1.46e−16
Response to stimulus	77	217	2,281	16,762	2.23e−16
Response to pest/pathogen or parasite	27	217	472	16,762	9.70e−11
Humoral immune response	16	217	162	16,762	3.38e−10
Response to external biotic stimulus	27	217	502	16,762	3.83e−10
Humoral defense mechanism	13	217	114	16,762	2.75e−09
Response to stress	34	217	929	16,762	3.76e−08
Antigen processing	8	217	45	16,762	9.90e−08
Antigen processing via MHC class I	5	217	14	16,762	6.32e−07
Antigen presentation	7	217	44	16,762	1.41e−06
Antimicrobial humoral response	9	217	85	16,762	1.52e−06
Antimicrobial humoral response	9	217	88	16,762	2.04e−06
Antigen presentation	4	217	13	16,762	1.78e−05
Cellular defense response	8	217	93	16,762	2.75e−05
Signal transduction	67	217	3,465	16,762	2.40e−04
Cell communication	77	217	4,177	16,762	3.11e−04
Apoptosis	16	217	458	16,762	3.20e−04

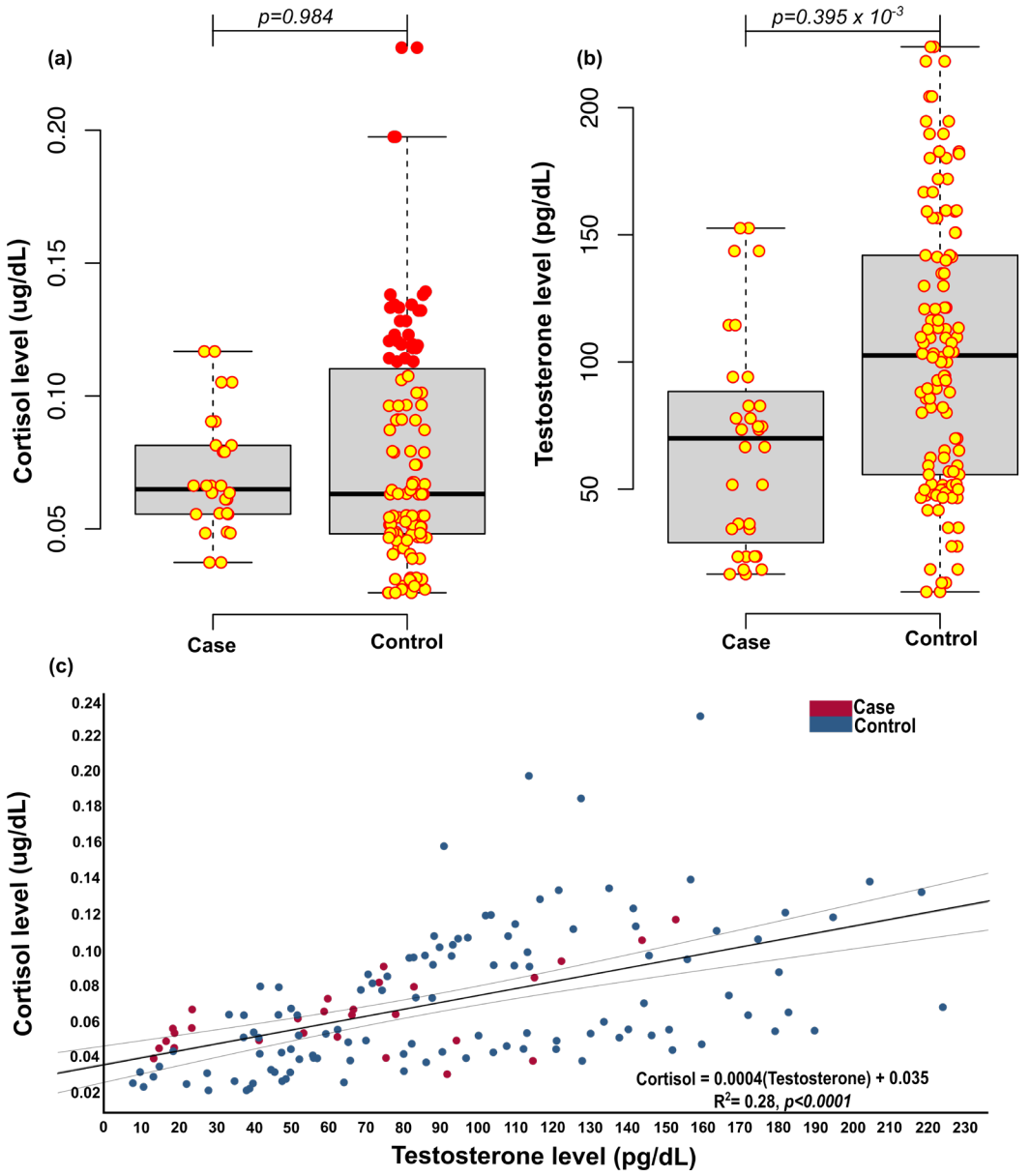
*Annotated genes in a GOBP term that are differently expressed (FDR, ≤30%) comparing tumors from African-American with those from European-American.
†All GOBP-annotated genes that are differently expressed in this comparison.
‡All annotated genes in a GOBP term.
§All GOBP-annotated genes.

Association of Cortisol with Testosterone

Solomon O. Rotimi, CaPTC PI

- Higher level of cortisol was observed in some individuals controls and our follow-up study will indicate if this levels influences their PCa risk later in life.
- PCa patients had significantly lower testosterone but higher levels were still observed in some individuals.
- Interestingly, we observed a positive correlation between cortisol and testosterone in our cohort.

CaPTC: Closing the CaP Gap



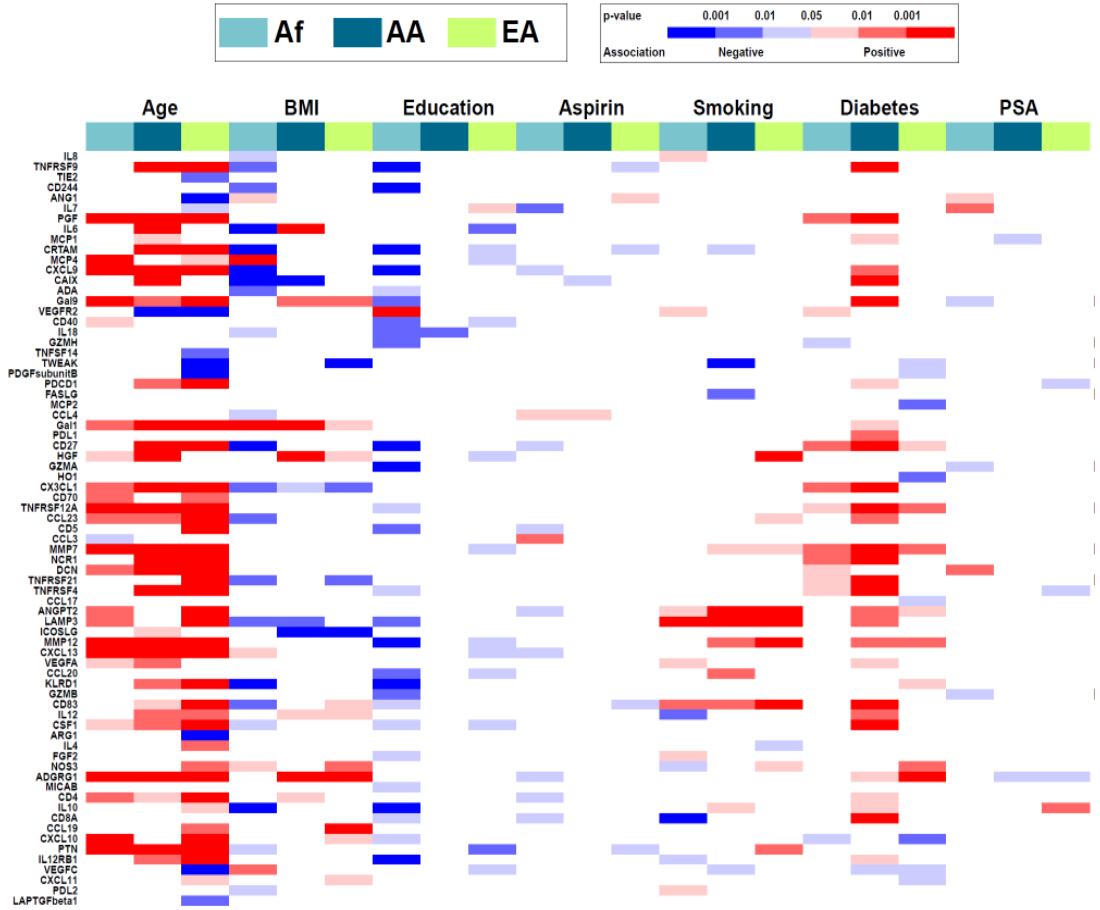
Correlating Serum Markers with Immunogenicity and Ancestry

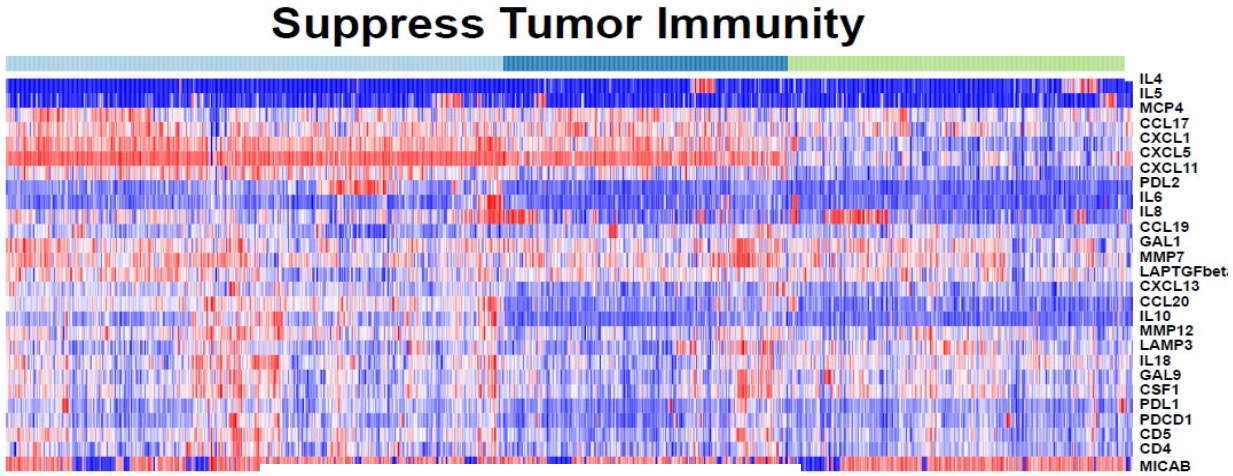
n=1482 (654 Af, 374 AA, and 454 EA)

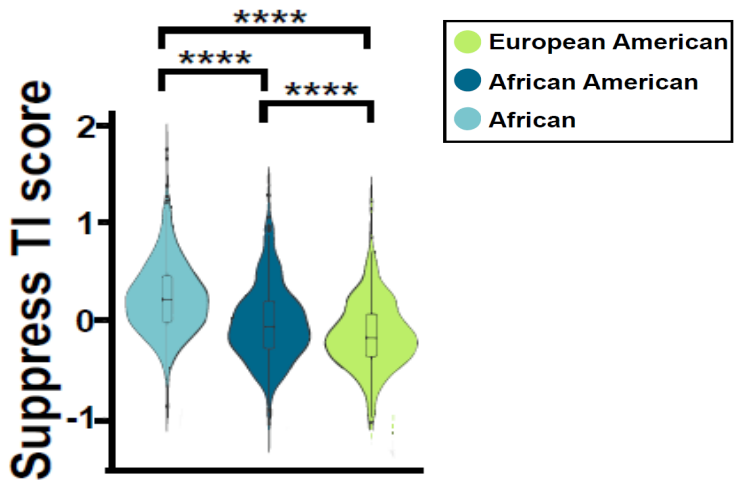
Collaborators

Stefan Ambs PhD
NCI

Rick Kittles PhD
Morehouse Medicine

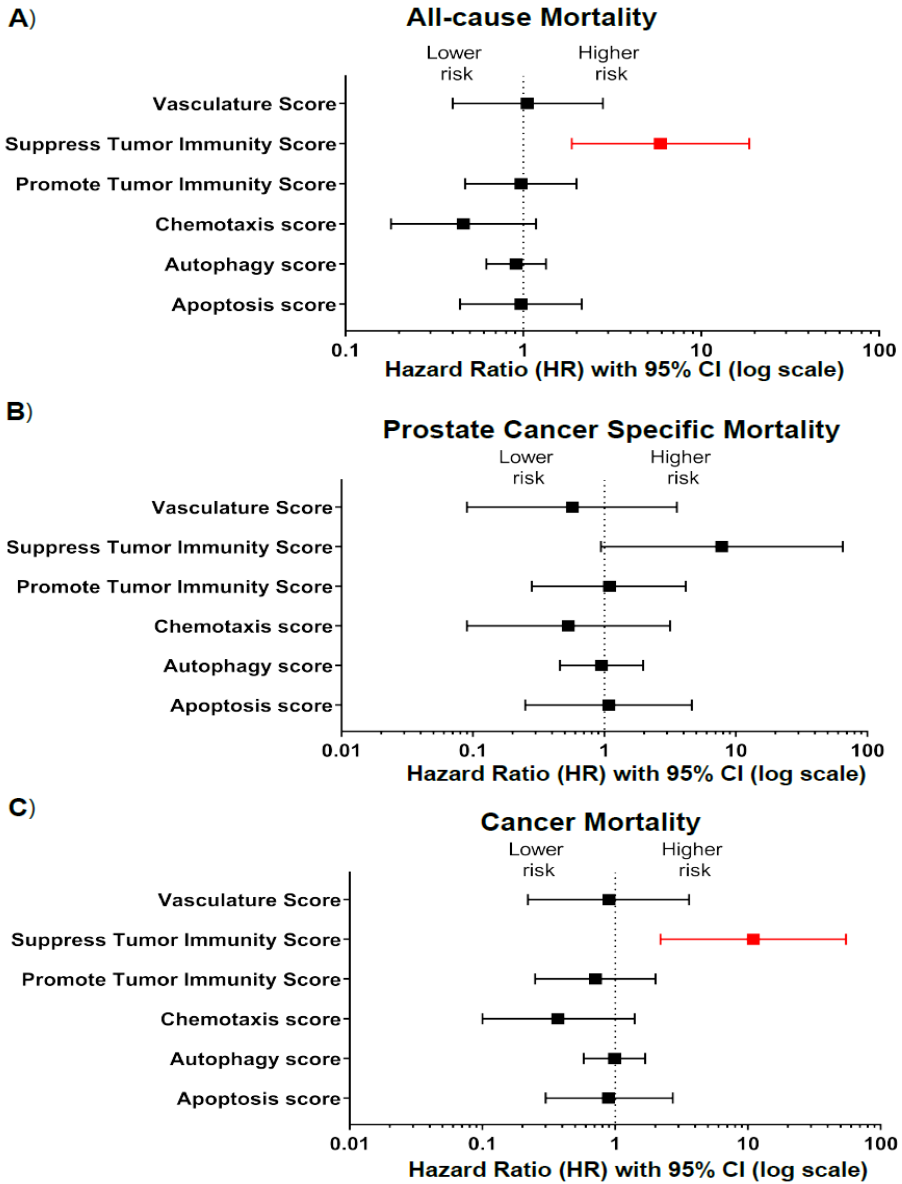


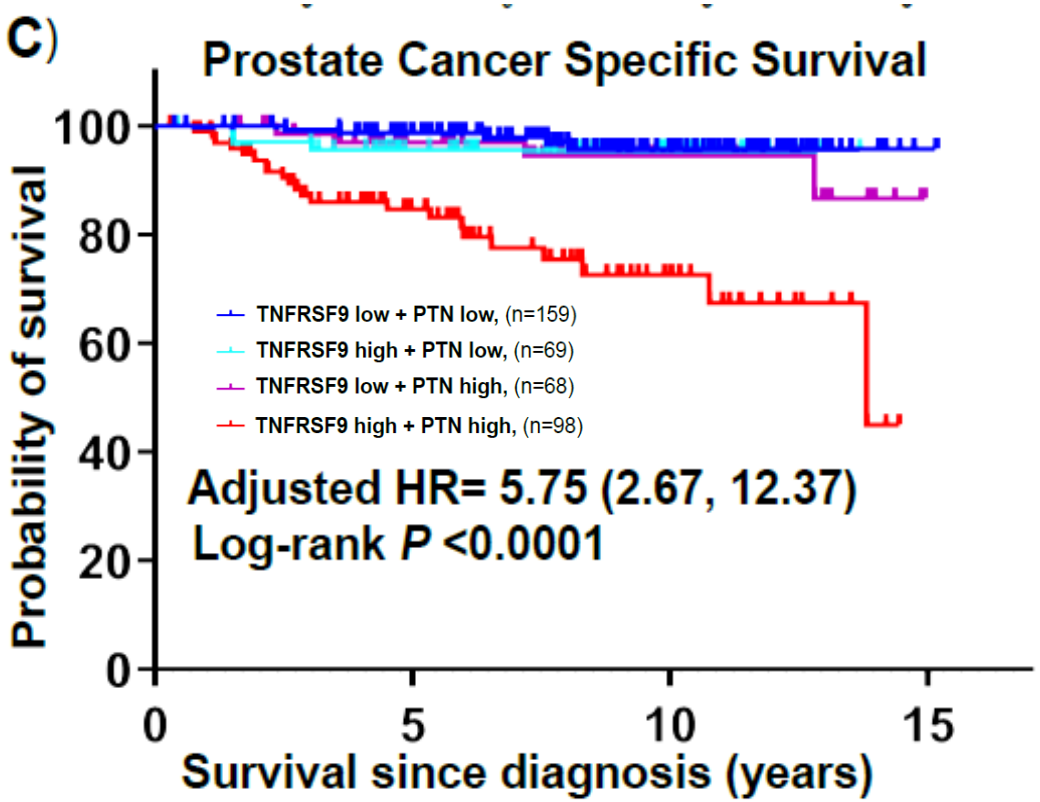




Minas et al Nature Communications **volume 13**, (2022)

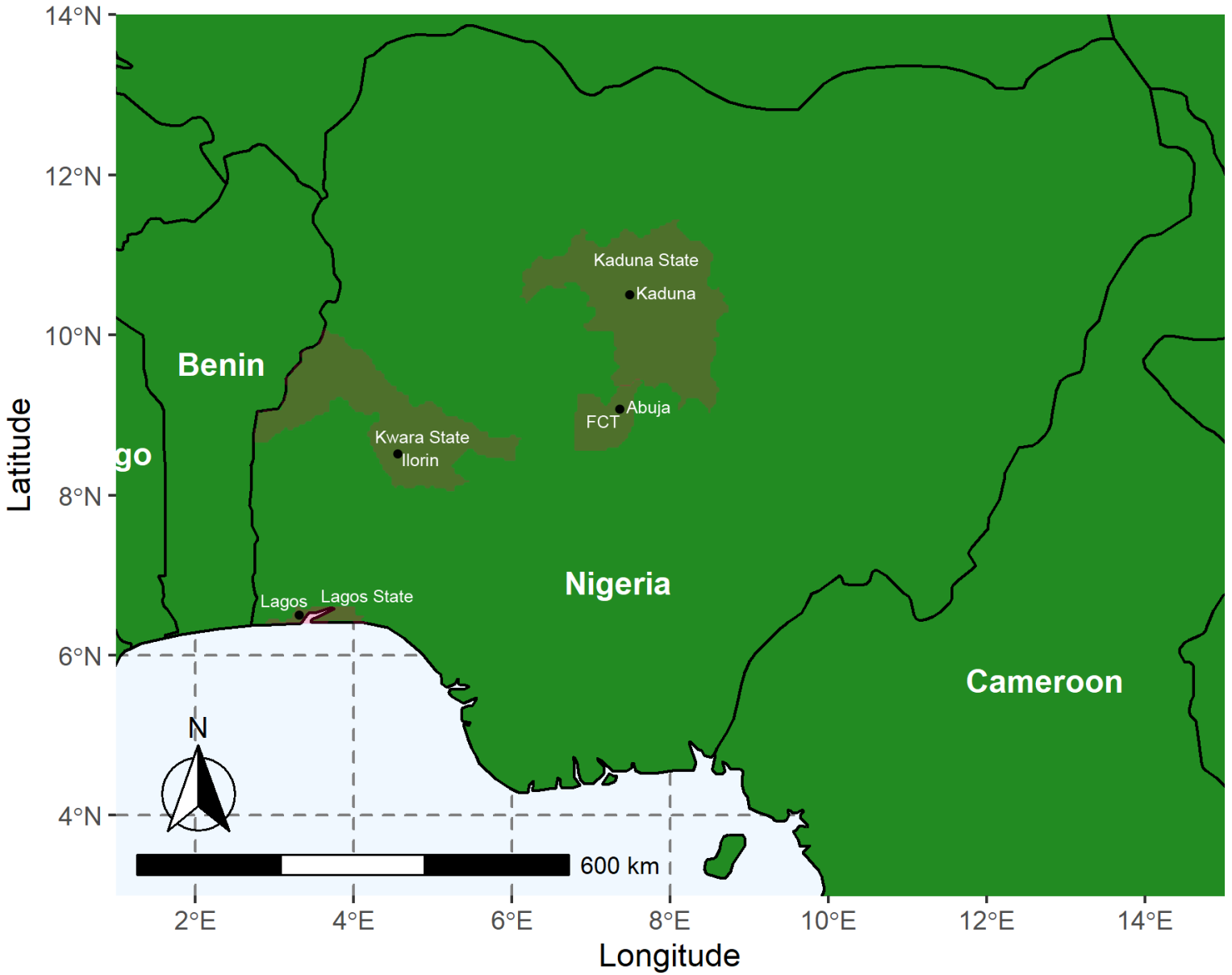
Tumor Suppressive Signature Correlates with Lower Survival in African Ancestry Prostate Cancer Patients





Minas et al Nature Communications **volume 13**, (2022)

Prostate Cancer Contributing Sites in Nigeria



Dr. Kayode Adeniji
Illorin

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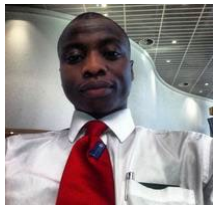
National Hospital
Abuja



Faruk Mohammed PhD
ABU- Zaria, Nigeria

	Nigerian CaPTC Tumors (N=45)
Patient Annotations	
Collection Site:	
FCT	17 (37.8%)
Kaduna State	20 (44.4%)
Kwara and Lagos State	8 (17.8%)
Tumor Aggression	
Aggressive (≥ 4+3)	37 (82.2%)
Indolent (≤ 3+4)	8 (17.8%)
Patient Age (yrs)	67

CANCER RESEARCH COMMUNICATIONS

AACR American Association for Cancer Research

CANCER RESEARCH COMMUNICATIONS

AACR American Association for Cancer Research

RESEARCH ARTICLE https://doi.org/10.1158/2767-9764.CRC-22-0136 OPEN ACCESS

Whole-exome Sequencing of Nigerian Prostate Tumors from the Prostate Cancer Transatlantic Consortium (CaPTC) Reveals DNA Repair Genes Associated with African Ancestry

Jason A. White[1], Ernest T. Kaninjing[2], Kayode A. Adeniji[3], Paul Jibrin[4], John O. Obafunwa[5], Chidiebere N. Ogo[6], Faruk Mohammed[7], Ademola Popoola[3], Omolara A. Fatiregun[5], Olabode P. Oluwole[8], Balasubramanyam Karanam[1], Isra Elhussin[1], Stefan Ambs[9], Wei Tang[9], Melissa Davis[10], Paz Polak[11], Moray J. Campbell[12], Kathryn R. Brignole[13], Solomon O. Rotimi[14], Windy Dean-Colomb[1,15], Folake T. Odedina[16], Damali N. Martin[17], and Clayton Yates[1]

ABSTRACT

In this study, we used whole-exome sequencing of a cohort of 45 advanced-stage, treatment-naive Nigerian (NG) primary prostate cancer tumors and 11 unmatched nontumor tissues to compare genomic mutations with African American (AA) and European American (EA) The Cancer Genome Atlas (TCGA) prostate cancer. NG samples were collected from six sites in central and southwest Nigeria. After whole-exome sequencing, samples were processed using GATK best practices. *BRCA1* (100%), *BARD1* (45%), *BRCA2* (27%), and *PMS2*(18%) had germline alterations in at least two NG nontumor samples. Across 111 germline variants, the AA cohort reflected a pattern *[BRCA1* (68%), *BARD1* (34%), *BRCA2* (28%), and *PMS2* (16%)] similar to NG samples. Of the most frequently mutated genes, *BRCA1* showed a statistically ($P \leq 0.05$) higher germline mutation frequency in men of African ancestry (MAA) and increasing variant frequency with increased African ancestry. Disaggregating gene-level mutation frequencies by variants revealed both ancestry-linked and NG-specific germline variant patterns. Driven by rs799917 (T>C), *BRCA1* showed an increasing mutation frequency as African ancestry increased. BRCA2_rs1571831 was present only in MAA, and BRCA2_rs766173 was elevated in NG men. A total of 133 somatic variants were present in 26 prostate cancer–associated genes within the NG tumor cohort. *BRCA2* (27%), *APC* (20%), *ATM* (20%), *BRCA1* (13%), *DNAJC6* (13%), *EGFR* (13%), *MADH11* (13%), *MLH1* (11%), and *PMS2* (11%) showed mutation frequencies >10%. Compared with TCGA cohorts, NG tumors showed statistically significant elevated frequencies of *BRCA2*, *APC*, and *BRCA1*. The NG cohort variant pattern shared similarities (cosign similarities ≥0.734) with Catalogue of Somatic Mutations in Cancer signatures 5 and 6, and mutated genes showed significant ($q < 0.001$) gene ontology (GO) and functional enrichment in mismatch repair and non-homologous repair deficiency pathways. Here, we showed that mutations in DNA damage response genes were higher in NG prostate cancer samples and that a portion of those mutations correlate with African ancestry. Moreover, we identified variants of unknown significance that may contribute to population-specific routes of tumorigenesis and treatment. These results present the most comprehensive characterization of the NG prostate cancer exome to date and highlight the need to increase diversity of study populations.

Significance: MAA have higher rates of prostate cancer incidence and mortality, however, are severely underrepresented in genomic studies. This is the first study utilizing whole-exome sequencing in NG men to identify West African ancestry-linked variant patterns that impact DNA damage repair pathways.

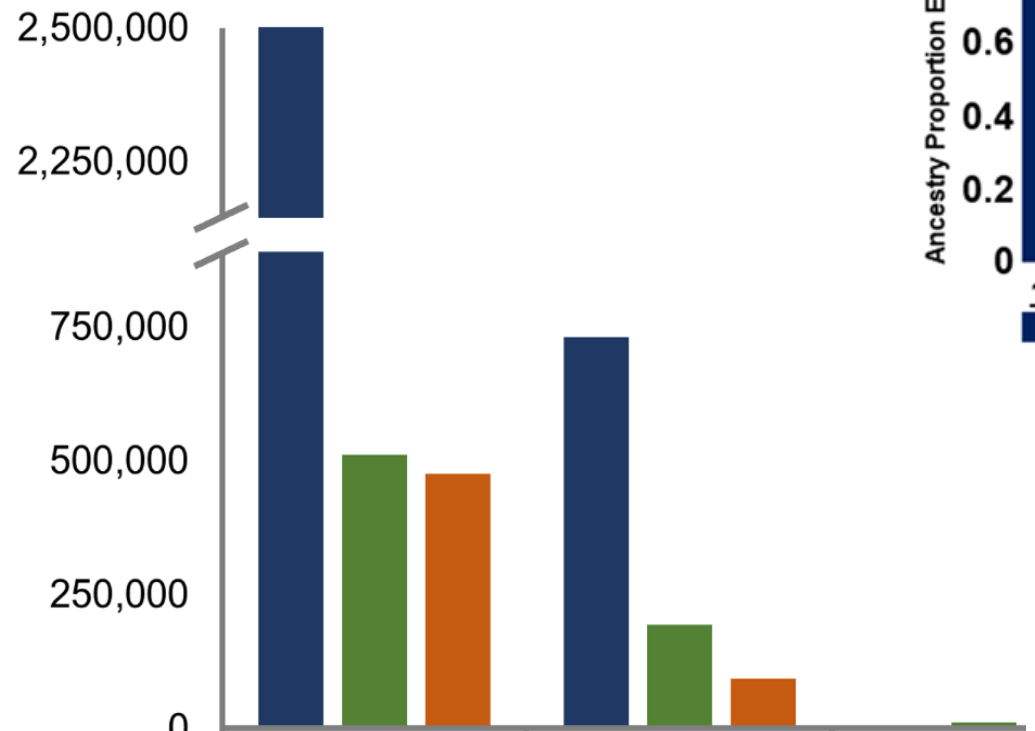
[1]Tuskegee University, Center for Cancer Research, Tuskegee, Alabama. [2]Georgia College & State University, Milledgeville, Georgia. [3]University of Ilorin Teaching Hospital, Nigeria, Ilorin. [4]National Hospital Abuja, Nigeria, Abuja. [5]Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria. [6]Federal Medical Centre, Abeokuta, Nigeria. [7]Ahmadu Bello University, Zaria Nigeria. [8]University of Abuja, FCT, Nigeria. [9]Molecular Epidemiology Section, Laboratory of Human Carcinogenesis, Center for Cancer Research, NCI, Bethesda, Maryland. [10]Department of Surgery, New York Presbyterian – Weill Cornell Medicine, New York, New York. [11]C2i Genomics, New York, New York. [12]Division of Pharmacoutics and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio. [13]University of North Carolina Chapel Hill, North Carolina. [14]Department of Biochemistry, Covenant University, Ota, Nigeria. [15]Piedmont Medical Oncology – Newnan, Newnan, Georgia. [16]Center for Health Equity and Community Engagement Research, Mayo Clinic, Jacksonville, Florida. [17]Division of Cancer Control and Population Sciences, NCI, Rockville, Maryland.

Corresponding Author: Clayton C. Yates, Biology and Center for Cancer Research, Tuskegee University, Carver Research Bldg. Rm 22, Tuskegee, AL 36088. Phone: 334-727-8949; E-mail: cyates@tuskegee.edu

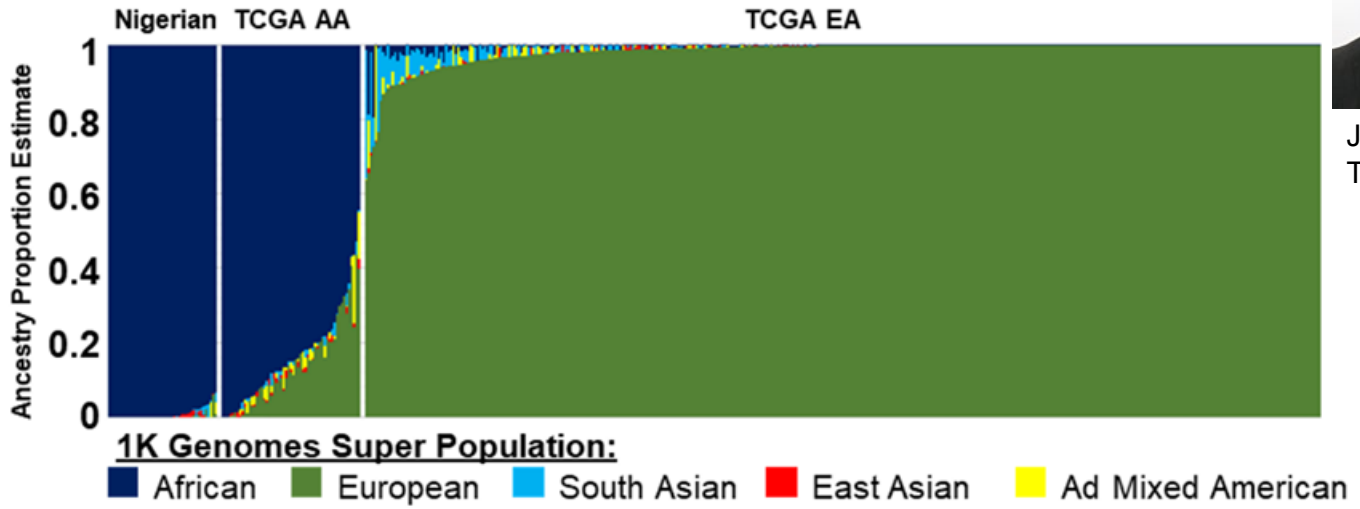
doi: 10.1158/2767-9764.CRC-22-0136

Nigerian Tumors have increased Variants of Unknown Sequences

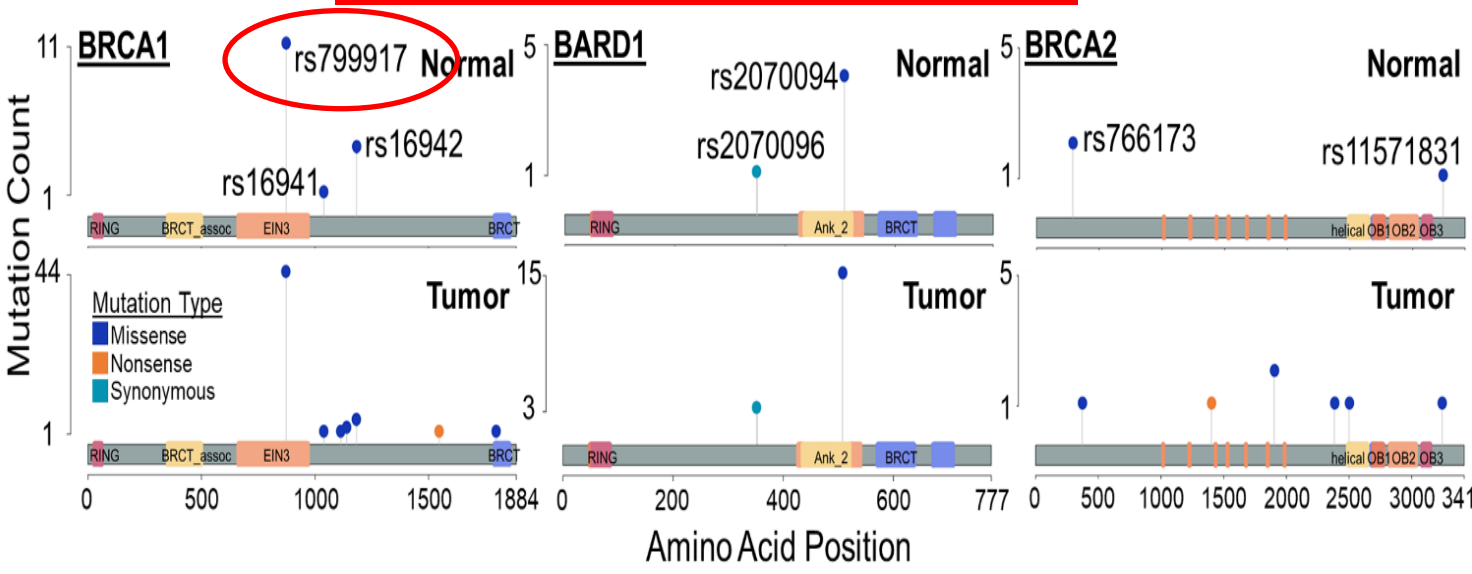
Jason White M.S
Tuskegee Univ.



	Tumor Only	Unmatched Normal	Matche Norma
Nigerian	2,506,254	730,285	
TCGA AA	511,007	193,703	11,20
TCGA EA	476,038	93,194	15,19

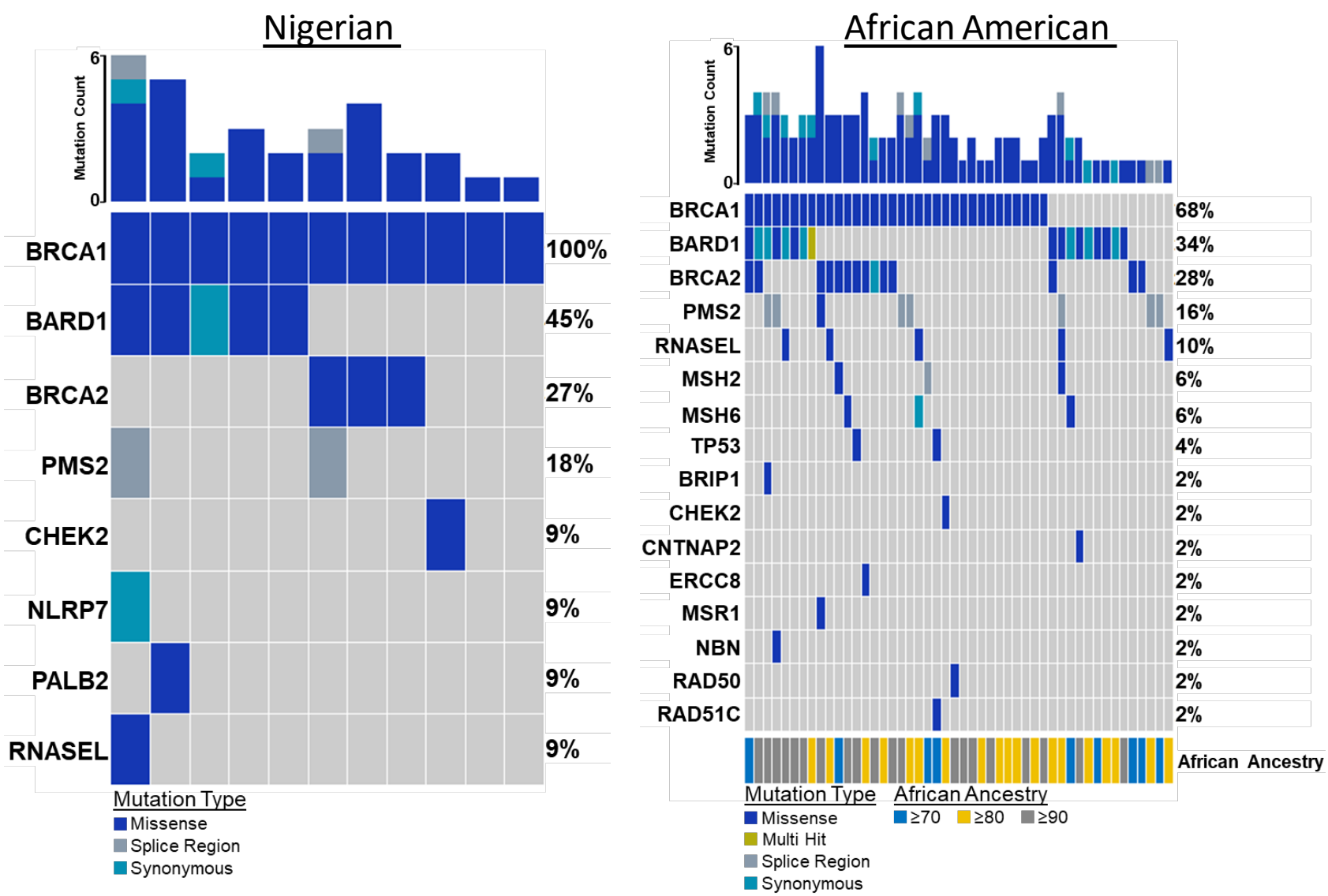


***Nigerian Specific Germline Variant



White et al Cancer Res Commun; 2(9) September 2022

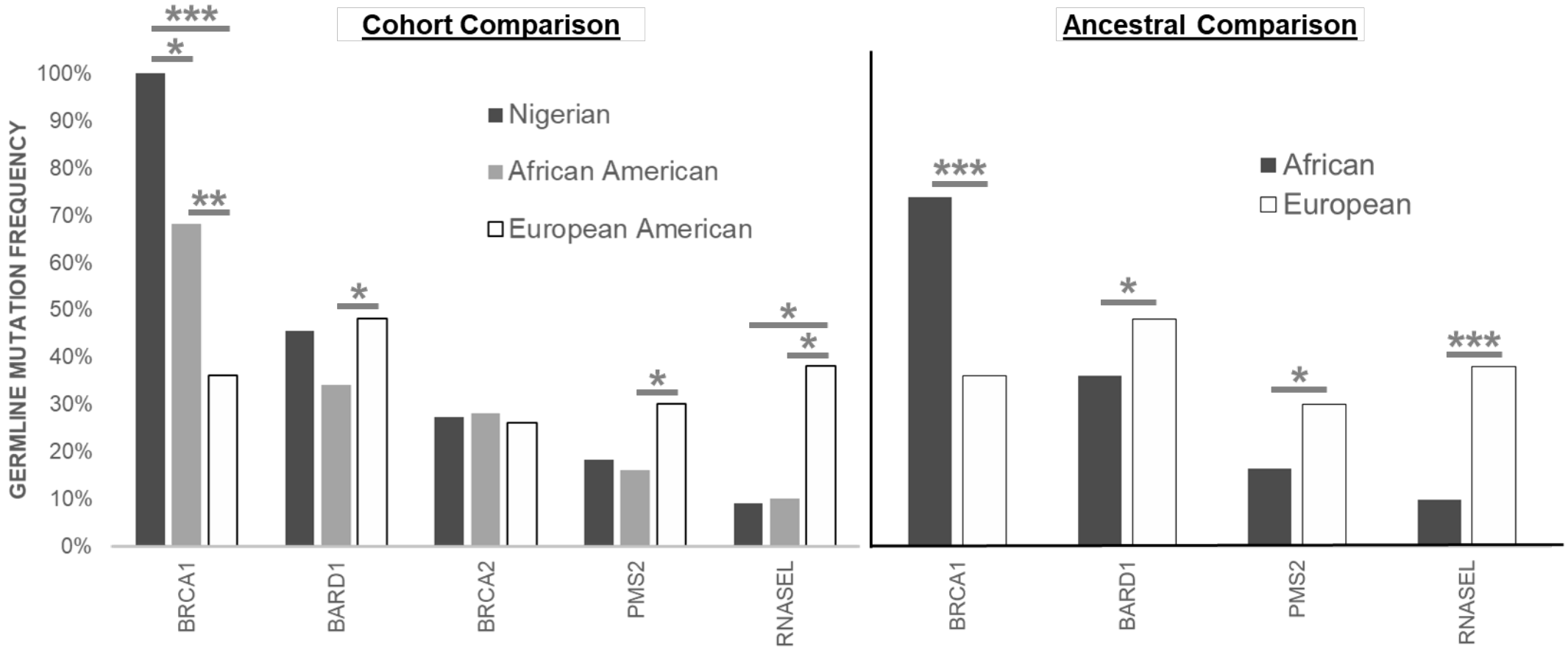
Germline Mutations in Ancestry populations



White et al Cancer Res Commun; 2(9) September 2022

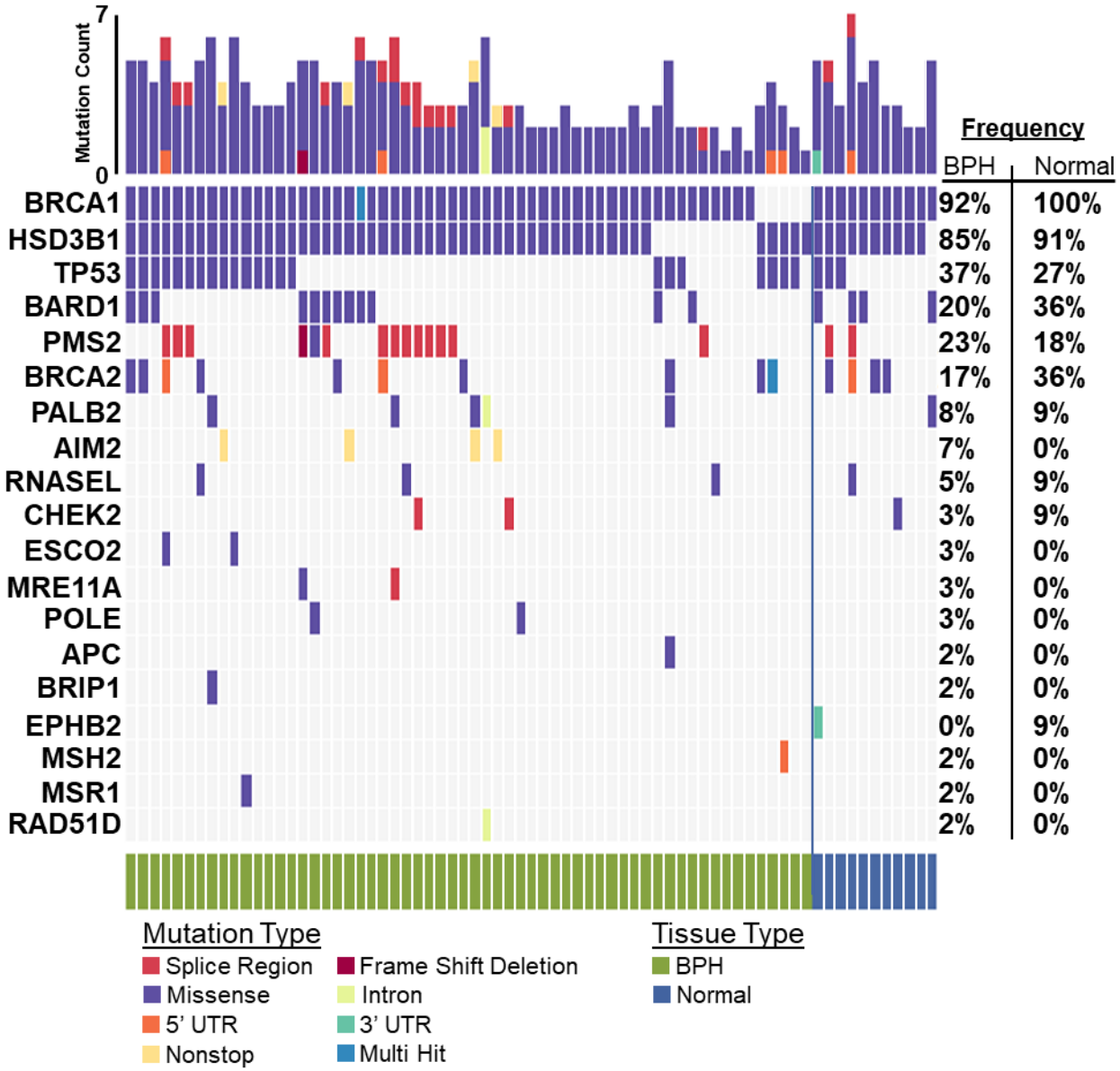
PCa variants based on Ancestry

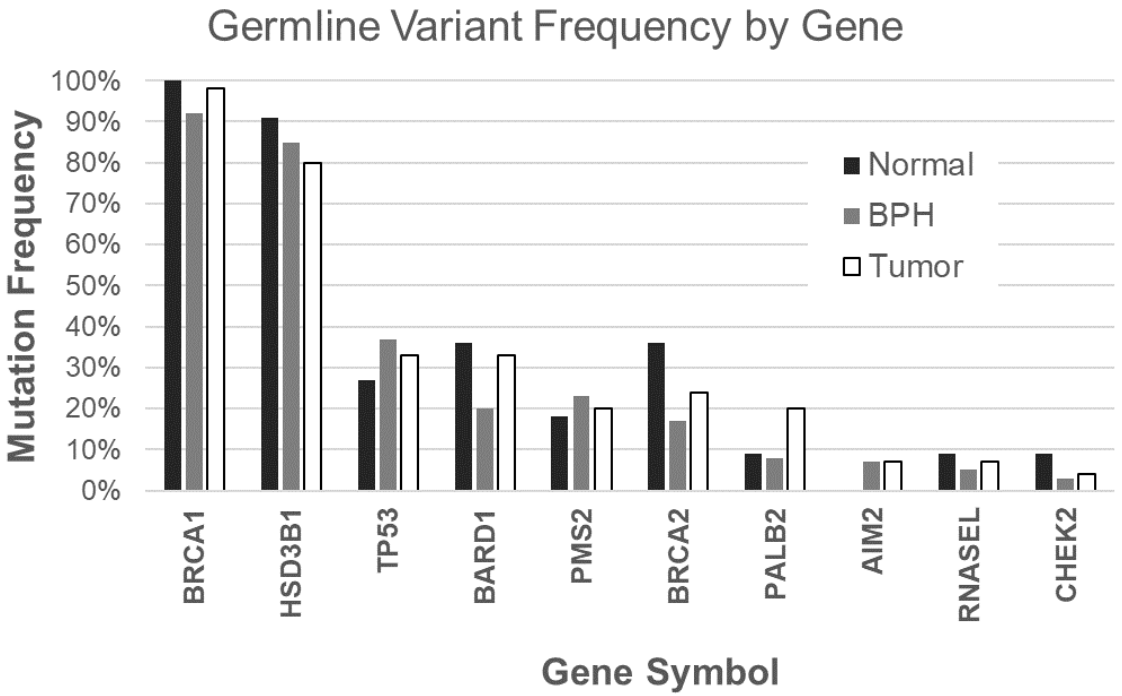
Jason White M.S
Tuskegee Univ.



White et al Cancer Res Commun; 2(9) September 2022

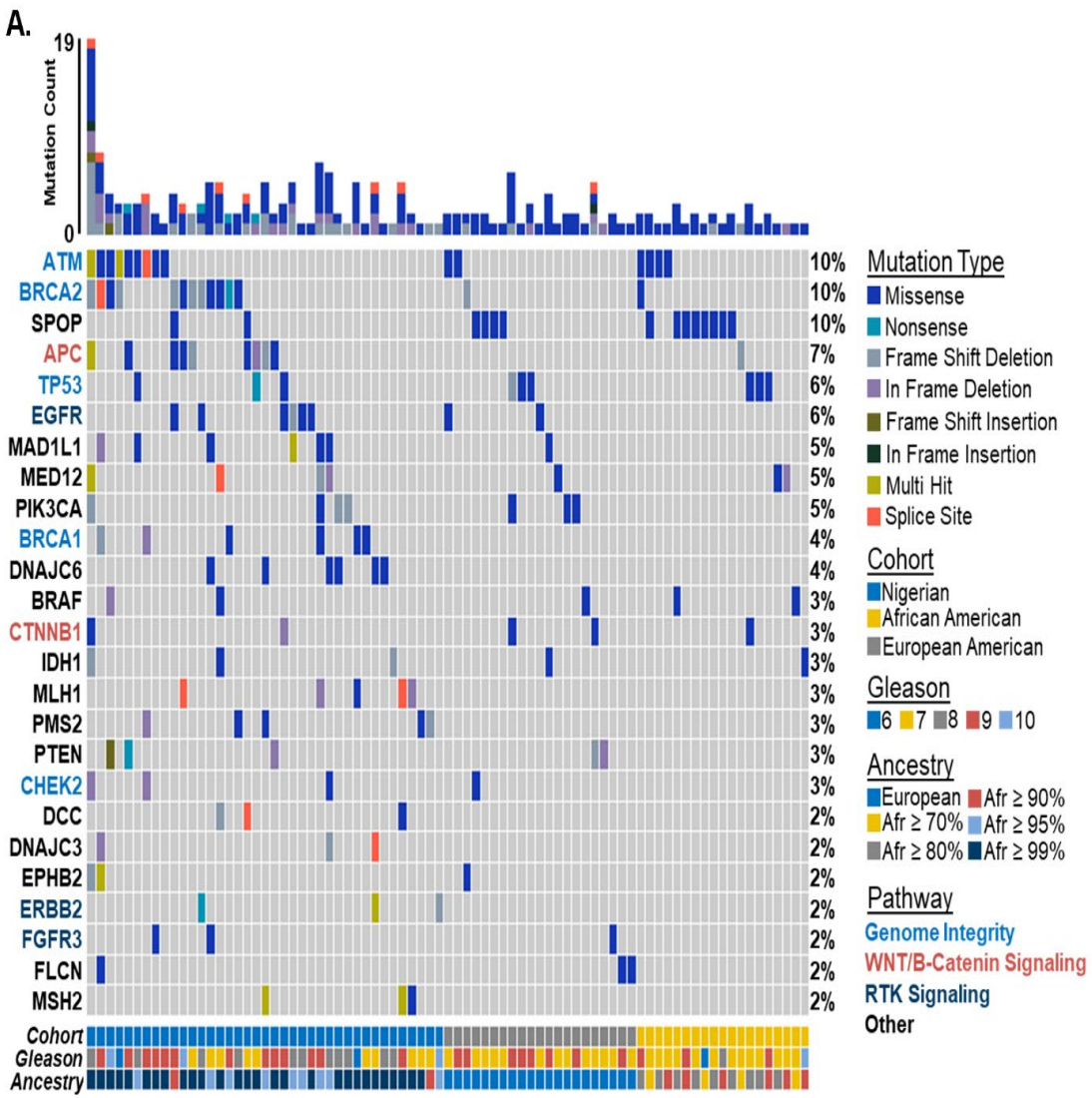
Nigerian Germline Variants in Benign Prostate Hyperplasia (BPH)

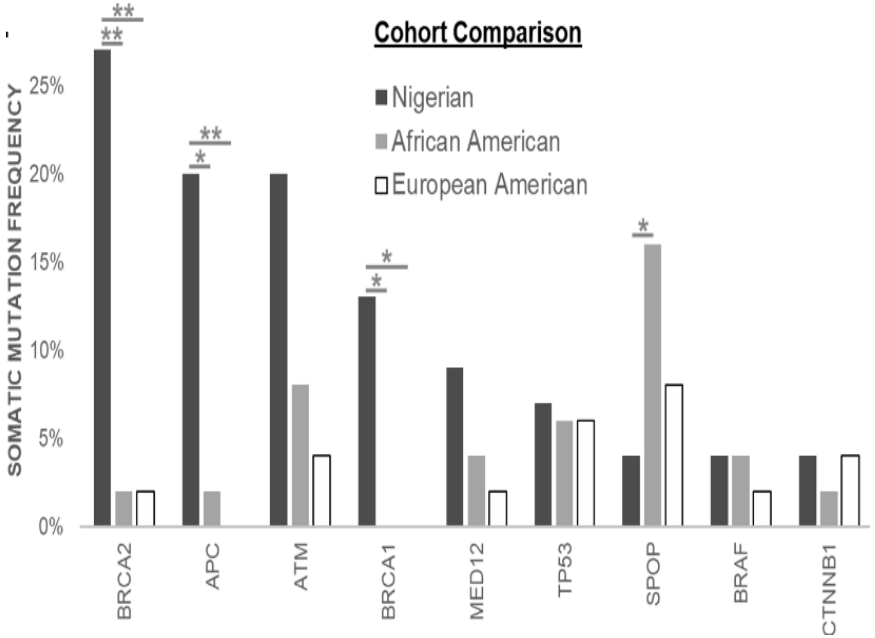


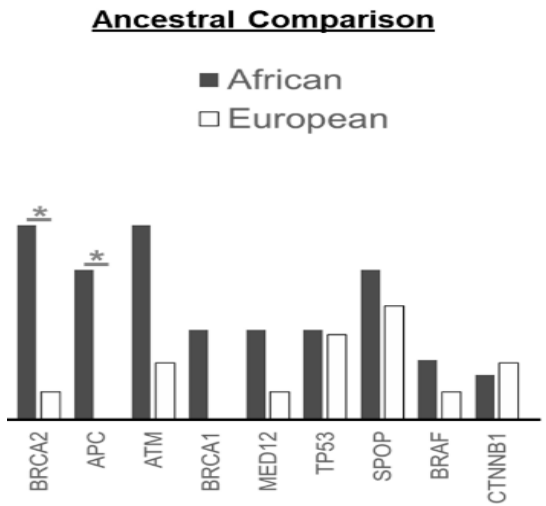


*Jason White et al **The Prostate** 2024*

Ancestry based Somatic mutations







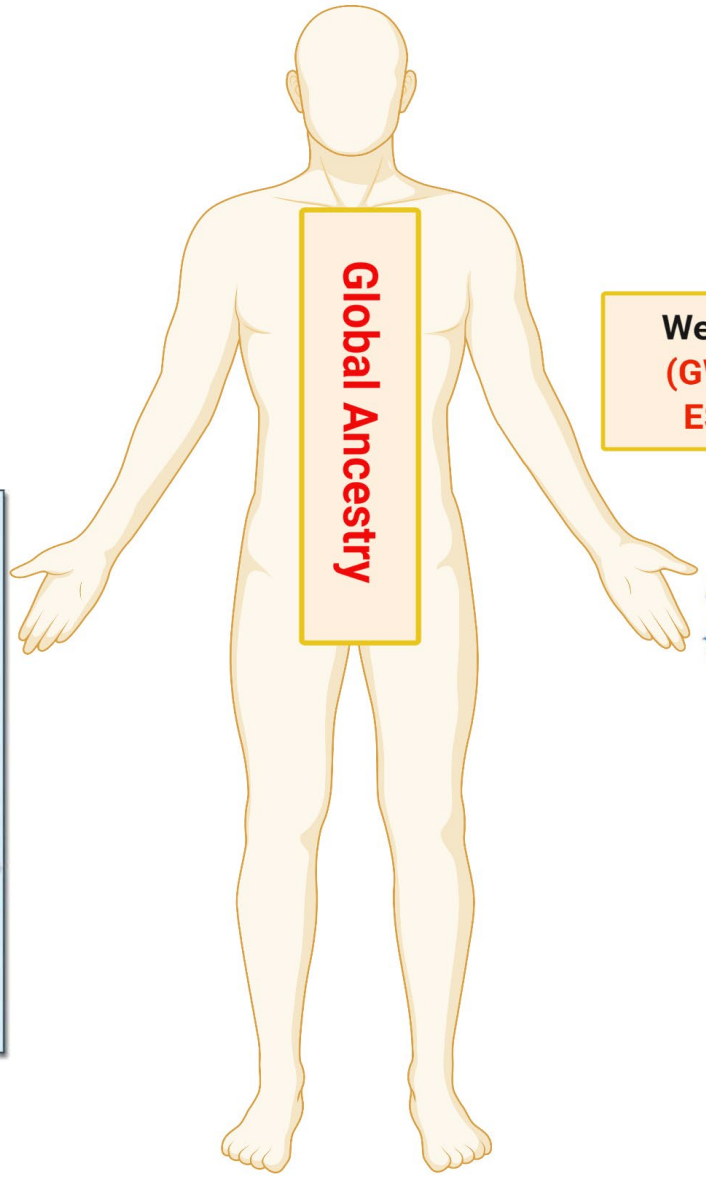
White et al Cancer Res Commun; 2(9) September 2022

Global Ancestry

Isra Elhussin MD, PhD
Johns Hopkins.

Super-Populations

AFR	African
EUR	European
SAS	South Asian
EAS	East Asian
AMR	Ad Mixed American



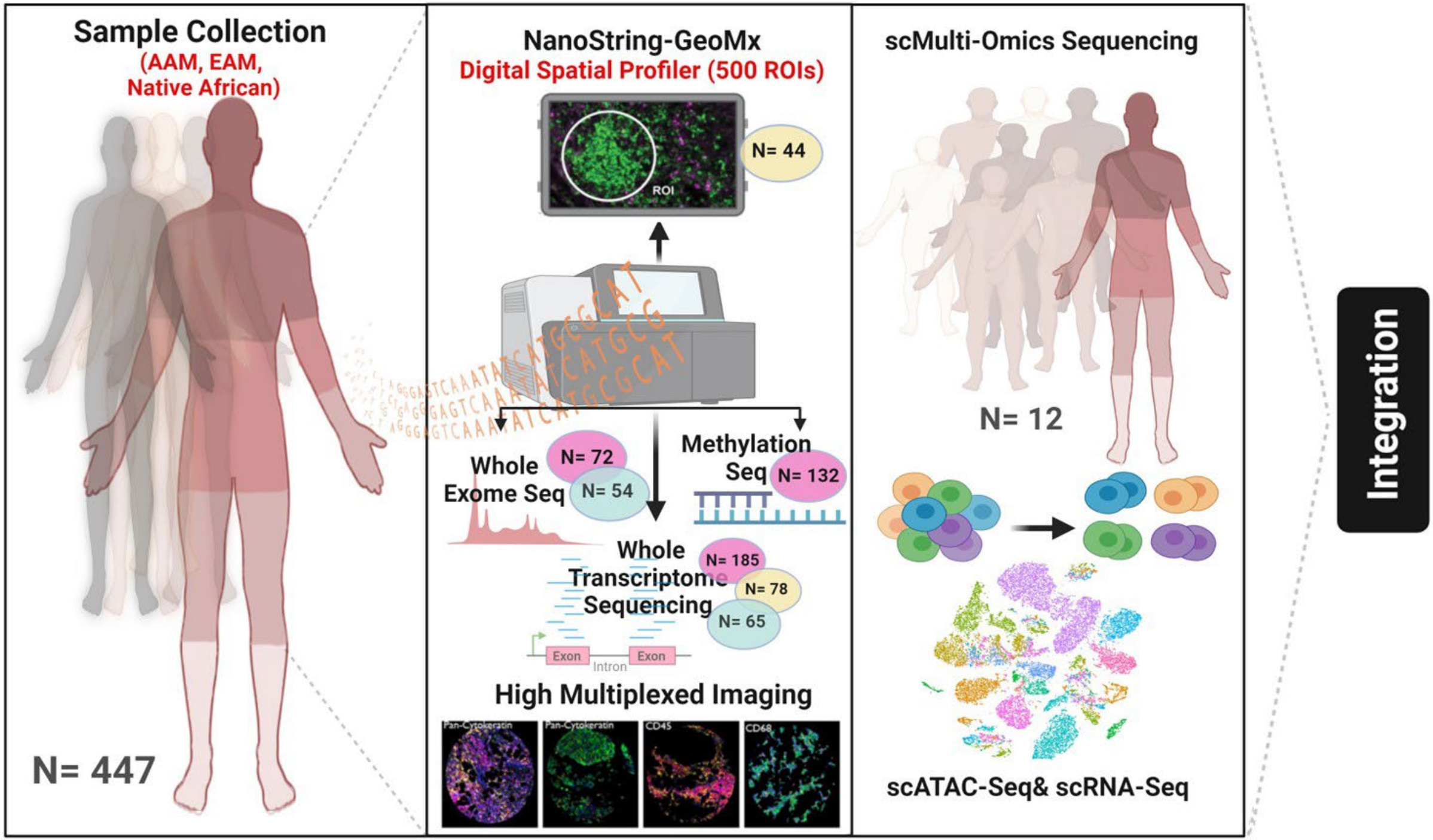
Sub-Populations

African Ancestry

West Africa (GWD, MSL, ESN, YRI)

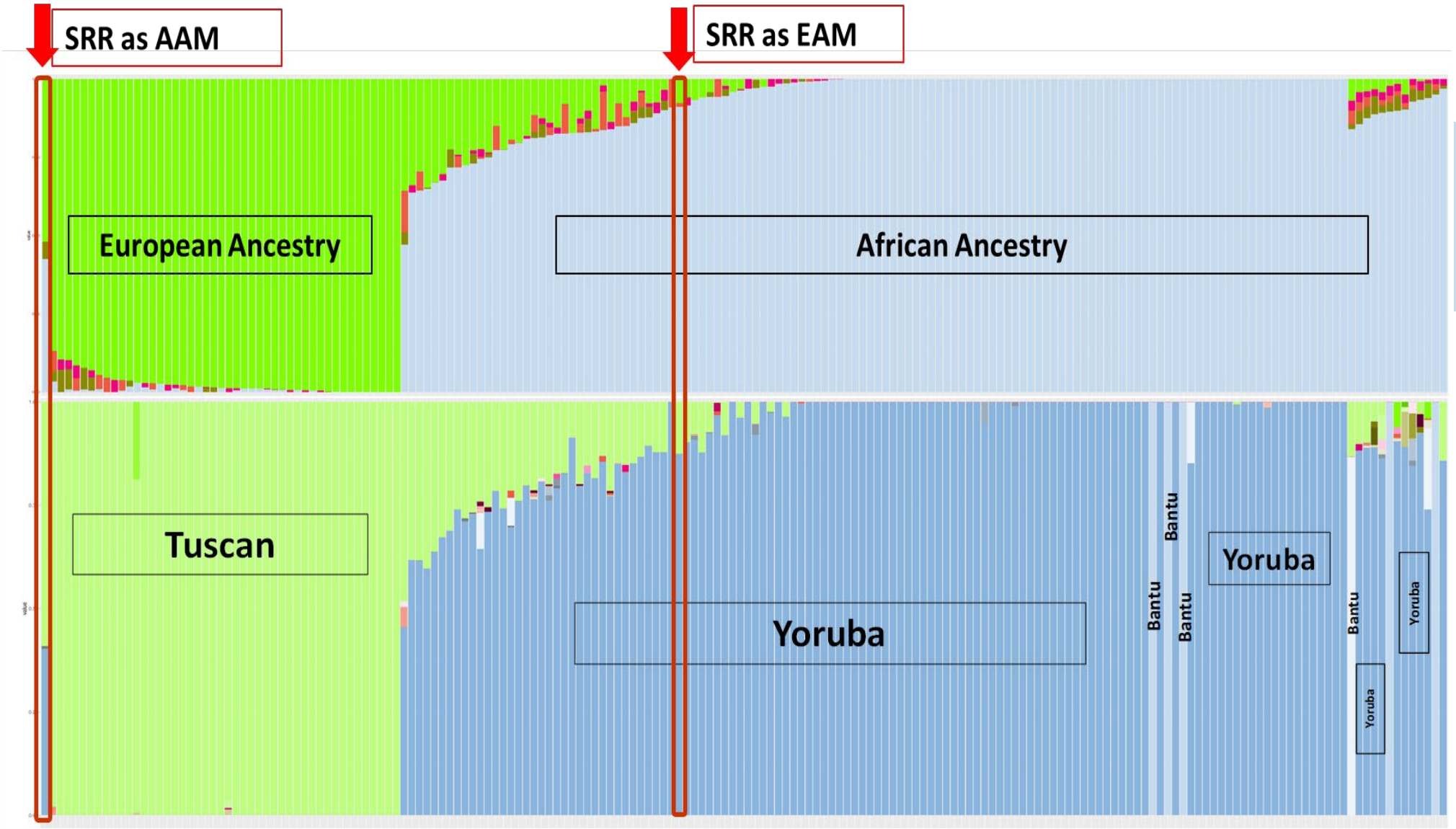
East Africa (LWK)

AFR Caribbean Ancestry (ACB)
American of African Ancesrty in SW USA (ASW)


Sample Collection
(AAM, EAM,
Native African)
N= 447
NanoString-GeoMx
Digital Spatial Profiler (500 ROIs)
ROI
N= 44
Whole
Exome Seq
N= 72
N= 54
Methylation
Seq
N= 132
Whole
Transcriptome
Sequencing
N= 185
N= 78
N= 65
Exon
Intron
Exon
High Multiplexed Imaging
Pan-Cytokeratin
Pan-Cytokeratin
CD45
CD68
scMulti-Omics Sequencing
N= 12
scATAC-Seq& scRNA-Seq
Integration

Prostate Cancer Signature in Nigerian Men

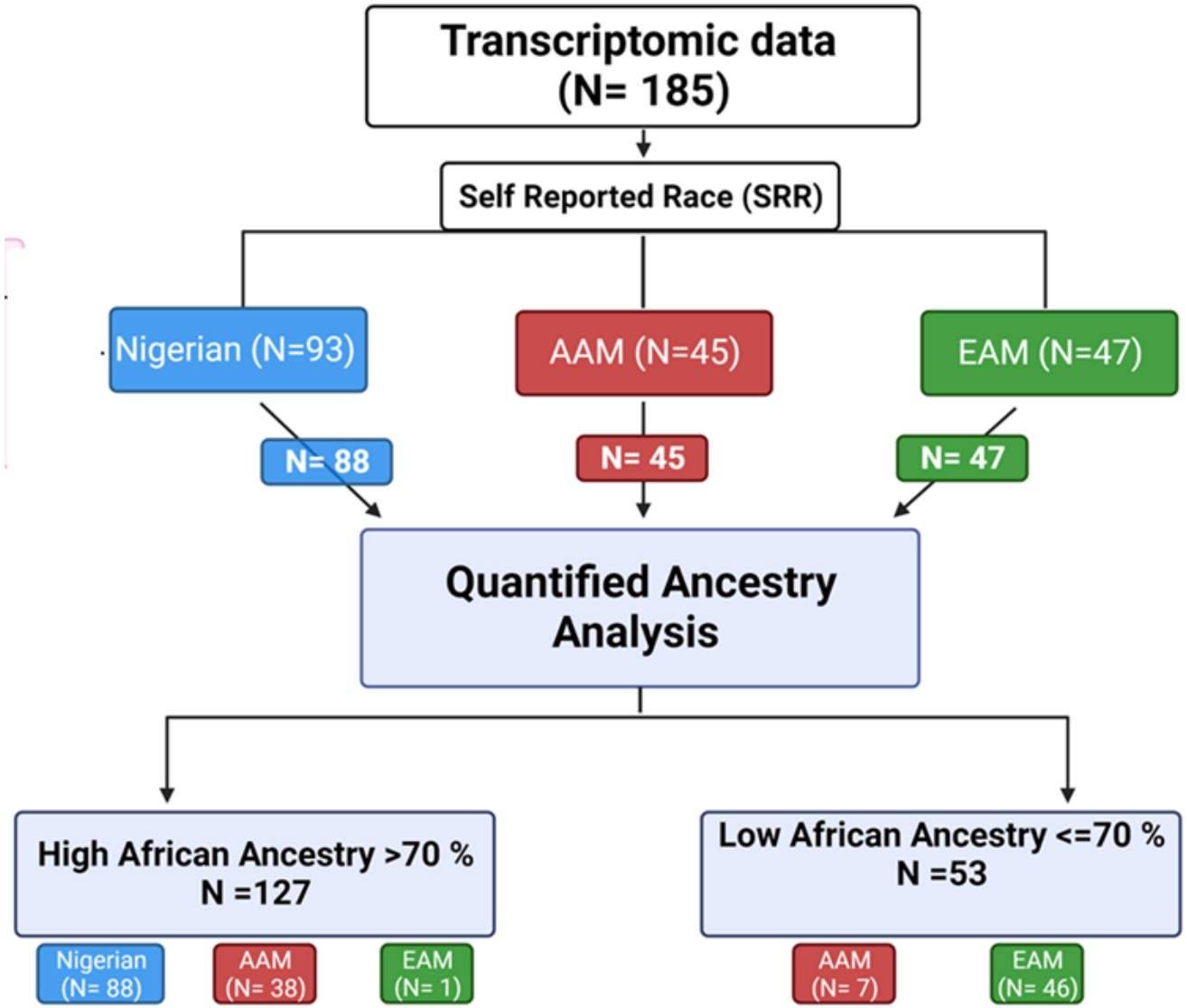
Isra Elhussin MD, PhD
Johns Hopkins.

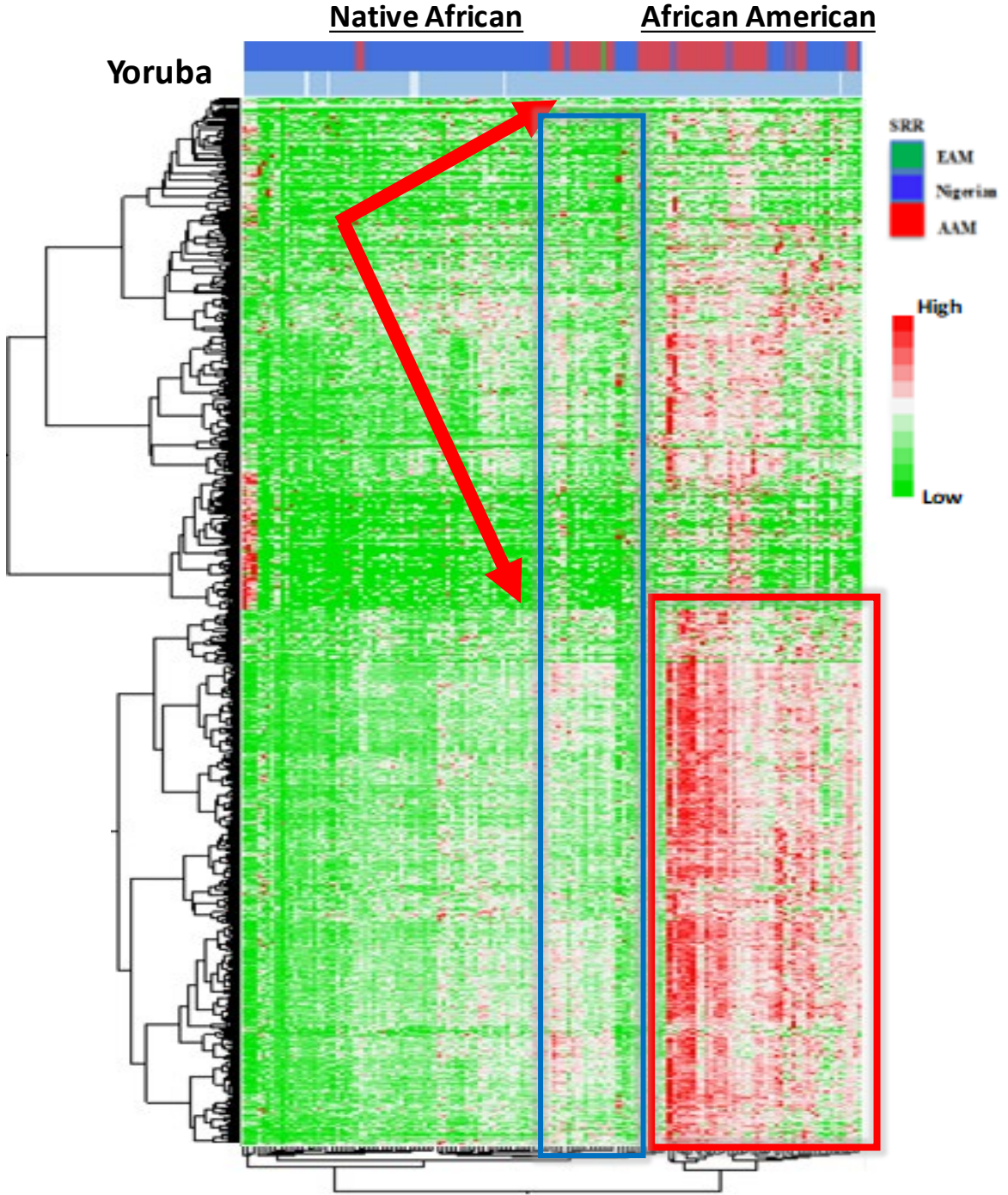


SuperPopulation	Ancestry_Group
European	EUR
East Asian	EAS
Ad Mixed American	AMR
South Asian	SAS
African	AFR

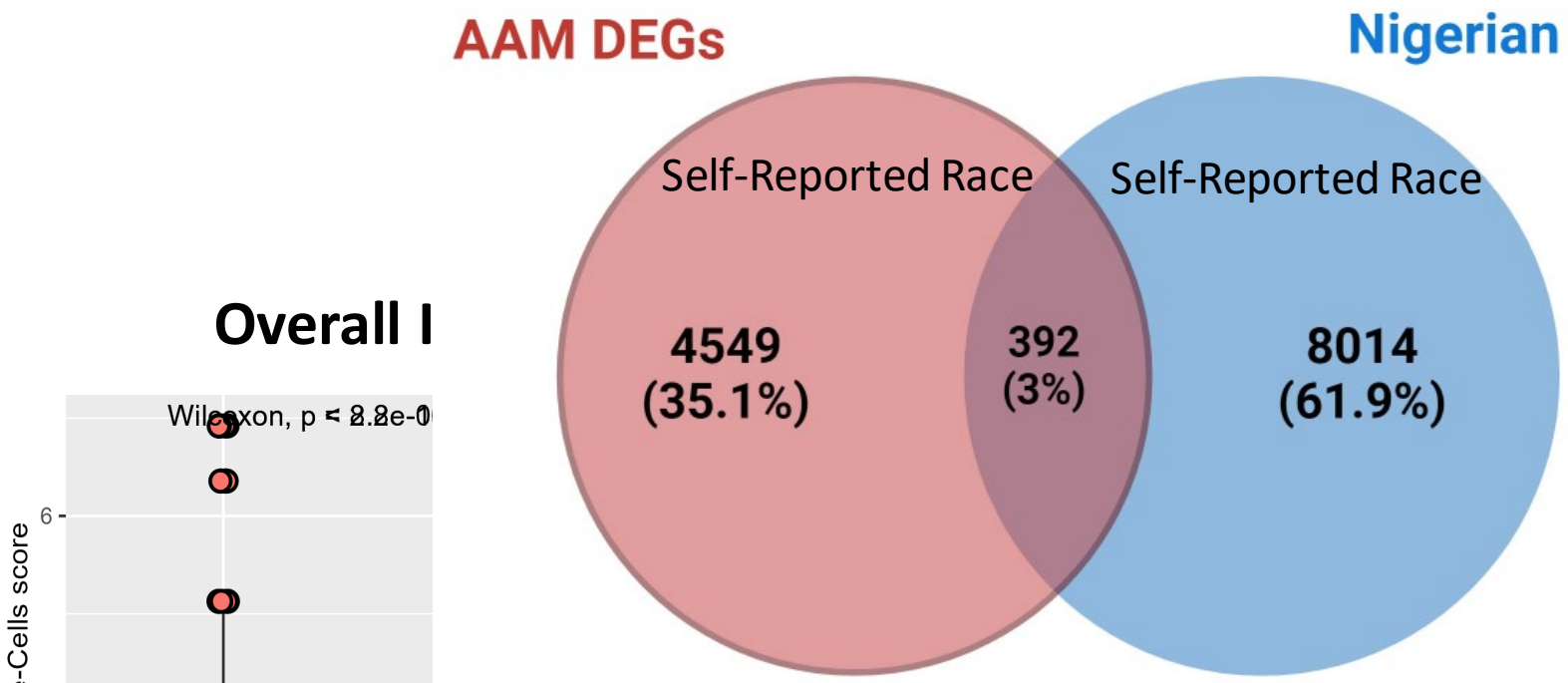
Ancestry Sub-Populations

Adygei	Lahu	Brahui
Basque	Miao	Burusho
BergamoItalian	Mongolian	Hazara
French	Naxi	Kalash
Orcadian	NorthernHan	Makrani
Russian	Oroqen	Pathan
Sardinian	She	Sindhi
Tuscan	Tu	Uygur
Bedouin	Tujia	Bougainville
Druze	Xibo	PapuanHighlands
Mozabite	Yakut	PapuanSepi
Palestinian	Yi	BantuKenya
Cambodian	Colombian	BantuSouthAfrica
Dai	Karitiana	Biaka
Daur	Maya	Mandenka
Han	Pima	Mbuti
Hezhen	Surui	San
Japanese	Balochi	Yoruba

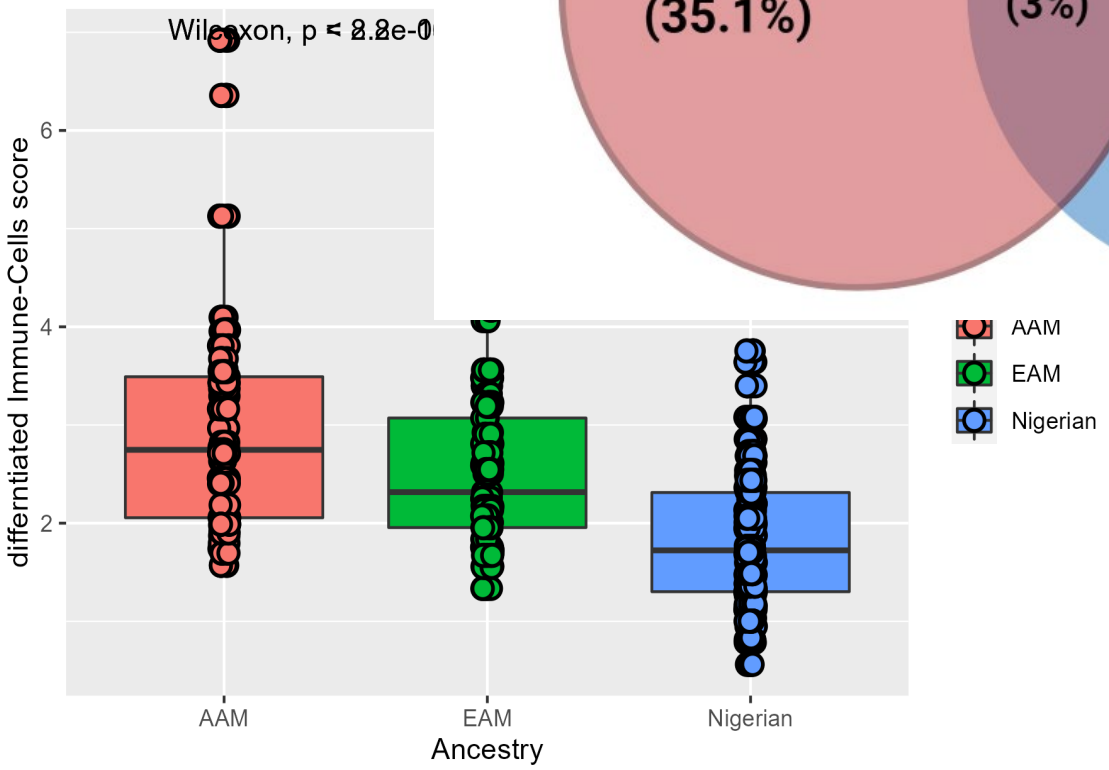

Transcriptomic data
(N= 185)
Self Reported Race (SRR)
Nigerian (N=93)
AAM (N=45)
EAM (N=47)
N= 88
N= 45
N= 47
Quantified Ancestry Analysis
High African Ancestry >70 %
N =127
Low African Ancestry <=70 %
N =53
Nigerian (N= 88)
AAM (N= 38)
EAM (N= 1)
AAM (N= 7)
EAM (N= 46)


Native African
African American
Yoruba
SRR
EAM
Nigerian
AAM
High
Low

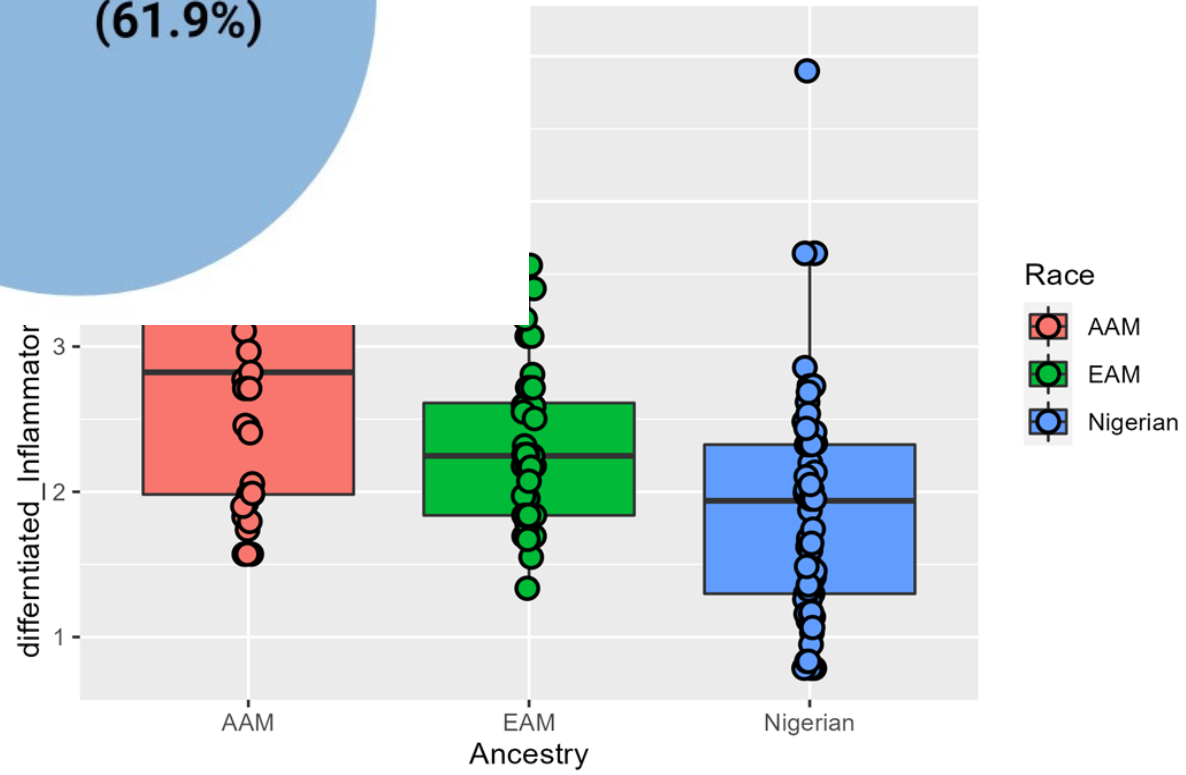
Prostate Cancer Signature in African Americans Compared to Nigerian Men



Overall I

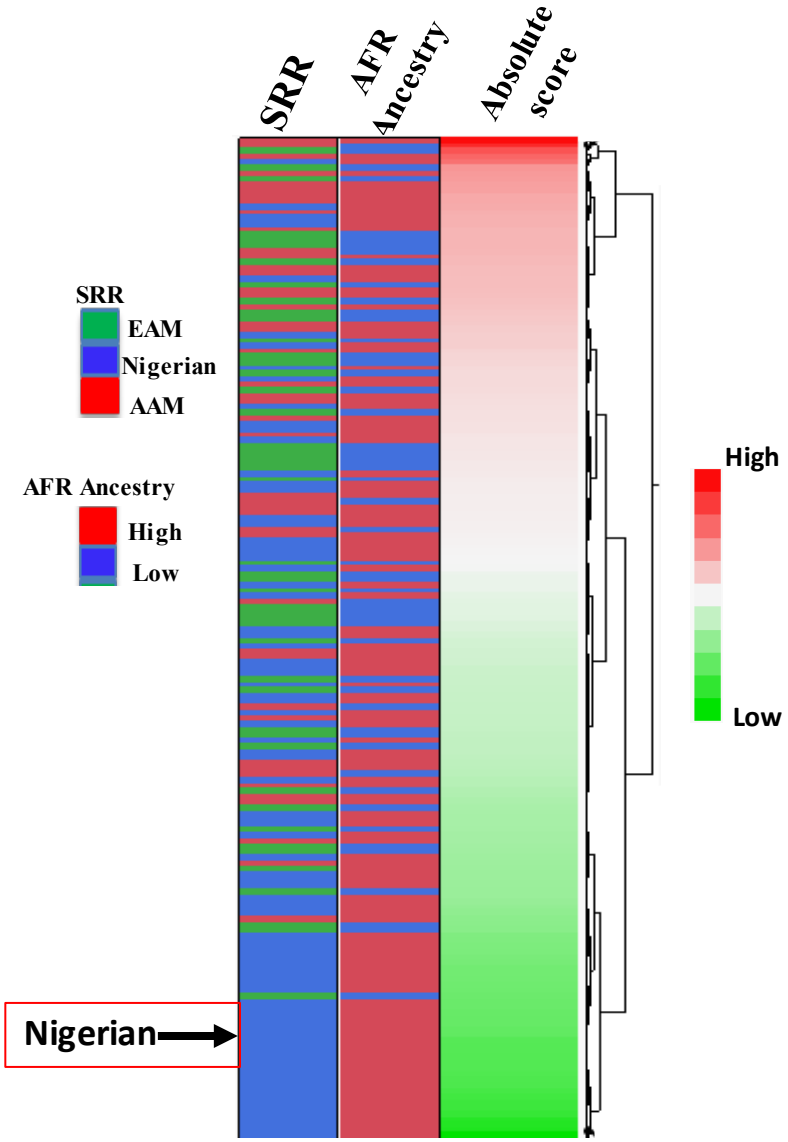


nmatory Score

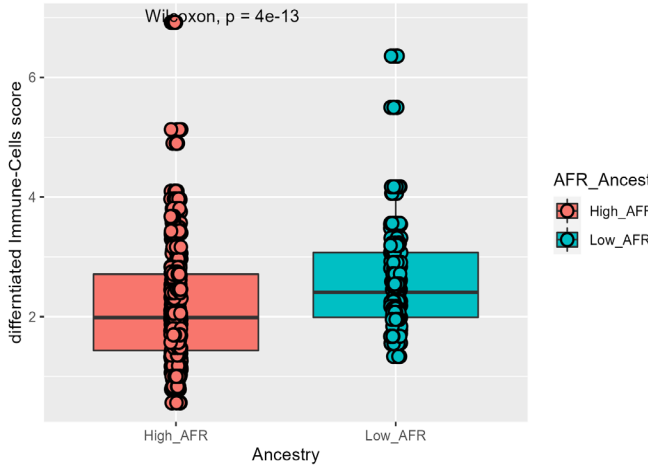


African Ancestry is Associated with Immune Suppression

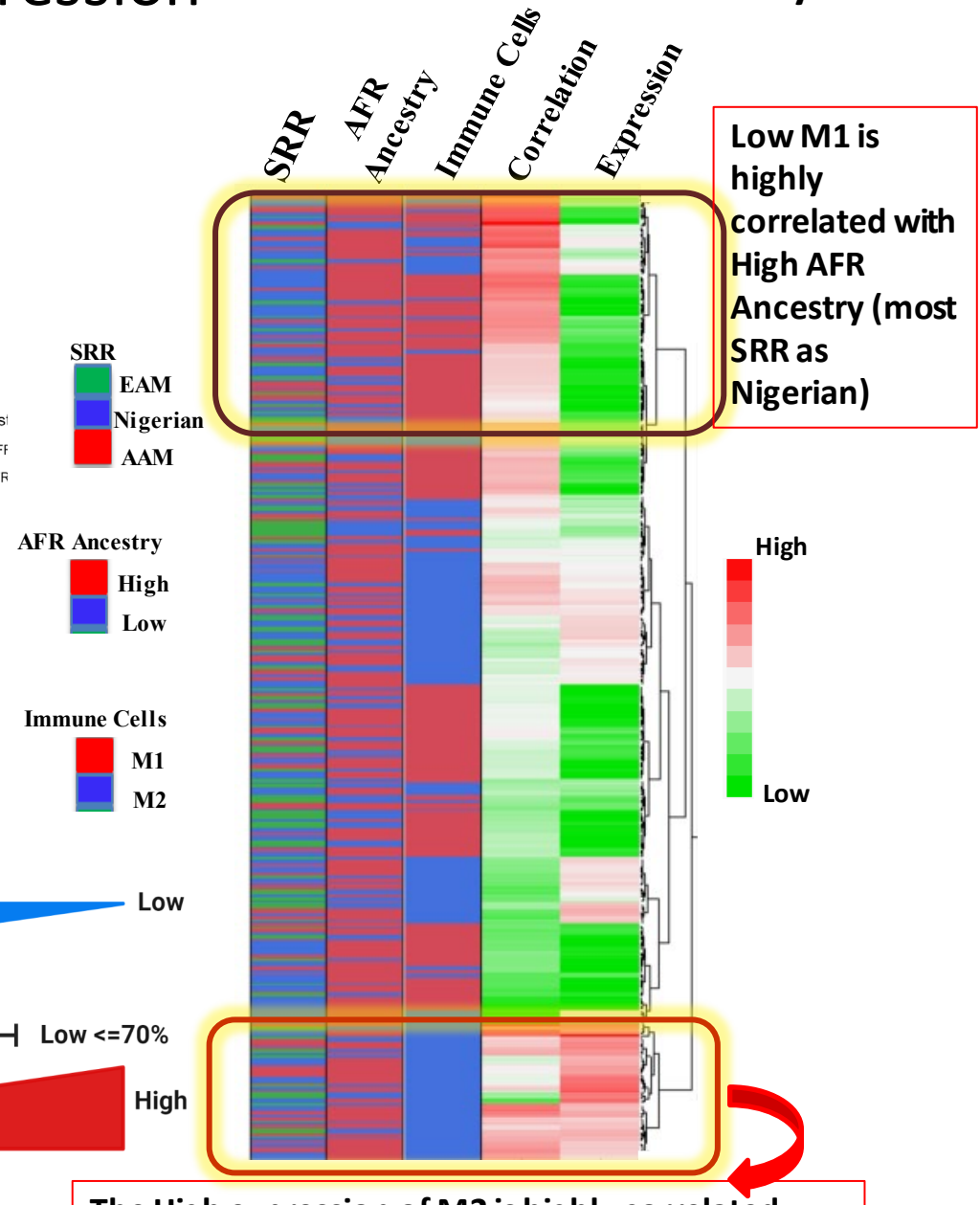
CiberSort Absolute score for all Immune Cells



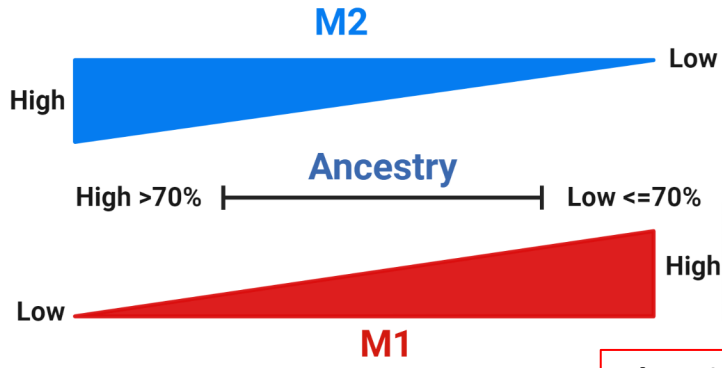
CiberSort overall Immune Cell populations score



Expression-Correlation of M1 & M2 with SRR and Ancestry

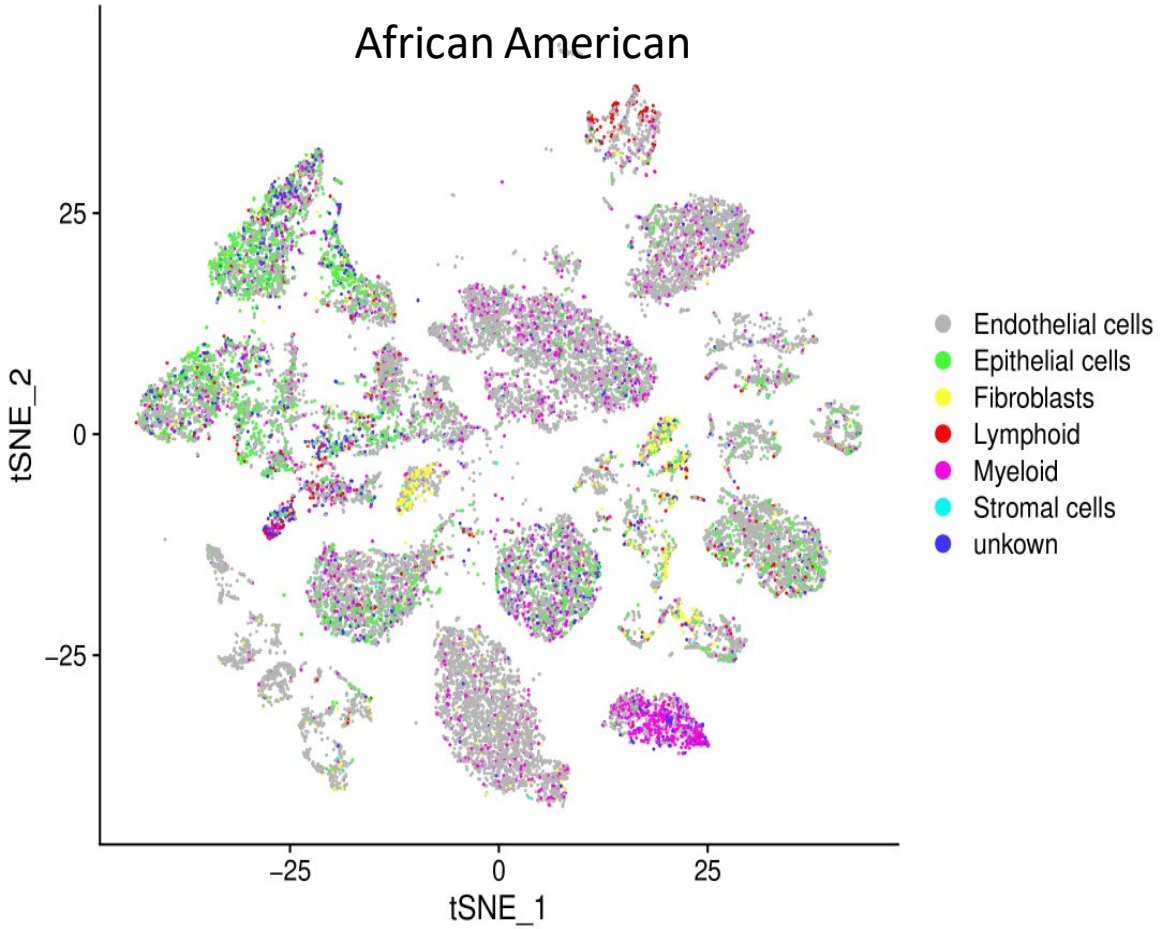


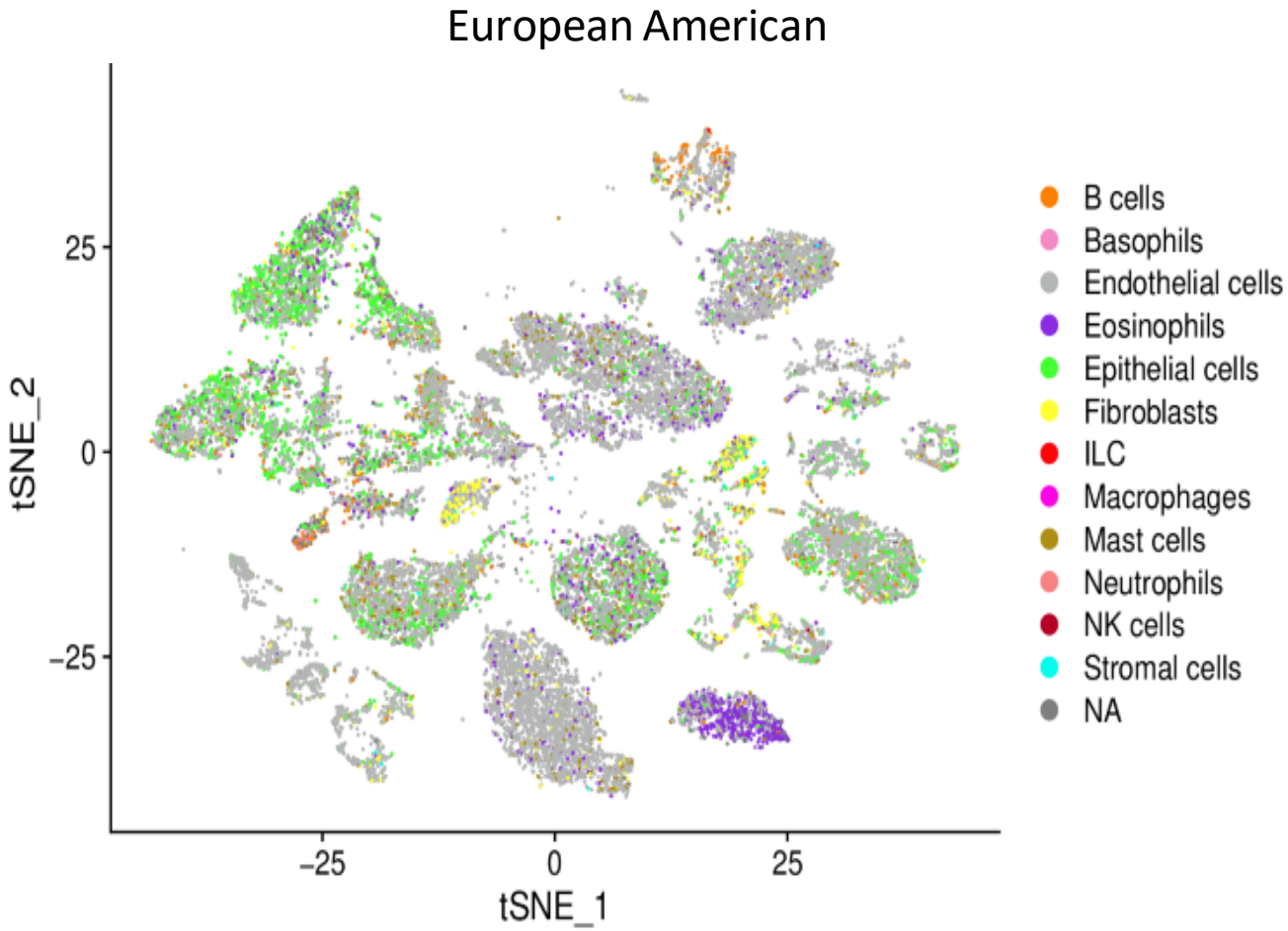
Low M1 is highly correlated with High AFR Ancestry (most SRR as Nigerian)



The High expression of M2 is highly correlated with High AFR Ancestry (most SRR as AAM)

African American Prostate Cancer Single Cell Sequencing

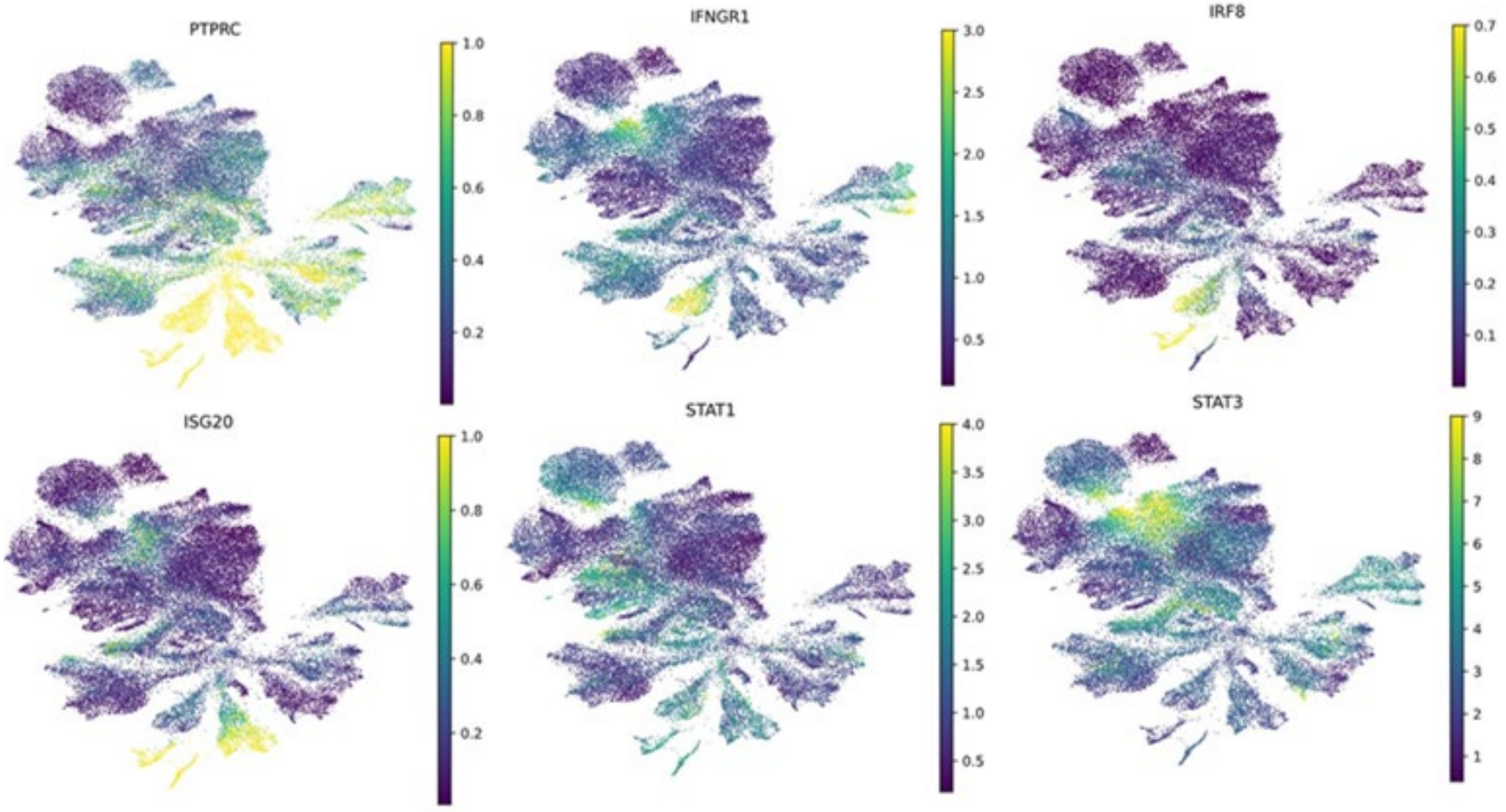




AAM have myeloid cell populations that infiltrate within the tumor cells

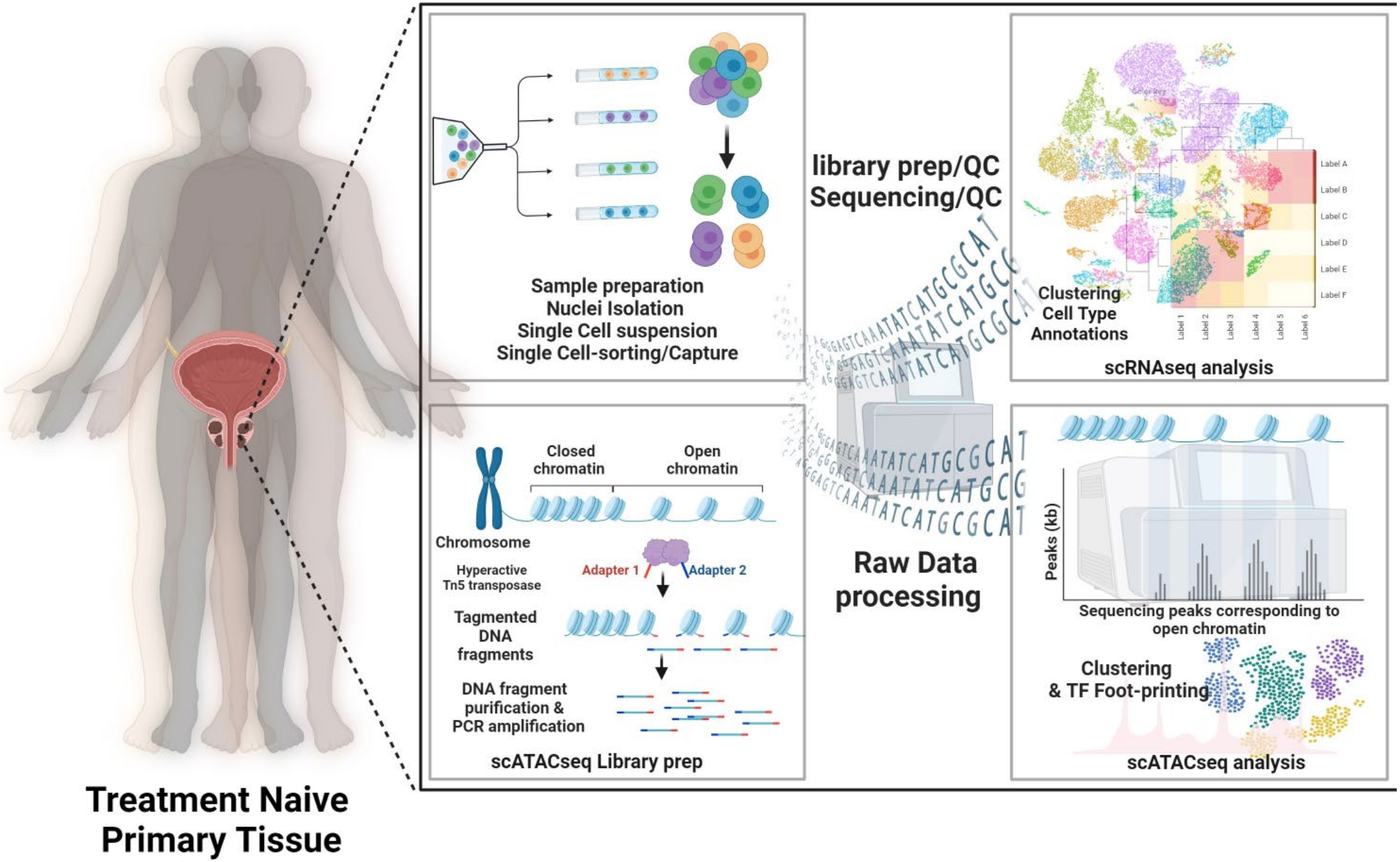
African American Tumors are enriched for Interferon Expressing Cells

(scRNA-seq)



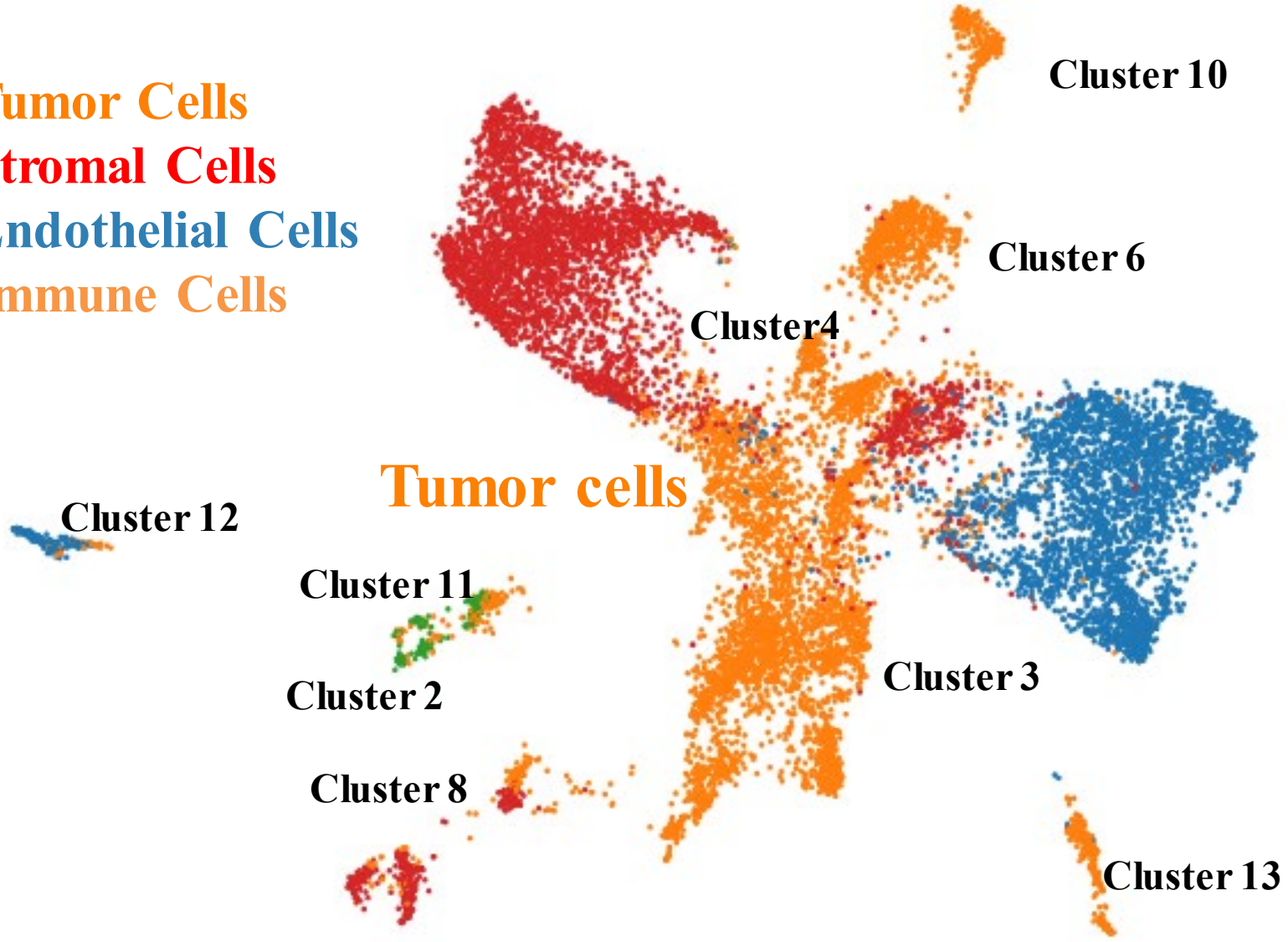
n = 41,731 cells (RP tumor specimens)

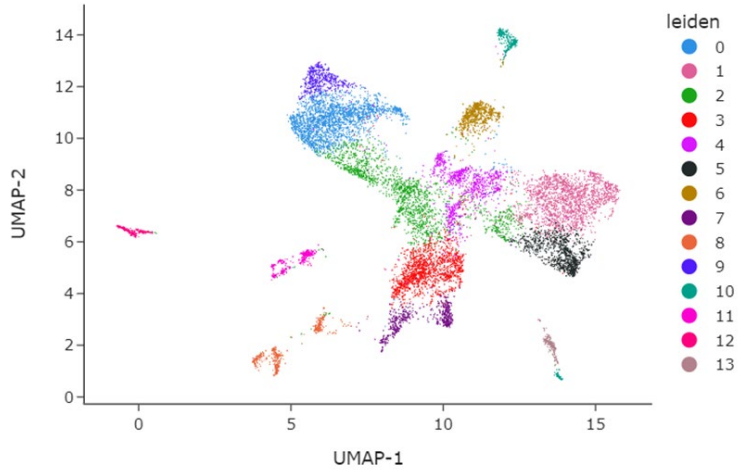
Single Cell Multi-Omics Sequencing (scRNA & scATAC-Seq)



African American Tumor Cells have increased Chromatin accessibility (scATAC-seq)

Tumor Cells
Stromal Cells
Endothelial Cells
Immune Cells





Motif_ID	Name	p-value	Cluster
STAT2+M09416_2.00	STAT2	0	13
STAT3+M11369_2.00	STAT3	8.16E-06	12
IRF8+M03336_2.00	IRF8	0.00015	3
IRF9+M03339_2.00	IRF9	0.000308	3
IRF7+M03337_2.00	IRF7	0.000446	3
IRF5+M05537_2.00	IRF5	0.000508	11
IRF4+M05539_2.00	IRF4	0.000837	11
IRF1+M10879_2.00	IRF1	0.00207	13
STAT4+M11362_2.00	STAT4	0.004392	13
STAT6+M11366_2.00	STAT6	0.00502	8
IRF6+M05528_2.00	IRF6	0.005414	12
STAT5B+M11371_2.00	STAT5B	0.011284	8

African American Enriched Motifs

Fragments = 35,549 cells (RP tumor specimens)

JAMA Network Open

Tsion Minas PhD
Johns Hopkins Sch Med

Stefan Ambs PhD
NIH/NCI

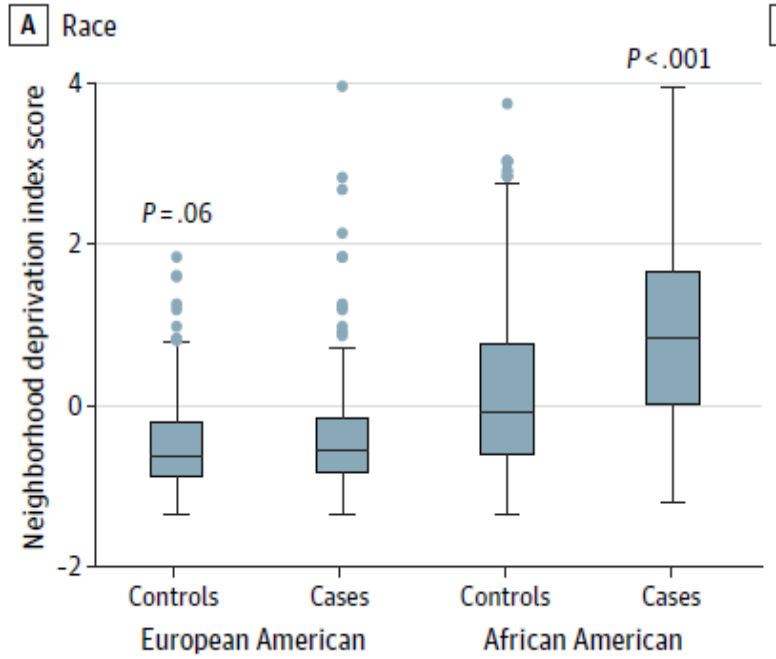
Original Investigation | Equity, Diversity, and Inclusion

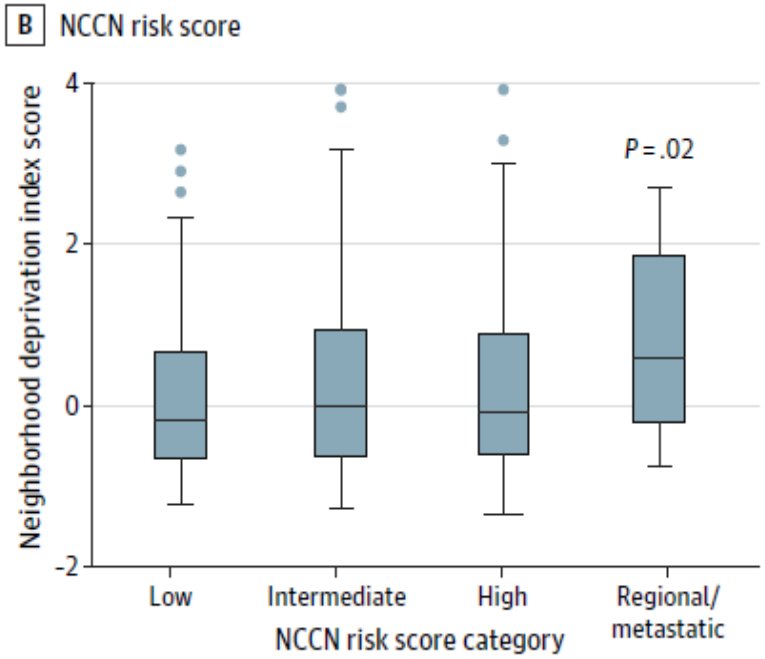
Association of Neighborhood Deprivation With Prostate Cancer and Immune Markers in African American and European American Men

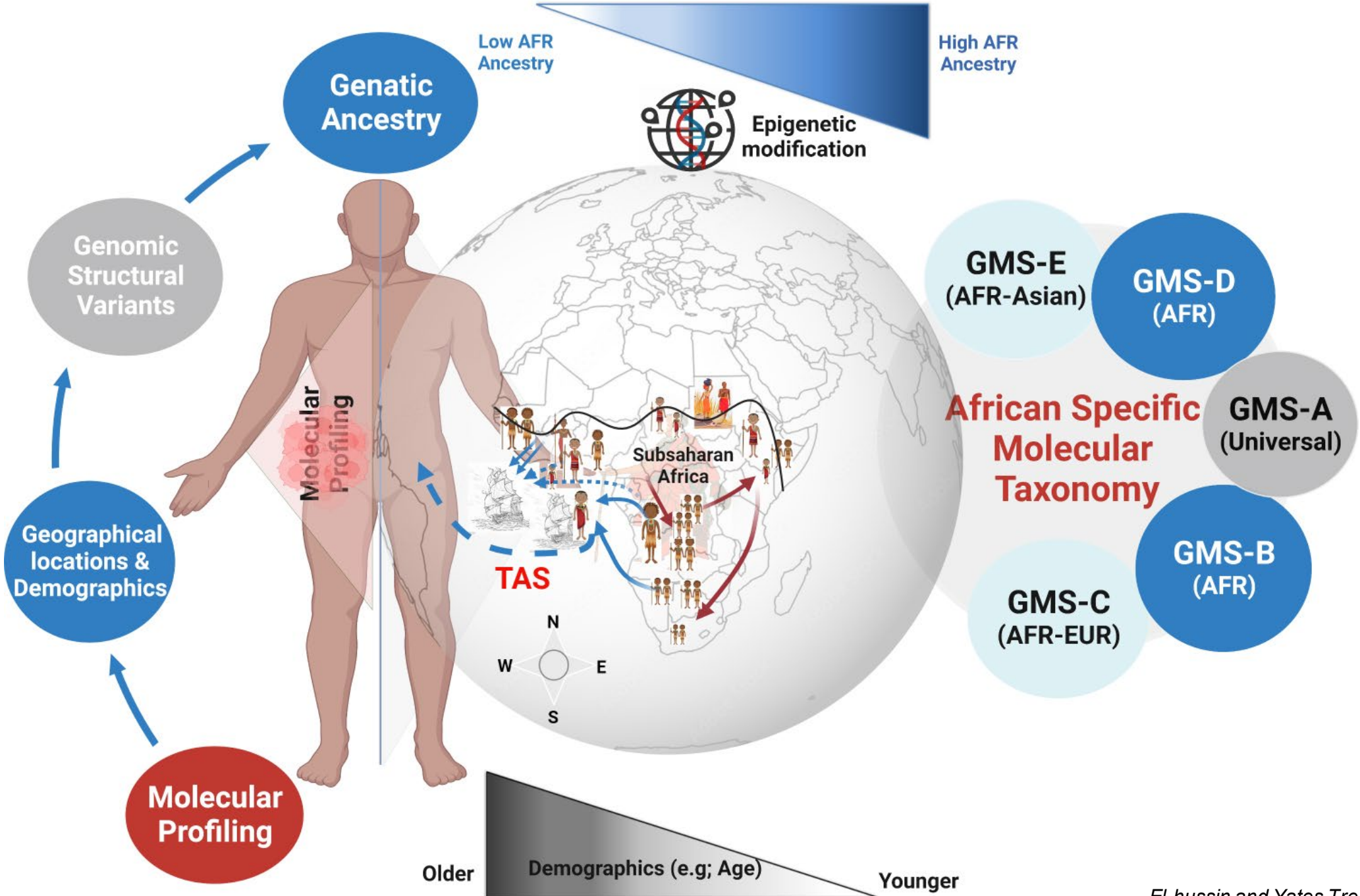
Margaret S. Pichardo, MD, PhD, MPH; Tsion Zewdu Minas, PhD; Catherine M. Pichardo, PhD; Maeve Bailey-Whyte, PhD, MPH; Wei Tang, PhD; Tiffany H. Dorsey, BS; William Wooten, MPH, MS; Brid M. Ryan, PhD, MPH; Christopher A. Loffredo, PhD; Stefan Ambs, PhD, MPH

Serum Inflammation Markers

	Model R-squared		
Select Immune Oncological Markers	Model 1	Model 2	Model 3
PTN	10.2%	1.5%	53.0%
CXCL5	49.4%	11.9%	52.2%
CXCL1	40.4%	10.9%	42.7%
CXCL9	4.2%	0.1%	0.271
MMP7	2.6%	1.1%	0.261
MMP12	0.0%	0.7%	0.241
ADGRG1	0.0%	0.1%	0.233
DCN	0.0%	0.2%	0.217
CD27	0.2%	1.7%	0.205
LAMP3	1.2%	0.7%	0.204
PGF	0.9%	0.2%	0.189
TNFRSF12A	0.1%	0.0%	0.183
CCL23	10.8%	1.9%	0.177
MCP2	15.0%	5.0%	0.177
TNFRSF9	2.4%	0.0%	0.175







El-hussin and Yates Trends in Cancer 2022

Quadruple Negative Breast Cancer (QNBC)

Windy Dean-Colomb MD
Tuskegee/Piedmont Health Car

Melissa Davis, PhD
Morehouse School of Medicine

PLOS ONE

RESEARCH ARTICLE

AR negative triple negative or "quadruple negative" breast cancers in African American women have an enriched basal and immune signature

Melissa Davis[1☯], Shweta Tripathi[2☯], Raymond Hughley[2], Qinghua He[3], Sejong Bae[4], Balasubramanyam Karanam[2], Rachel Martini[1], Lisa Newman[5], Windy Colomb[6], William Grizzle[7], Clayton Yates[2]*

Translational Oncology
www.transonc.com
Volume 12 Number 3 March 2019 pp. 493–501 493

Quadruple Negative Breast Cancers (QNBC) Demonstrate Subtype Consistency among Primary and Recurrent or Metastatic Breast Cancer

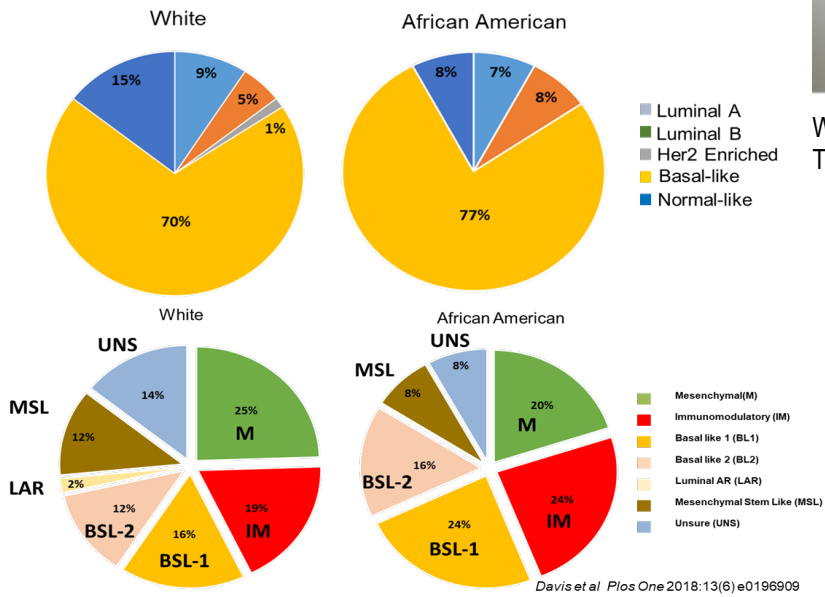
Anusha Angajala[*,1], Essynce Mothershed[*,1], Melissa B. Davis[†], Shweta Tripathi[*], Qinghua He[‡], Deepa Bedi[§], Windy Dean-Colomb[¶] and Clayton Yates[*]

www.nature.com/scientificreports
scientific reports

OPEN MicroRNAs within the Basal-like signature of Quadruple Negative Breast Cancer impact overall survival in African Americans

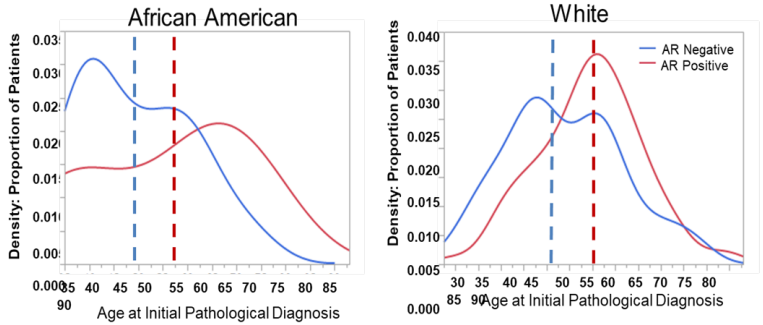
Anusha Angajala[1,2], Hughley Raymond[1], Aliyo Mohammad[1,2], Md Shakir Uddin Ahmed[1,2], Saadia Haleema[1], Monira Haque[1], Honghe Wang[1], Monay Campbell[1], Rachel Martini[4], Balasubramanian Karanam[3], Andrea G. Kahn[5], Deepa Bedi[5], Melissa Davis[4], Ming Tan[3], Windy Dean-Colomb[1,2] & Clayton Yates[1,2,3,4,5]

TNBC vs QNBC



Davis et al Plos One 2018:13(6) e0196909

Age of Diagnosis TNBC vs QNBC

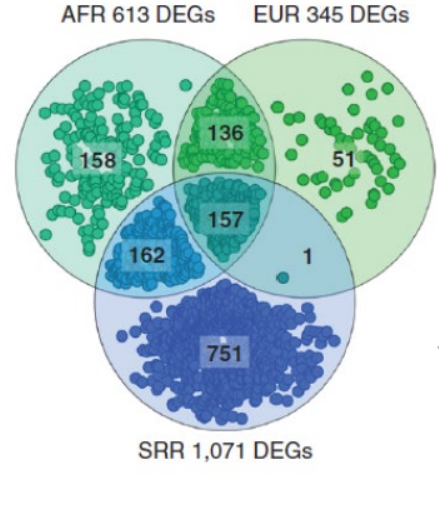


Average Age of Diagnosis
AR positive 56
AR negative 49

Average Age of Diagnosis
AR positive 59
AR negative 53

RESEARCH ARTICLE

African Ancestry-Associated Gene Expression Profiles in Triple-Negative Breast Cancer Underlie Altered Tumor Biology and Clinical Outcome in Women of African Descent

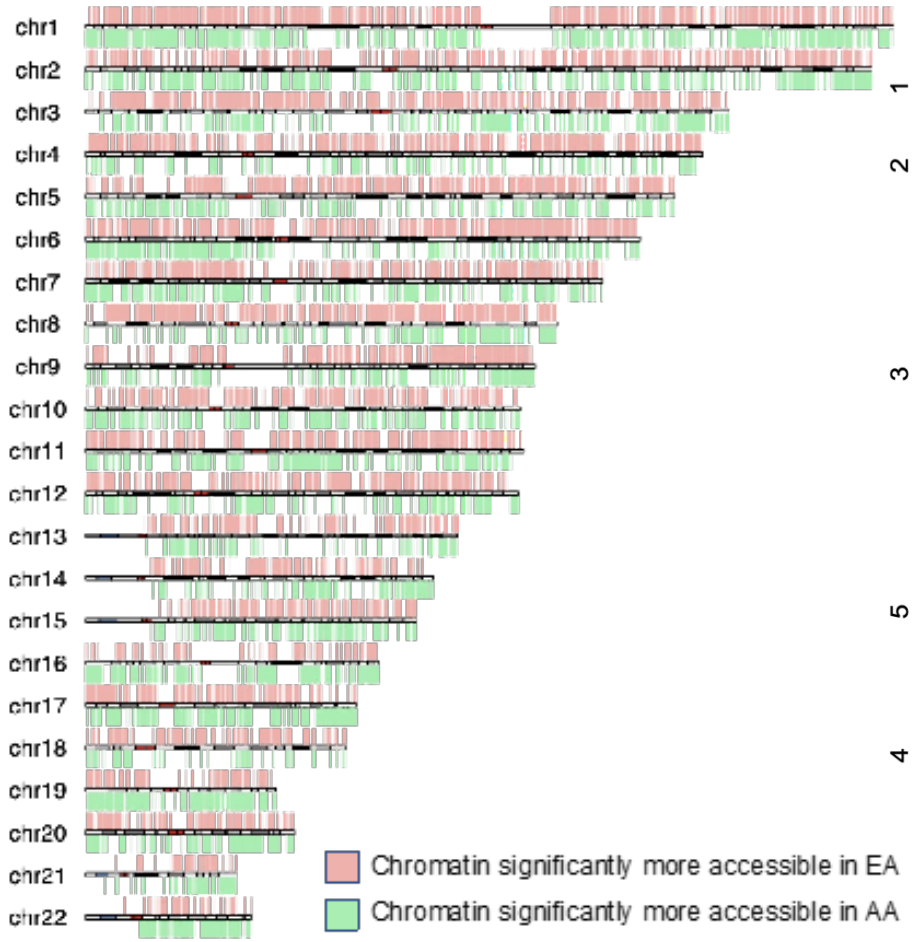


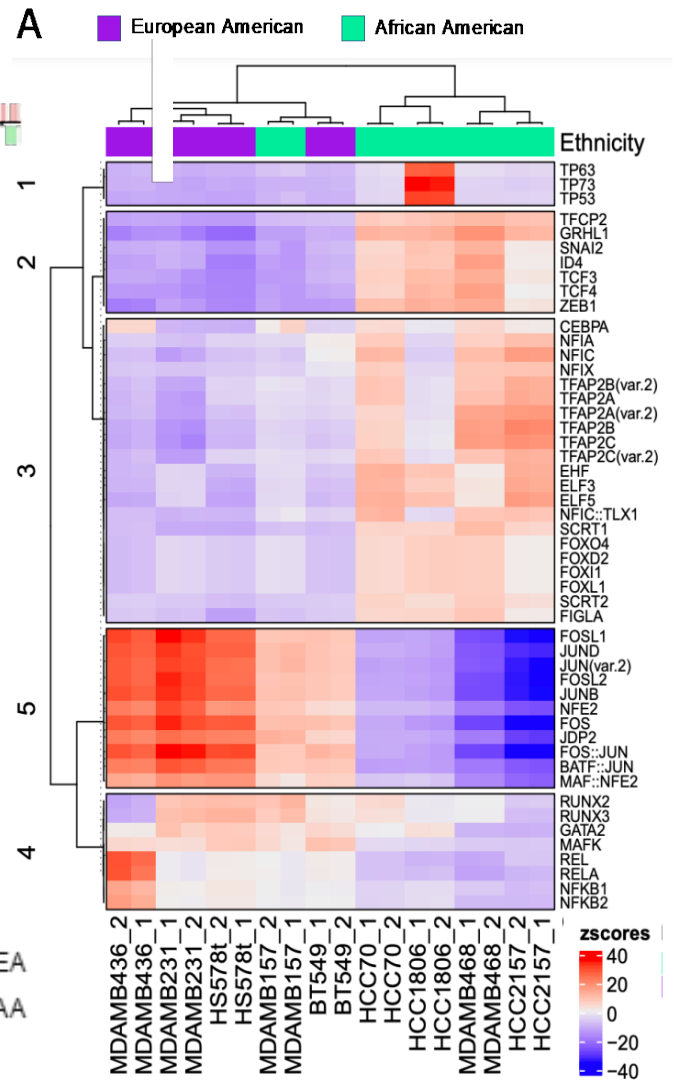
Ancestry Specific Regions of Open Chromatin African American Breast Cancer Patients

Brittany Lord PhD
Johns Hopkins

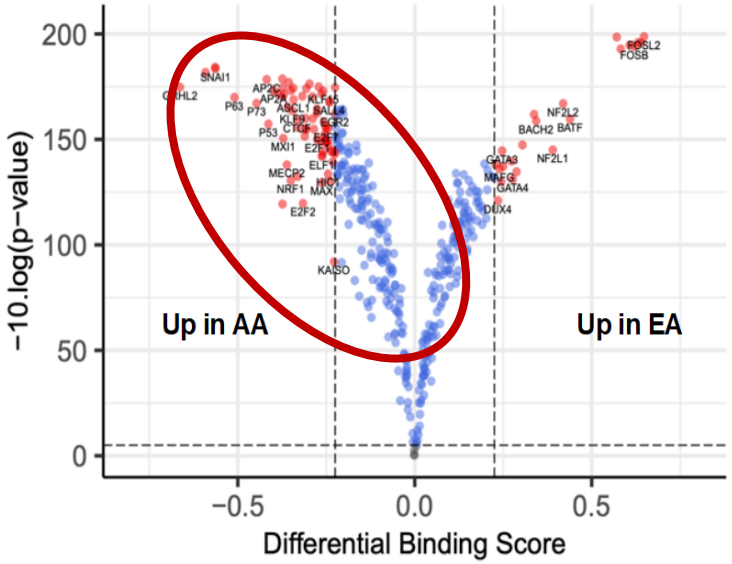
Alexandra R. Harris, Ph.D
NCI

Chromosome Map





Differential ATAC Signal Analysis

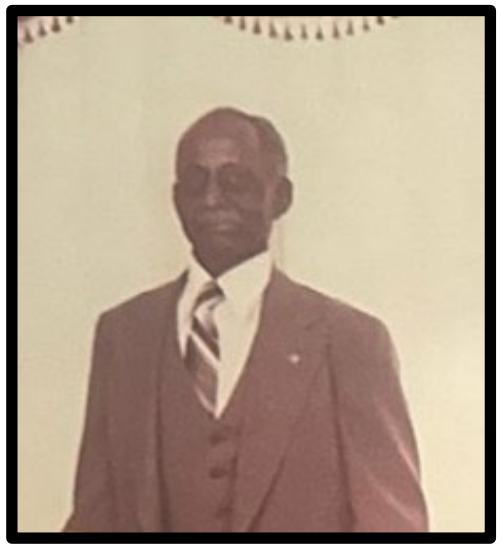


C

Top Transcription Factors in EA			Top Transcription Factors in AA		
TF	Differential Binding Score	FDR	TF	Differential Binding Score	FDR
FOSL2	0.71	3.8E-204	GRHL2	-0.68	8.0E-186
FOSL1	0.71	5.9E206	ZEB1	-0.57	2.7E-193
FOS	0.69	2.5E-205	SNAI2	-0.56	7.9E-179
FOSB	0.67	9.3E-203	SNAI1	-0.55	2.0E-177
JUN	0.66	3.3E-210	ZBT14	-0.47	3.8E-132
JUND	0.64	3.1E-203	P63	-0.45	1.0E-169
JUNB	0.62	2.0E-200	AP2C	-0.42	1.0E-180
NF2L2	0.44	1.3E-175	AP2A	-0.41	1.1E-186
BATF	0.44	2.1E-176	THAP1	-0.40	6.5E-178
NF2L1	0.40	1.4E-174	P73	-0.39	1.2E-157

Harris …. Yates et al Cancer Res Commun. 2023 Oct; 3(10): 2014–2029.

Cancer is in my Family



Boyd Chisholm
Grandfather
Passed 1993
Prostate Cancer

Francis Chisholm
Grand-Mother
Passed 2009
Breast Cancer Survivor
Passed of Colon Cancer

Hattie Yates
Grand-Mother
Passed 2019
Pancreatic Cancer

Cynthia Henderson
Maternal Aunt 2019
Passed 2023
Colorectal Cancer

Research Article

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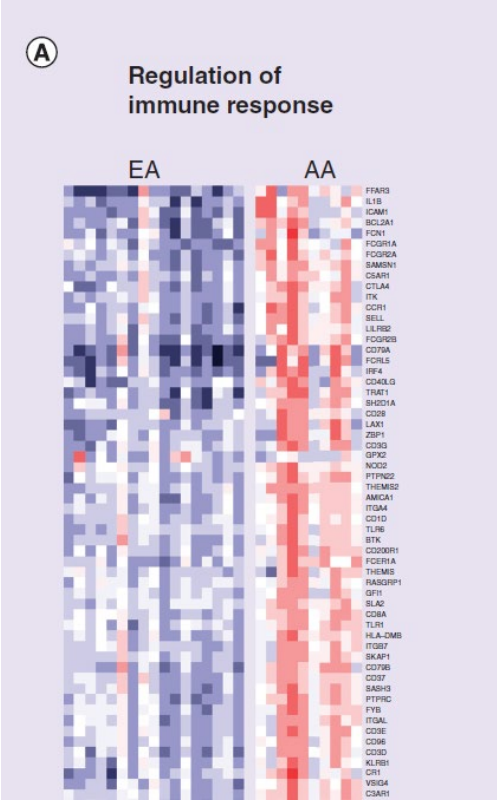
Pharmacogenomics

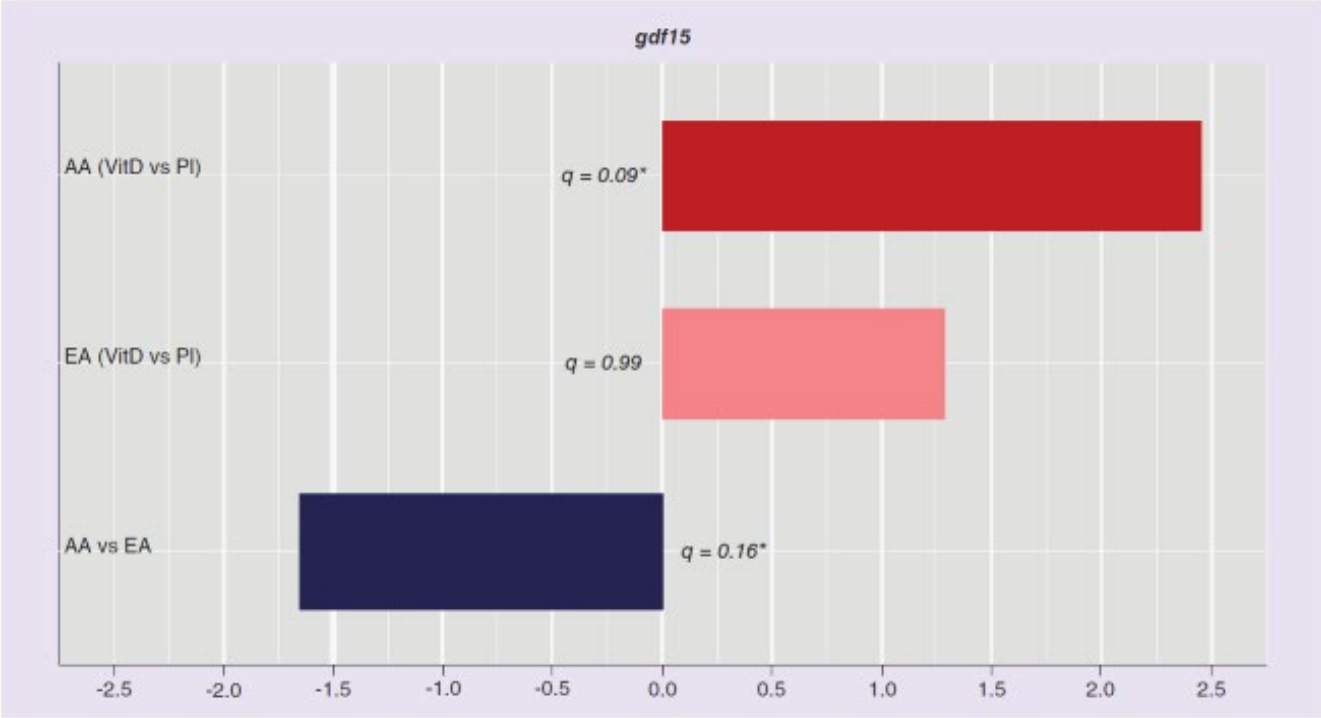
Systems analysis of the prostate transcriptome in African–American men compared with European–American men

Vit-D reversed the immune signatures and aggressiveness in AA patients

Chanita Hughes-Halbert PhD
USC

AA Patients Receiving Vitamin D (VitD) prior to Surgery





AA = African American EA= European American

Hardman et al Pharmacogenomics. 2016 Jul;17(10):1129-1143

Ancestry Specific Response to Vitamin D

Solomon Rotimi PhD
Covenant Univ.

Adelani Isaacson PhD
Johns Hopkins

CANCER RESEARCH COMMUNICATIONS

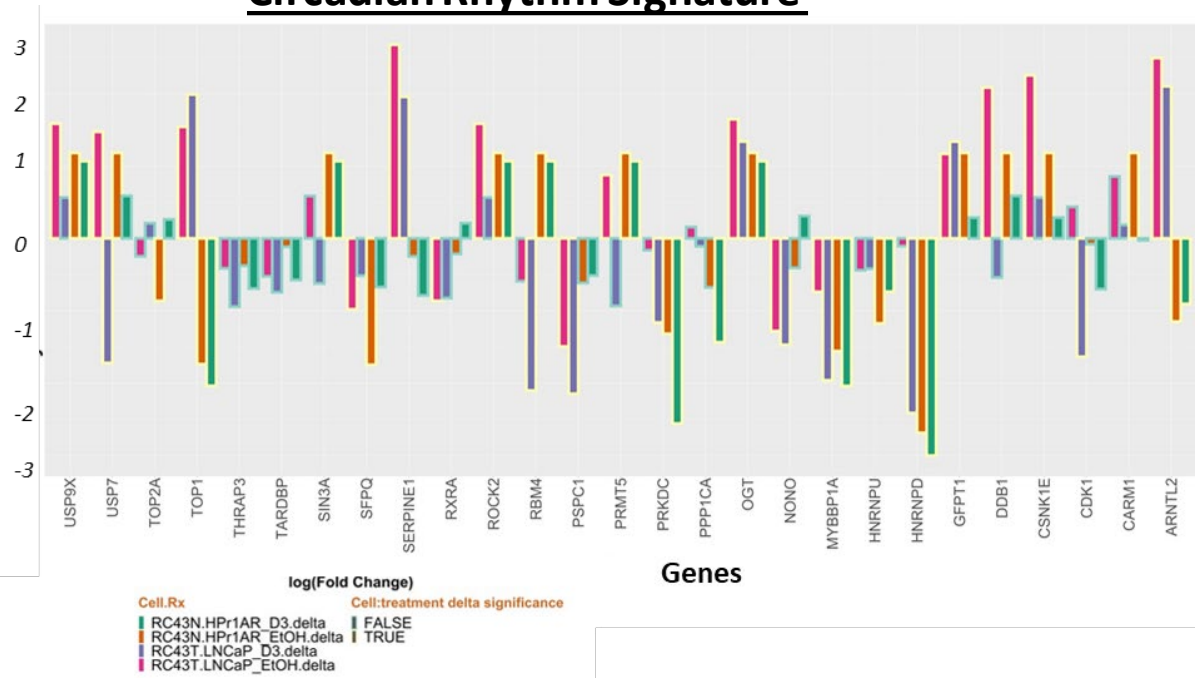
AACR American Association for Cancer Research

RESEARCH ARTICLE https://doi.org/10.1158/2767-9764.CRC-22-0389 OPEN ACCESS

African American Prostate Cancer Displays Quantitatively Distinct Vitamin D Receptor Cistrome-transcriptome Relationships Regulated by BAZ1A

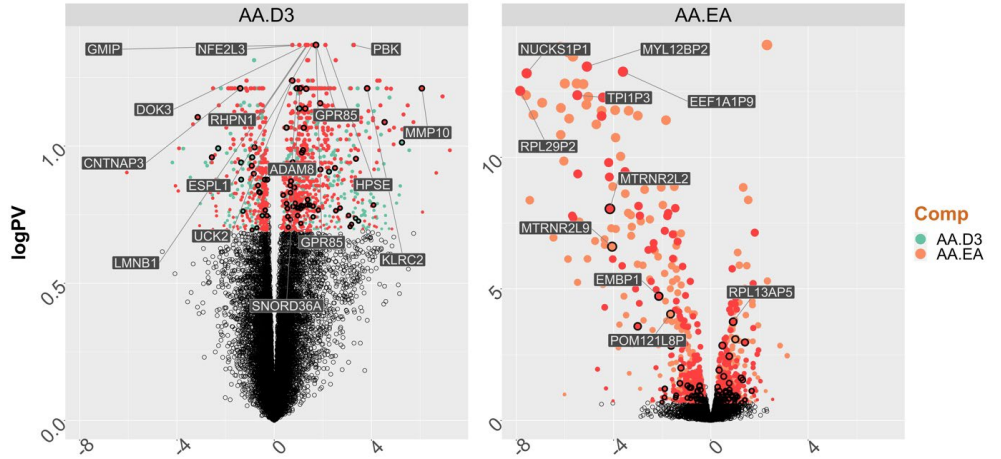
Manjunath Siddappa[1], Shahid Hussain[1], Sajad A. Wani[1], Jason White[2], Hancong Tang[1], Jaimie S. Gray[1], Hedieh Jafari[1], Hsu-Chang Wu[1], Mark D. Long[3], Isra Elhussin[2], Balasubramanyam Karanam[2], Honghe Wang[2], Rebecca Morgan[4], Gary Hardiman[4,5], Isaacson B. Adelani[6], Solomon O. Rotimi[6], Adam R. Murphy[7], Larisa Nonn[8], Melissa B. Davis[9], Rick A. Kittles[10], Chanita Hughes Halbert[11,12], Lara E. Sucheston-Campbell[13,14], Clayton Yates[2,15,16,17], and Moray J. Campbell[1]

Circadian Rhythm Signature

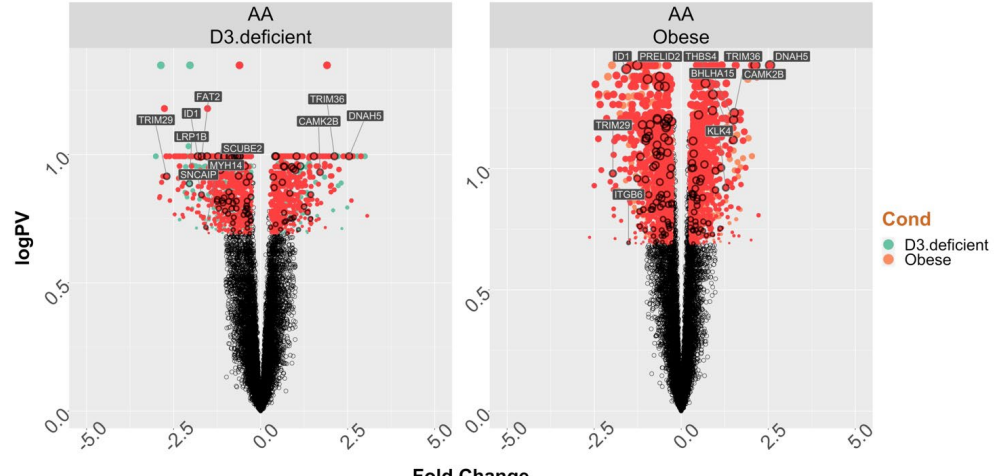


Vitamin D Treated Prostate Cancer Patients

Medical University South Carolina



Northwestern University



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Mannose receptor (CD206) activation in tumor-associated macrophages enhances adaptive and innate antitumor immune responses

Jaynes *et al.*, *Sci. Transl. Med.* **12**, eaax6337 (2020) 12 February 2020

Collaborators

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Department of Biology

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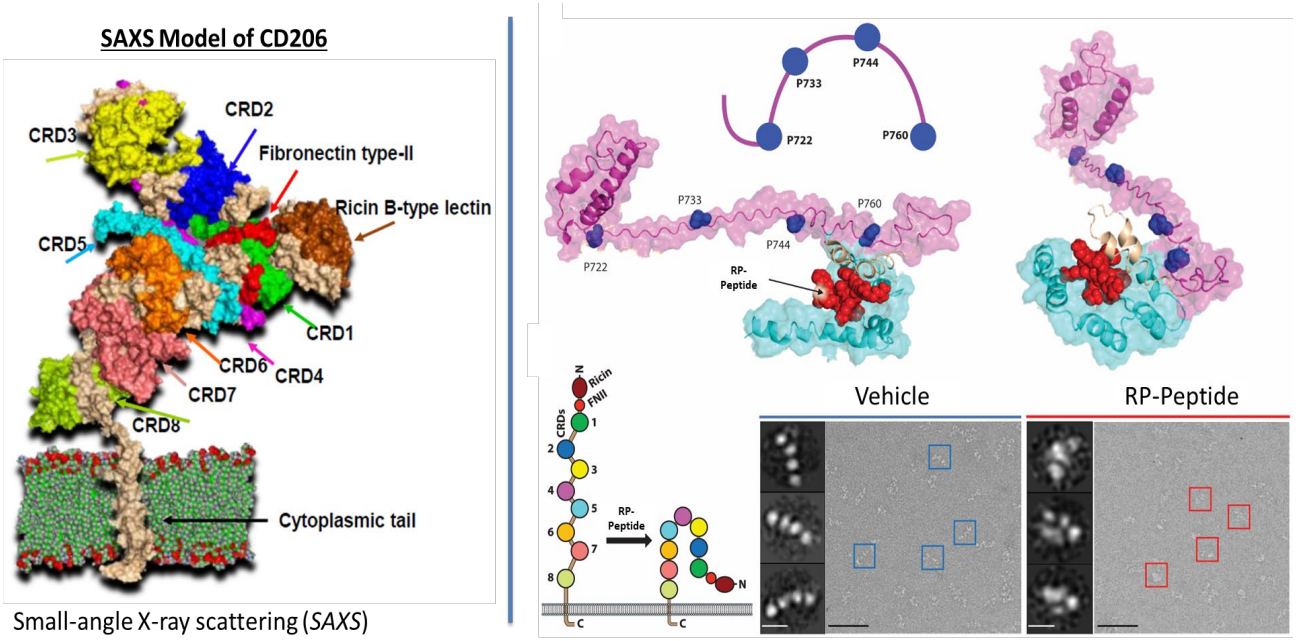
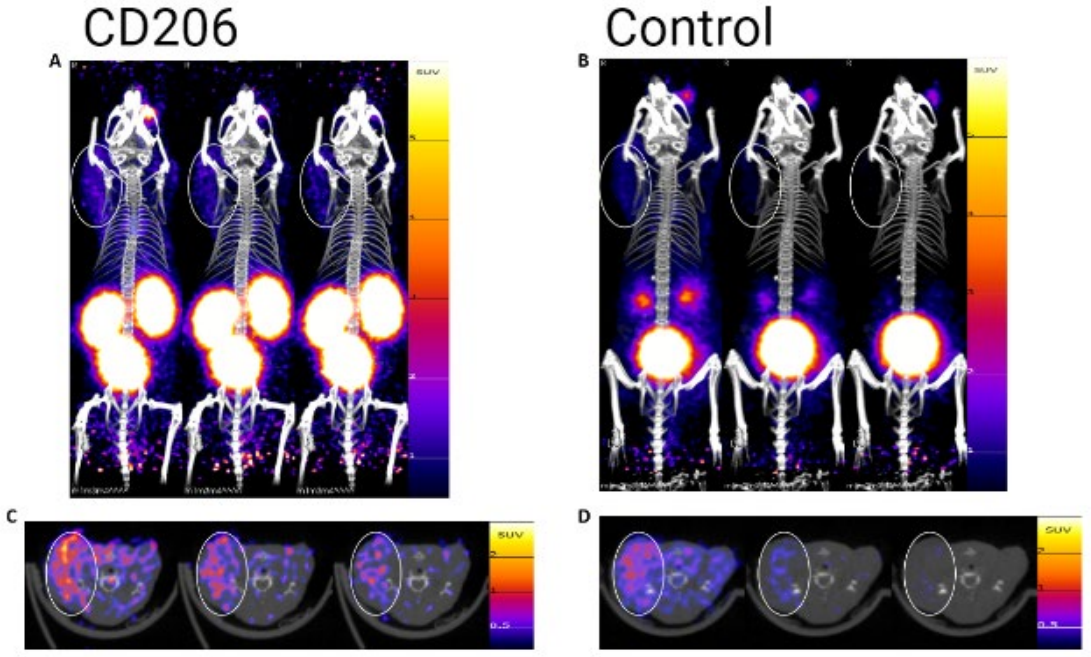
National Institutes of Health
NCI/CCR

Macrophage Targeted Therapeutic



Small-angle X-ray scattering (*SAXS*)

Macrophage Targeted Molecular Imaging



Parker et al Mol. Pharmaceutics 2023

nature reviews drug discovery

RESEARCH HIGHLIGHTS

IMMUNOTHERAPY

Tapping the therapeutic potential of the innate immune system

Macrophages are the main effectors of the innate immune response and are programmed to detect and eliminate diseased cells including cells with mutated genomes. Solid tumours can co-opt these innate immune cells, including infiltrating macrophages, and promote a change in their phenotype to pro-tumorigenic tumour-associated macrophages (M2-TAMs), which induce immune suppression. To circumvent this M2-TAM-mediated immune evasion by tumours, Jaynes et al. identified a peptide that reprogrammes M2-TAMs to exhibit antitumour activity as observed by M1-like TAMs (M1-TAMs) in vivo. This innate immune response-enabled antitumour activity was observed in mouse models across different cancer types and was enhanced in combination with PD-L1 checkpoint inhibition in a pancreatic cancer model.

Innate defence regulators are an emerging class of immunomodulators that are inspired by an ancient component of the inherent immune system: the naturally occurring host defence peptides (HDPs). As the first line of defence, HDPs form the immediate response to injury and infection by attracting immune cells to these sites. Despite the high sequence divergence of HDPs, the amphipathic α-helical structure is conserved to retain the HDP function. Given the emerging roles of HDPs in immunomodulation and regulation of pro-inflammatory or anti-inflammatory responses, the authors sought to find HDPs that could potentially reprogramme innate defence mechanisms for the improvement of disease outcomes.

The authors started by screening more than 400 HDPs using an in silico biophysical homology screening programme that sorts amino acids by chemical nature. They identified a highly conserved 10-mer peptide sequence, which was further optimized to yield RP-182. In silico screening revealed a receptor exclusively expressed on M2 macrophages and M2-TAMs, mannose receptor 1 (CD206), as the target of RP-182.

RP-182 induces the closed conformation of CD206 at low micromolar activity, as seen by electron microscopy. In bone marrow-derived M2 macrophages, RP-182 treatment induces a significant upregulation of genes associated with M1-like pro-inflammatory pathways as well as processes such as endocytosis, phagocytosis, autophagy and apoptosis.

By analysing The Cancer Genome Atlas pan-cancer and pancreatic adenocarcinoma datasets, the authors found a negative correlation between CD206 expression levels in M2-TAMs and CD8+ T cell antitumour immune function. This association between CD206^{high}-expressing M2-TAMs and poor antitumour immunity was also observed in murine pancreatic cancer models and might explain the lower survival observed in patients with CD206^{high}-pancreatic cancers.

> Jaynes et al. identified a peptide that reprogrammes M2-TAMs to exhibit antitumour activity as observed by M1-like TAMs ... in vivo

In mouse models that recapitulate human pancreatic cancer biology, treatment with RP-182 in combination with gemcitabine exhibited significant antitumour activity and extended survival beyond either as monotherapy. RP-182 treatment led to improved CD8+ T cell function, increasing antitumour immunogenicity by promoting an M2-TAM to M1-TAM transition. RP-182 also showed anti-tumour activity in CD206^{high} patient-derived pancreatic cancer xenografts and in other cancer mouse models including colon and prostate cancer, breast tumours and melanoma.

Because RP-182 activates T cell function at tumour sites specifically, the authors evaluated RP-182 in combination with PD-L1 checkpoint inhibition. In vivo, the combination treatment enhanced antitumour activity. In addition, as a result of activating the CD206-mediated innate immune activation, RP-182 also induced cancer cell phagocytosis by reprogrammed M2-TAMs. Beyond cancer, in a CD206-positive, bleomycin-induced lung fibrosis mouse model, RP-182 treatment led to an increase in animal weight and survival, as well as a decrease in pulmonary fibrosis.

The broad activity of RP-182 in different cancer models and lung fibrosis, as well as its novel mechanism, highlight the untapped therapeutic potential of the innate immune system. The authors are now investigating modulating CD206 in other preclinical inflammation models such as inflammatory bowel disease, multiple sclerosis and non-alcoholic steatohepatitis.

Stacey-Lynn Paiva

ORIGINAL ARTICLE Jaynes, J. M. et al. Mannose receptor (CD206) activation in tumor-associated macrophages enhances adaptive and innate antitumor immune responses. *Sci. Transl. Med.* **12**, eaax6337 (2020)
RELATED ARTICLES Cassetta, L. & Pollard, J. W. Targeting macrophages: therapeutic approaches in cancer. *Nat. Rev. Drug Discov.* **17**, 887–904 (2018)

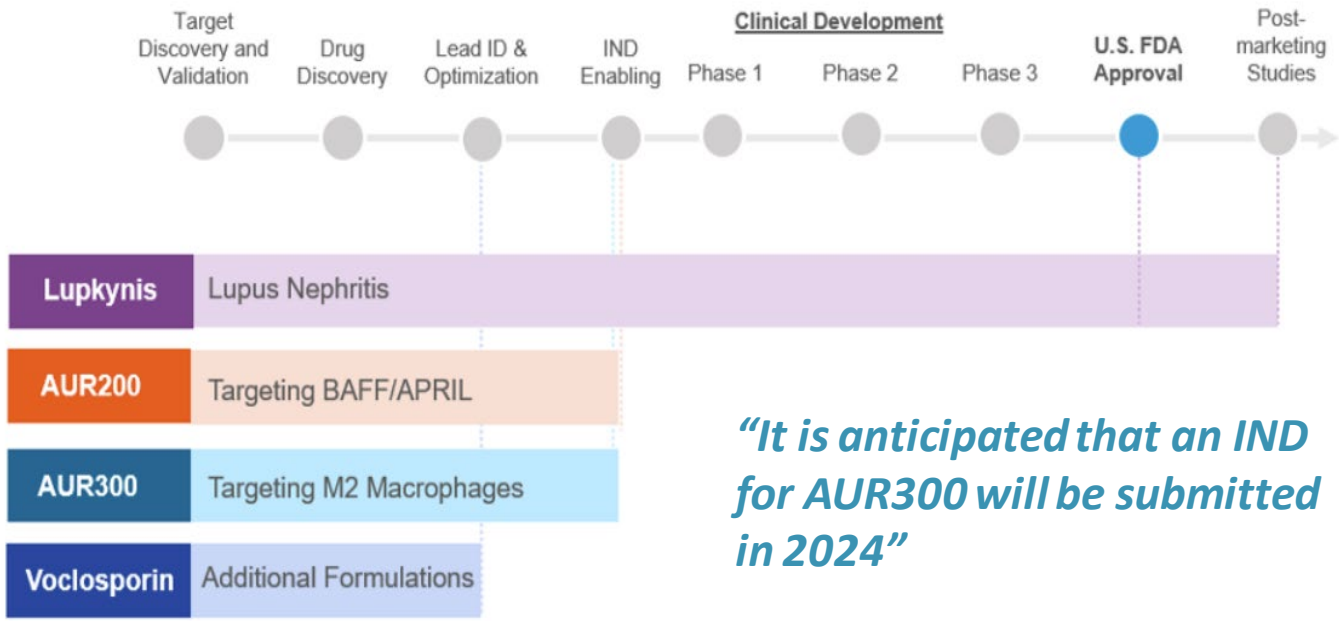
Nature Reviews Drug Discovery **19**, 236 (2020) https://doi.org/10.1038/d41573-020-00040-0

Aurinia acquires pipeline assets for autoimmune and kidney diseases

Aurinia obtained the recombinant Fc protein from Thunderbolt Pharma and the peptide therapy from Riptide Bioscience.

RIPTIDE BIOSCIENCE

Aurinia™



"It is anticipated that an IND for AUR300 will be submitted in 2024"

https://www.auriniapharma.com/our-pipeline

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Grant Support: NIH/NCI U54CA118623-01; DoDPC073977; DoD PC120913; NIH/NIMHDU54-MD007585-26; NIH/NCI 1R21CA188799-01,

The SAMBAI Cohort

Societal, Ancestry and Molecular Biology Analyses of Inequities

CANCER GRAND CHALLENGES

- Target population-40K African Ancestry Patients. (Prostate - Breast – Pancreatic)
- Specific Sites - Recruitment
- Intersection between Biology and Social Determinants of Health

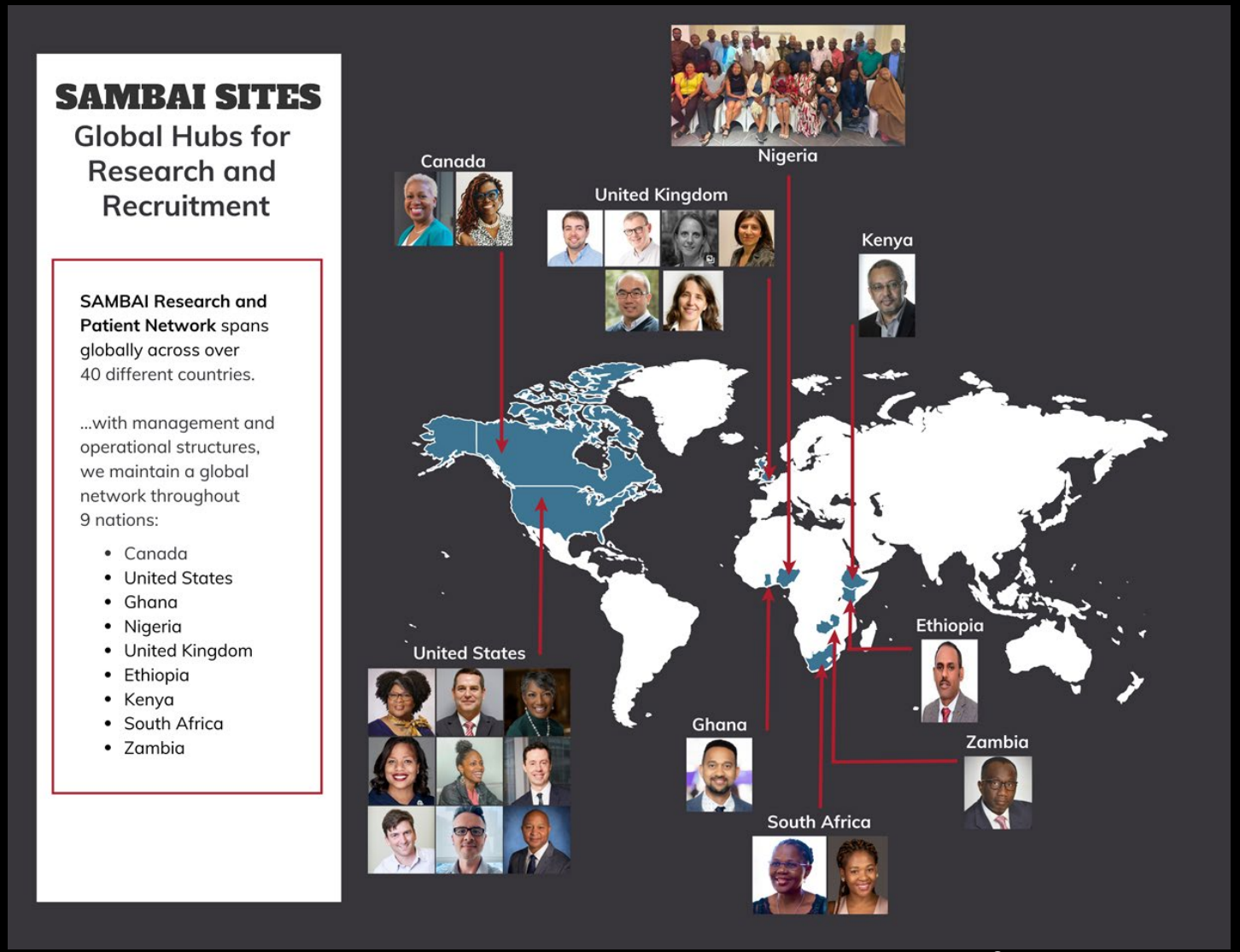
SAMBAI SITES

Global Hubs for Research and Recruitment

SAMBAI Research and Patient Network spans globally across over 40 different countries.

...with management and operational structures, we maintain a global network throughout 9 nations:

- Canada
- United States
- Ghana
- Nigeria
- United Kingdom
- Ethiopia
- Kenya
- South Africa
- Zambia



Institutions 14 **Countries-** Nigeria**,** Ghana, South Africa, US, UK