RISE UP 2024

Breast Cancer and Maternal Mortality Disparities in African American Women: Connection or Coincidence?

Co Chairs:

Olufunmilayo Olopade, MD University of Chicago

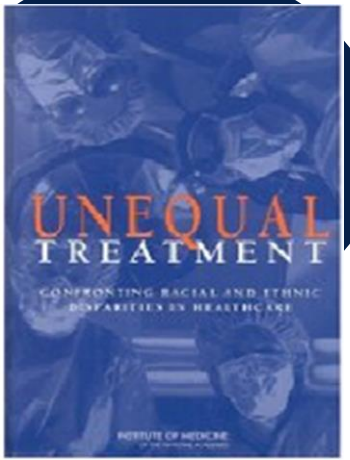
Andrea Jackson, MD UCSF

Health Inequities in Breast & Perinatal Health

- Breast cancer
  - 5% lower incidence, 38% higher mortality
  - Lowest survival rate for every stage, higher likelihood triple negative
- Maternal Morbidity and Mortality
  - Preterm birth
  - Maternal and Neonatal death
  - 80% preventable

Source: https://www.cdc.gov/nchs/data/hestat/maternal-mortality/2021/maternal-mortality-rates-2021.htm

Access



Social determinants of health

Healthcare disparities

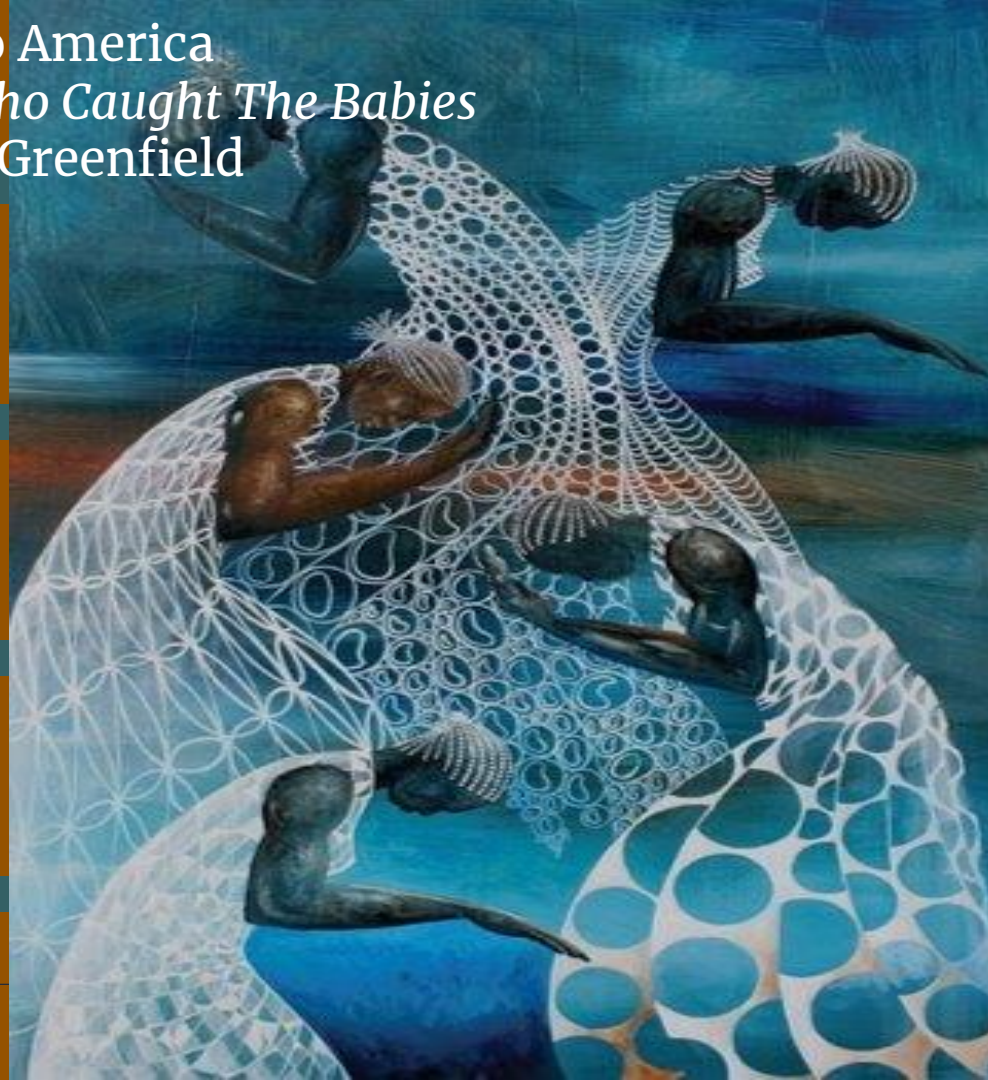
Racial or ethnic diff ealth care that are ***not*** due to acce al needs, preferences, and a ion.

Braveman, P. Ann Rev Pub Health

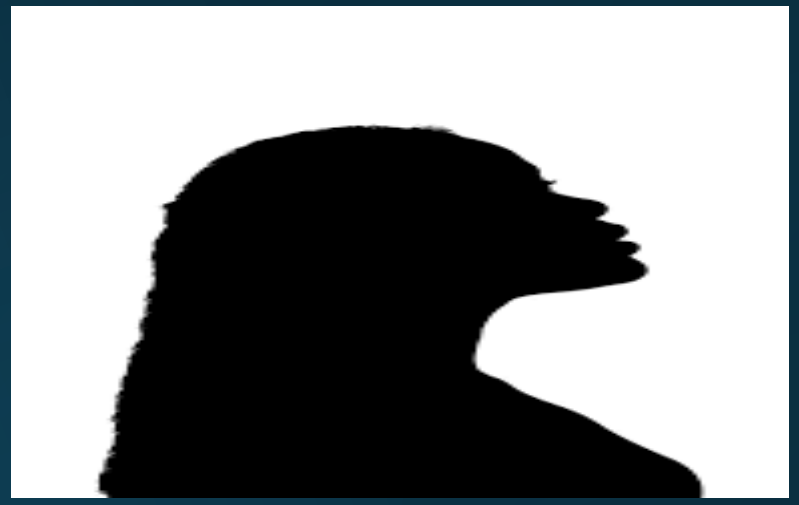
Institute of Medicine. Unequal Treatment.

Africa to America
from *The Women Who Caught The Babies*
by Eloise Greenfield

Somewhere in the African past,
Before the guns, Before the shackles,
Before the kidnappings of
Storytellers and sky-readers,
Musicians, Dancers,
Doctors, Sculptors,
Teachers, Planters,
Hunters, Historians,
Mothers, Fathers, and Children.
Before all that,
There were the women who caught babies
and guided them into the world,
with gentle, loving hands.



Pelvic Floor Disorders in Black Women



Oluwateniola (Teni) Brown, MD FACOG

Assistant Professor, Obstetrics and Gynecology
Urogynecology and Reconstructive Pelvic Surgery
Northwestern University Feinberg School of Medicine

Disclosures

- No financial relationships to disclose
- Consultant: None
- Grant/Research support: Robert Wood Johnson Harold Amos Faculty Development Award
- Employee: Northwestern University Feinberg School of Medicine

I will not discuss off label use and/or investigational use in my presentation

Black Women Have Poorer Outcomes Across Several Gynecologic Conditions

- Higher burden of Fibroids

- Infertility- 2-fold increased odds of infertility

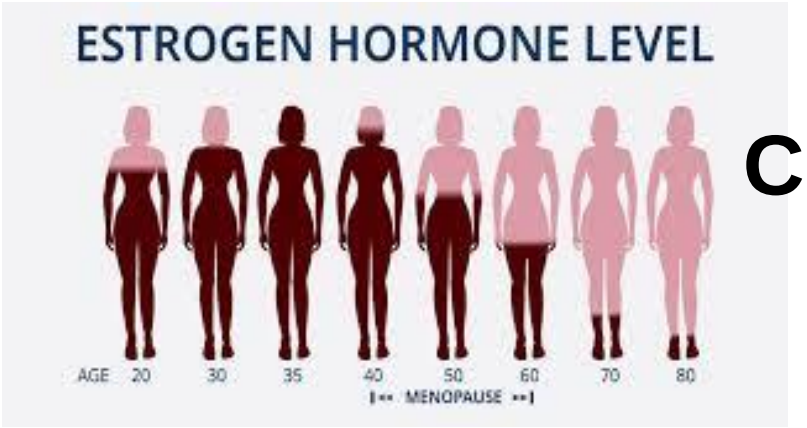
  aOR 2.04 (1.39–3.01)

- Bladder Health and Pelvic Floor Disorders

Marsh et al. Fertility and Sterility. 2013
Marsh et al. J Woimens Health 2018
Eltouhki. Am J Obstet Gynecol. 2014
Wellons et al. *Fertility and Sterility* 2011

Bladder Health and Pelvic Floor Disorders

RISK FACTORS



COMORBIDITIES

Overactive Bladder

Pelvic Organ Prolapse

Racial Disparity in Bladder Health and Pelvic Floor Disorders

Overactive Bladder (OAB)

Black women…

- Higher prevalence
- More severe symptoms
- have 55% higher odds of OAB medication non-adherence
- are 17-34% less likely to receive advanced therapies
- have the lowest odds of progressing to advanced therapies

Patel et al. Urogynecology,. 2022
Coyne et al. BJU 2008
Rashid et al. 2017
Yeowell et al 2018
Syan et al. 2020
Jericevic et al 2024

Inequities in Filled Overactive Bladder Medication Prescriptions in the US

IN A STUDY OF FILLED OAB PRESCRIPTIONS IN THE 2019 AHRQ MEPS DATABASE

54% less likely to fill β3-agonist prescription

(aOR, 0.46; 95% CI, 0.22-0.98)

90% lower odds of filling a β3-agonist prescription vs. anticholinergic

(aOR, 0.10; 95% CI, 0.04-0.27)

Adjusted ORs were derived from multivariable logistic regression model controlling for race and ethnicity, poverty level, insurance status, educational attainment, sex, diagnosis of high blood pressure, and cognitive impairment

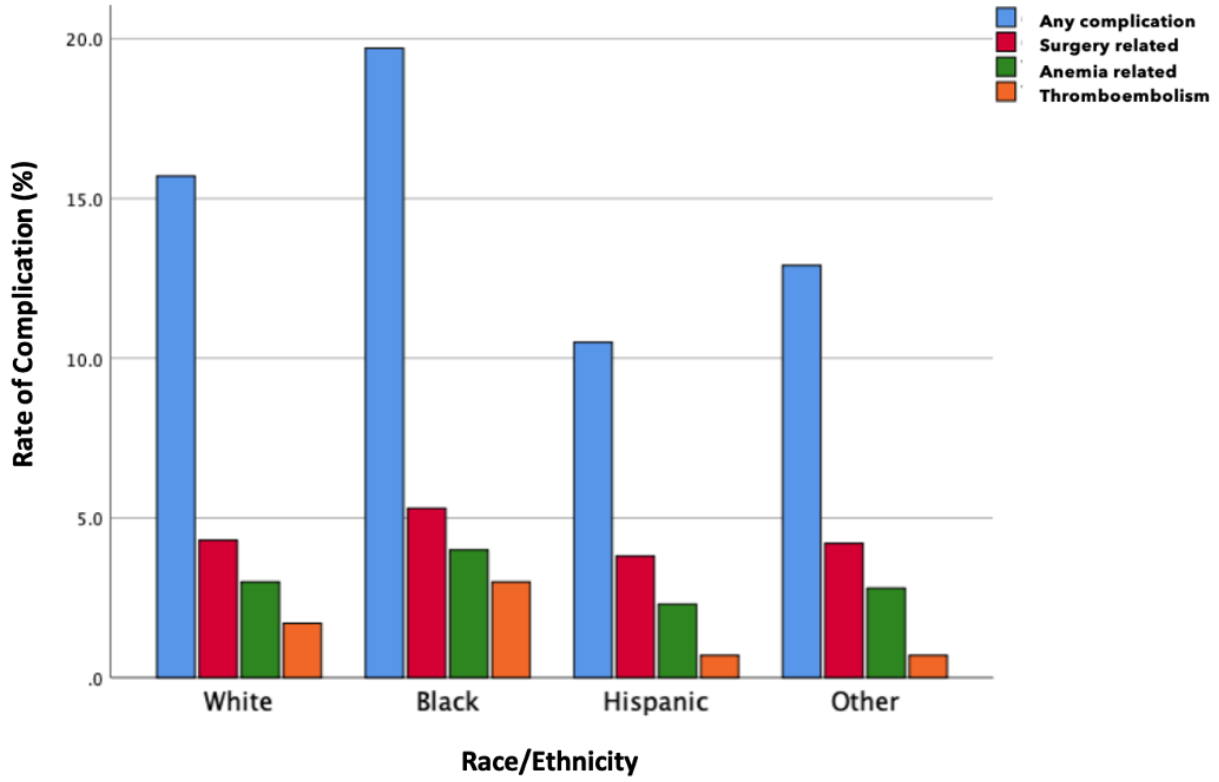
JAMA Network | Open

Doug Luchristt, Emi C .Bretschneider, Kimberly Kenton, Melissa Simon, Oluwateniola Brown
Inequities in Filled Overactive Bladder Medication Prescriptions in the US
JAMA Network 2023;6(5):e2315074

Pelvic Organ Prolapse Surgery Complications

Higher odds of postoperative complications for Black patients compared to their White counterparts.

Figure 1- Complication rates by race/ethnicity



Black patients

21%

Increased odds

of postoperative complications when compared to White patients.

(OR 1.21 95% CI 1.03-1.43)

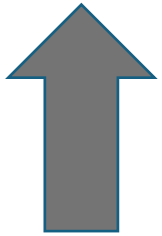
Oluwateniola Brown et al. IUJ 2021

Pelvic Organ Prolapse Surgery Complications

Female Urology

Disparities in Complications After Prolapse Repair and Sling Procedures: Trends From 2010-2018

Nancy E. Ringel, Oluwateniola Brown, Kristin J. Moore, Erin T. Carey, and Alexis A. Dieter



Vascular complication (venous thromboembolism or transfusion)
(aOR 2.50, 95% CI 2.05-3.04)

Black patients

15%

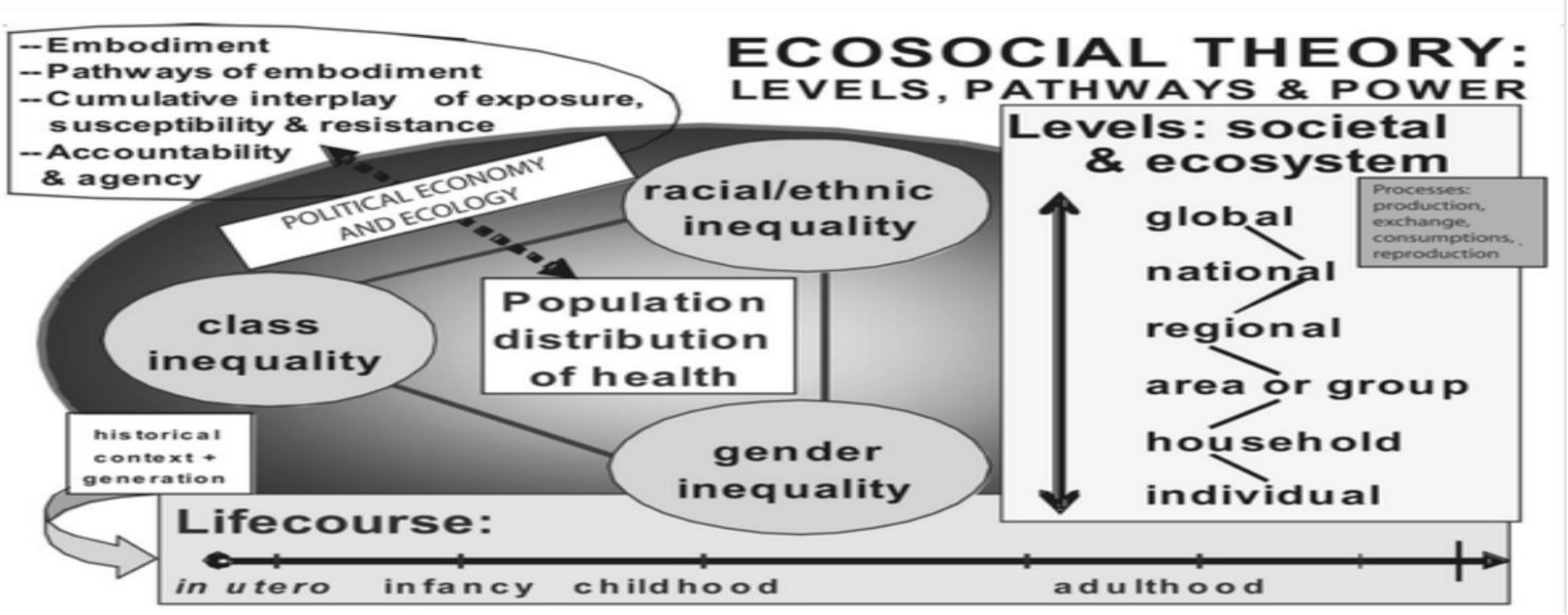
Increased odds

of postoperative complications when compared to White patients.

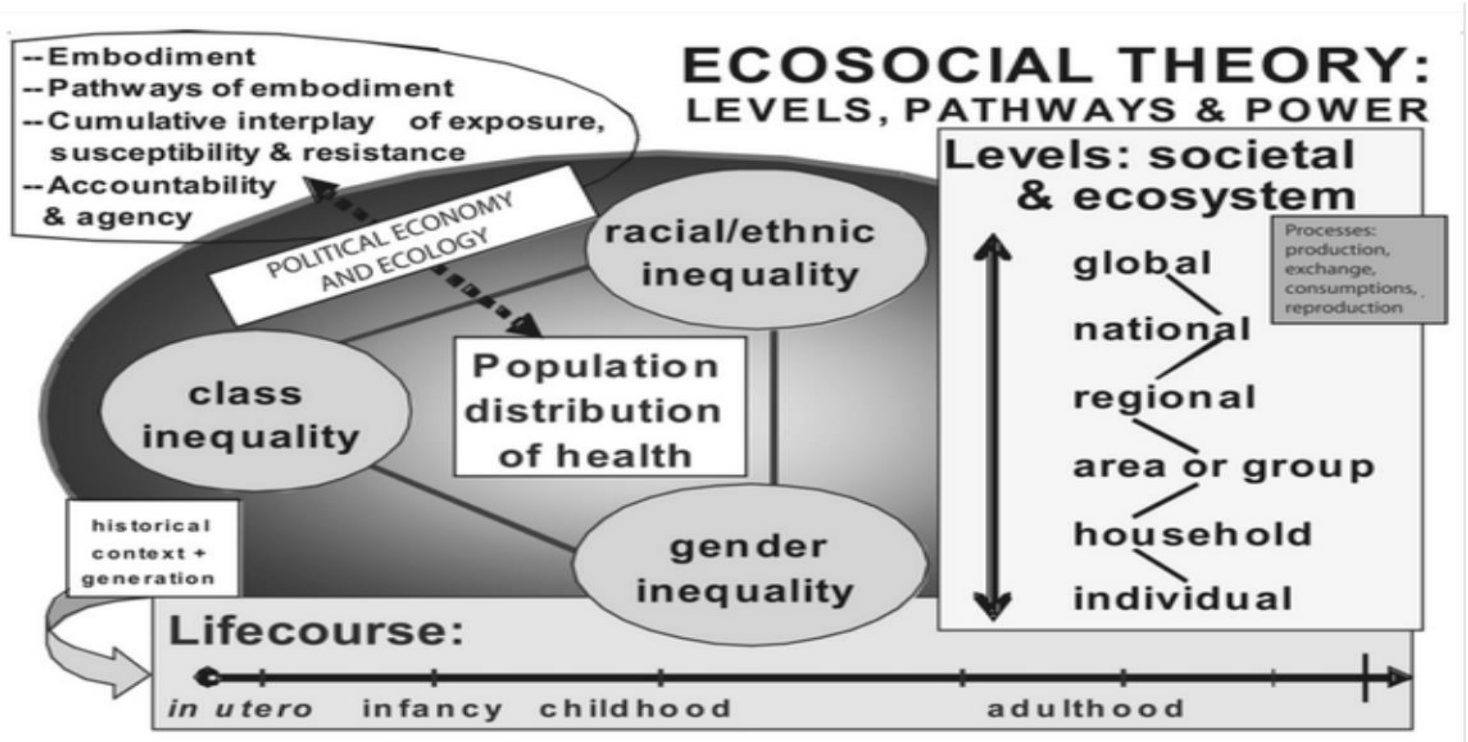
(OR 1.15 95% CI 1.03-1.29)

Ringer et al. Urology 2023

CONCEPTUAL FRAMEWORK (Eco-social Theory of Disease)



CONCEPTUAL FRAMEWORK



Race is a Proxy for Biological and Psychosocial Vulnerability

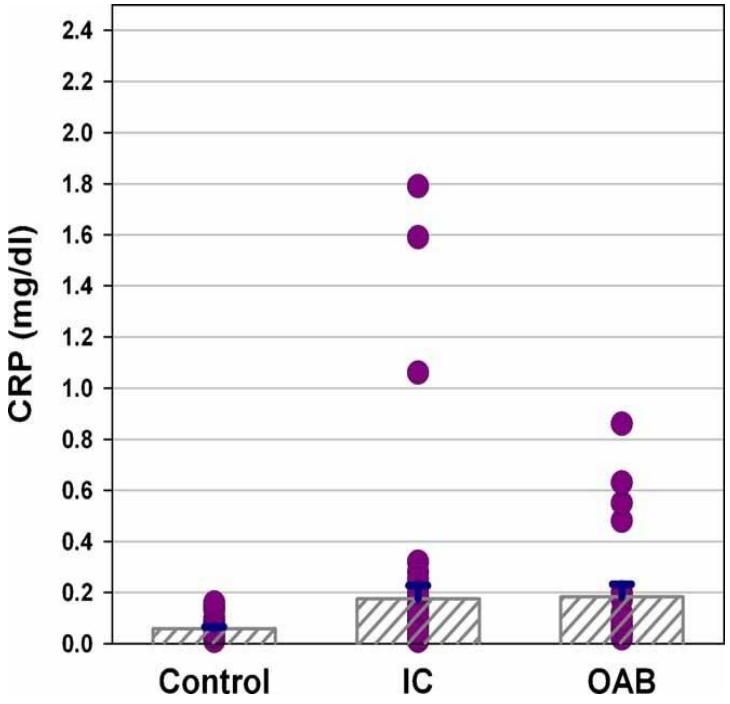
The Role of Inflammation

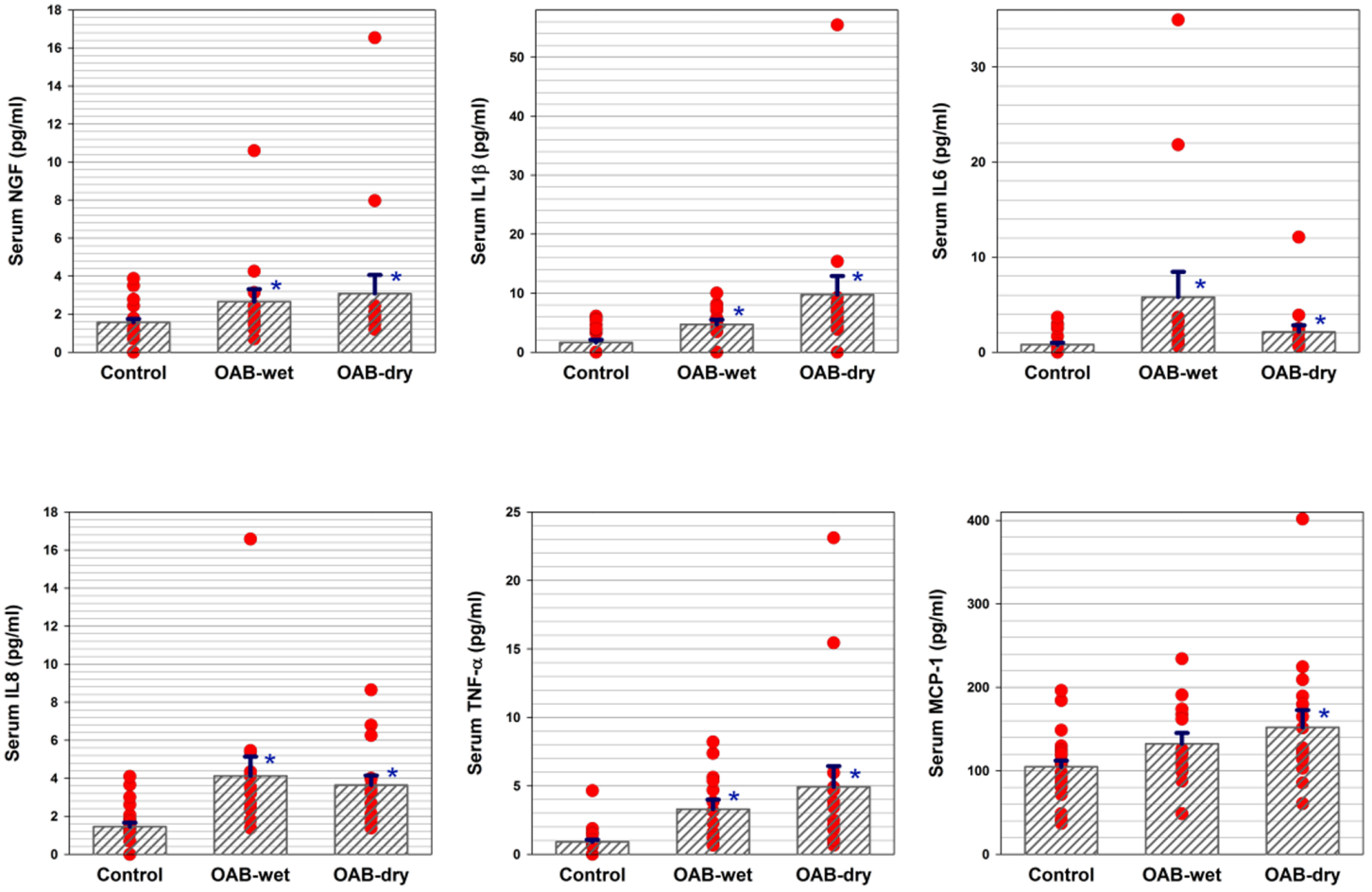
- In female reproduction, tightly regulated inflammatory processes participate in the key events of ovulation, menstruation, implantation and labor onset, menopause.

- However, inflammation can derail normal reproductive health processes and outcomes.

Inflammation and Overactive Bladder

- Higher levels of CRP, prostaglandins, adipokines, NGF, BDF in serum and urine of patients with OAB



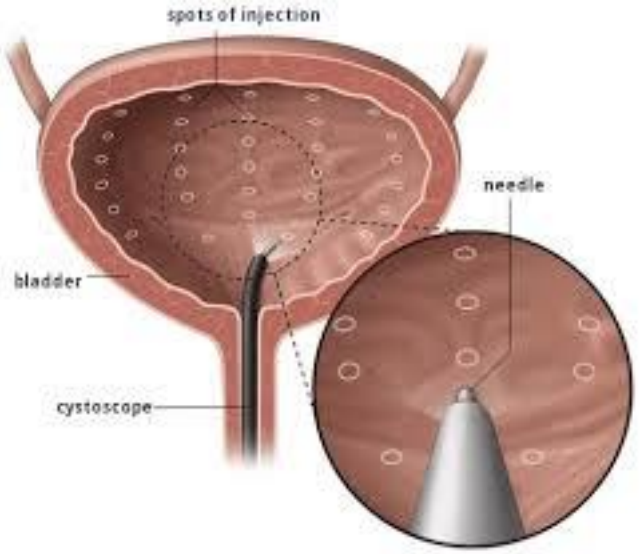


*:P<0.05 as compared with control group

Chung et al. Neurourology and urodynamics. 2011
Lui et al. PLoSONE 2013
Jhang et al. Biomedicines 2023

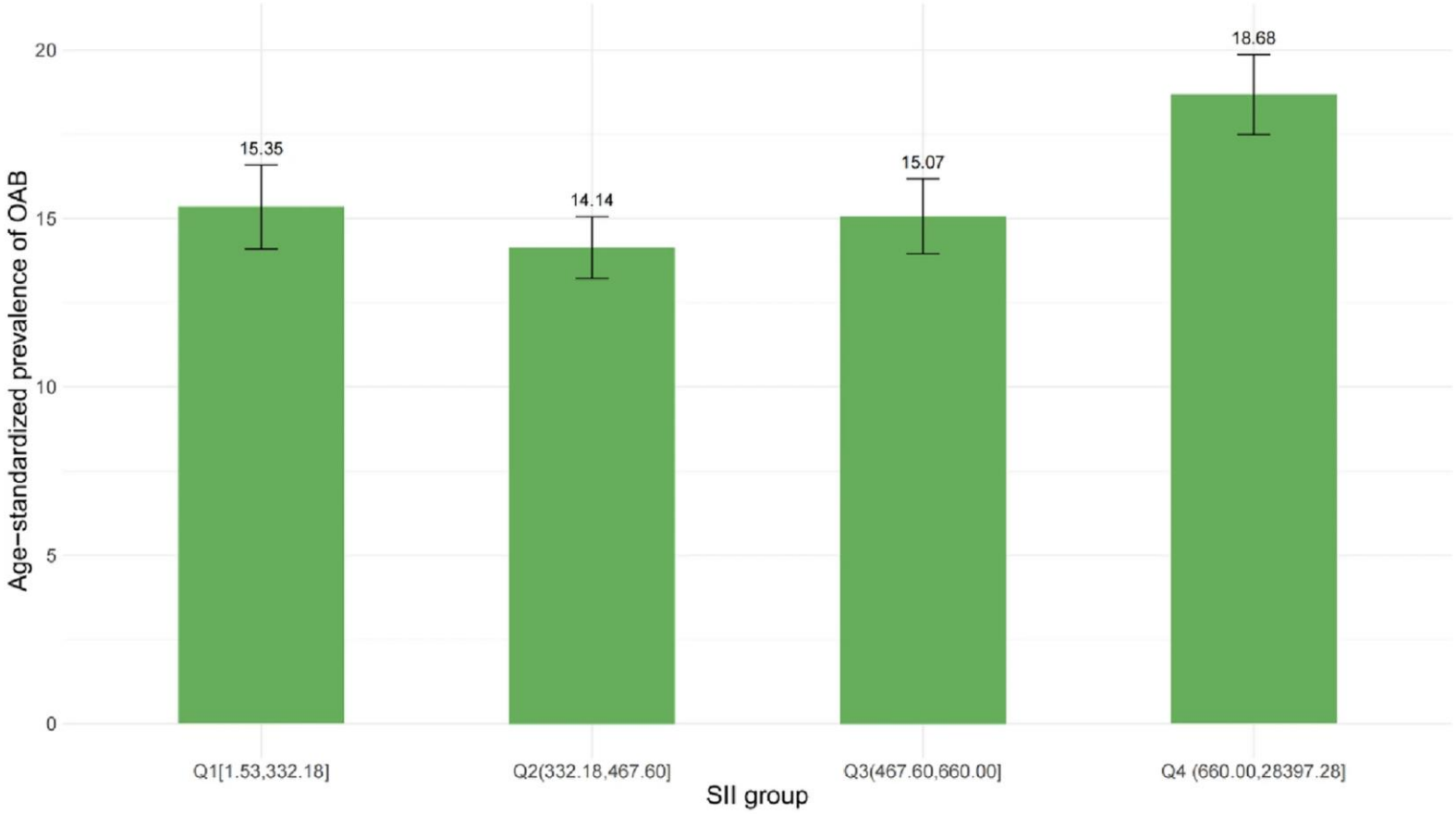
Inflammation and Overactive Bladder

Inflammation can lead to peripheral afferent nerve hyperexcitability, which causes a series of OAB symptoms such as urinary frequency and urgency



Grundy, Let al. *Front. Neurosci.* 2018

Systemic Inflammation and Overactive Bladder



Age-adjusted prevalence of OAB in different levels of SII. Numbers at the top of the bars represent the weighted percentage. Bar whiskers represent the 95% confidence level.

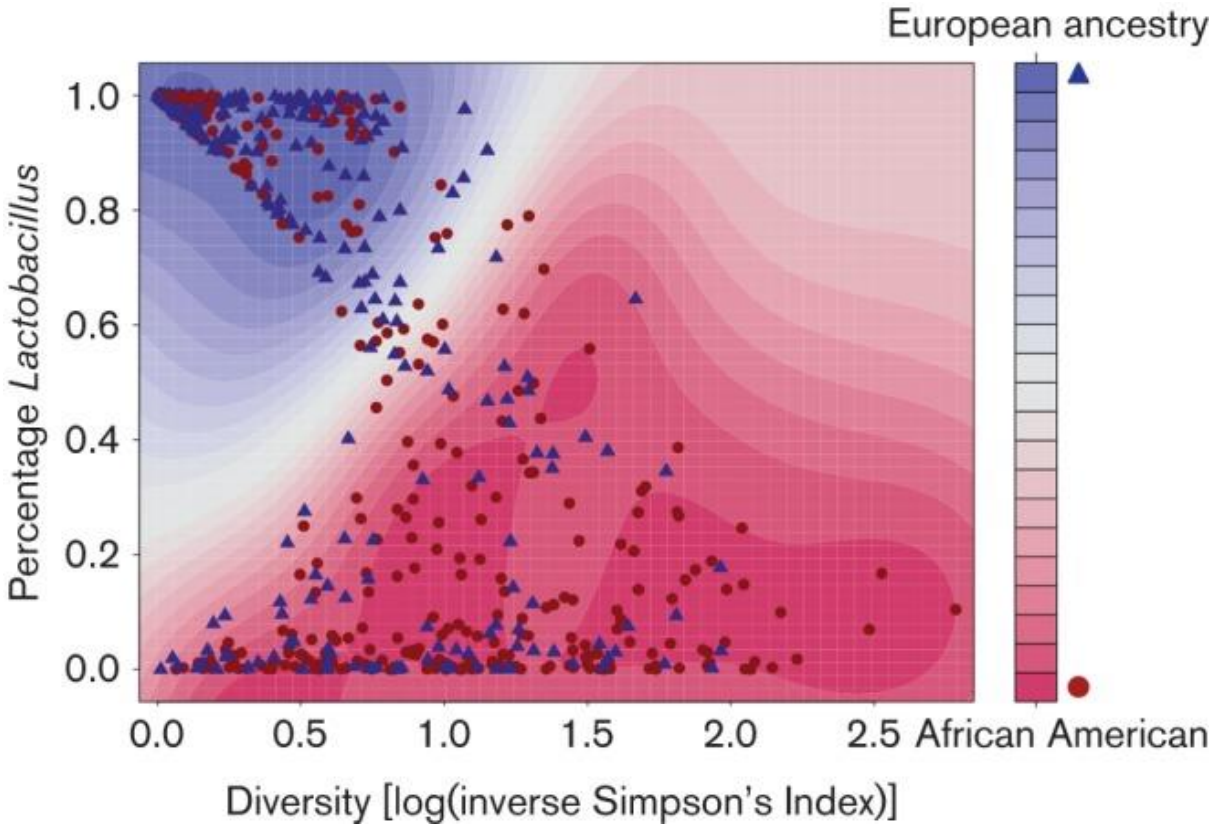
Higher Systemic Immunity Index (SII) levels are associated with an increased likelihood of developing OAB.

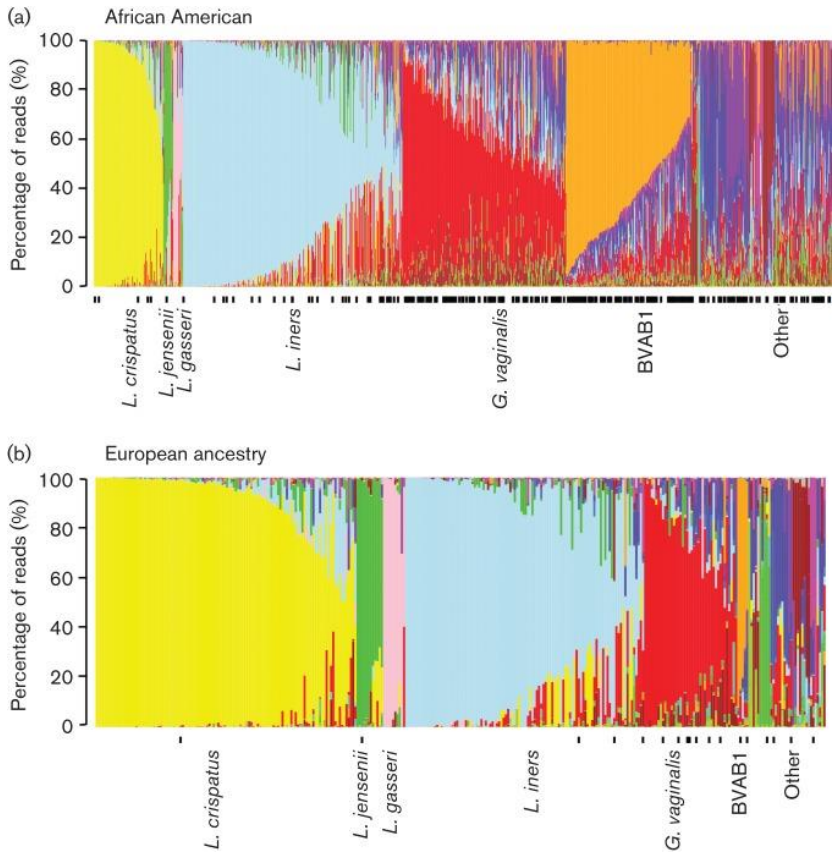
Black Individuals
(OR 1.246, 95% CI 1.079–1.439)

Wei, B et al . *Sci Rep* 2024

Vaginal Microbiome

Black women more likely to have a vaginal microbiome that promotes inflammation





Fettweiss et all. Microbiology. 2014

Adverse Childhood Experiences (ACES), Inflammation, Bladder Symptoms

- Higher ACE scores associated with increased odds of LUTS. (aOR 1.26, 95% CI 1.07-1.48
- The association between ACEs and LUTS may be partially mediated by the inflammation biomarker IL-6.
- Higher levels of IL-6 associated with increased odds of LUTS (aOR 1·24, 95% CI 1·05-1·47).

Brady et al. Journal of Urology 2023

Physical and Built Environment: Neighborhood context

Racial and Economic Residential Segregation

- Increased Perceived Stress
- Increased cortisol levels
- Allostatic Load
- Decreased Access of services and resources

Krieger N et al. *American journal of public health* 2016
Massey DS. Et al Sociology 2010
Krieger N et al. *J Urban Health* 2017
Yang et al. Maternal Child Health J. 2015
Barrington et al. Health Place. 2014
Ribeiro et al. *nt J Environ Res Public Health*. 2018

Racial and Economic Segregation and Adverse postoperative outcomes after Prolapse Surgery

Associations Between Racial and Economic Segregation and 90- Day Complications

Ref: Quintile 5	ICE Race RR Unadjusted	ICE Race RR Adjusted	ICE Income RR Unadjusted	ICE income RR Adjusted	ICE Race +Income RR Unadjusted	ICE Race +Income RR Adjusted
Quintile 1	**1.44 (1.03-2.03)**	**1.44 (1.02-2.03)**	0.75 (0.53-1.06)	0.73 (0.52-1.02)	1.01 (0.76-1.35)	1.02 (0.76-1.35)
Quintile 2	**1.59 (1.14-2.23)**	**1.55 (1.11-2.16)**	0.94 (0.68-1.28)	0.90 (0.66-1.22)	0.89 (0.64-1.23)	0.86 (0.62-1.19)
Quintile 3	1.27 (0.88-1.82)	1.17 (0.81-1.68)	0.82 (0.57-1.18)	0.82 (0.57-1.18)	0.80 (0.56-1.15)	0.80 (0.57-1.12)
Quintile 4	1.30 (0.89-1.89)	1.26 (0.87-1.84)	1.05 (0.75-1.46)	0.99 (0.71-1.37)	0.95 (0.70-1.30)	0.94 (0.69-1.27)

Covariates: Age, Dual enrollment in Medicaid, Charlson comorbidity score, Type of prolapse surgery, hysterectomy concomitant anti-incontinence procedure

Oluwateniola Brown et. al Urogynecoology 2024

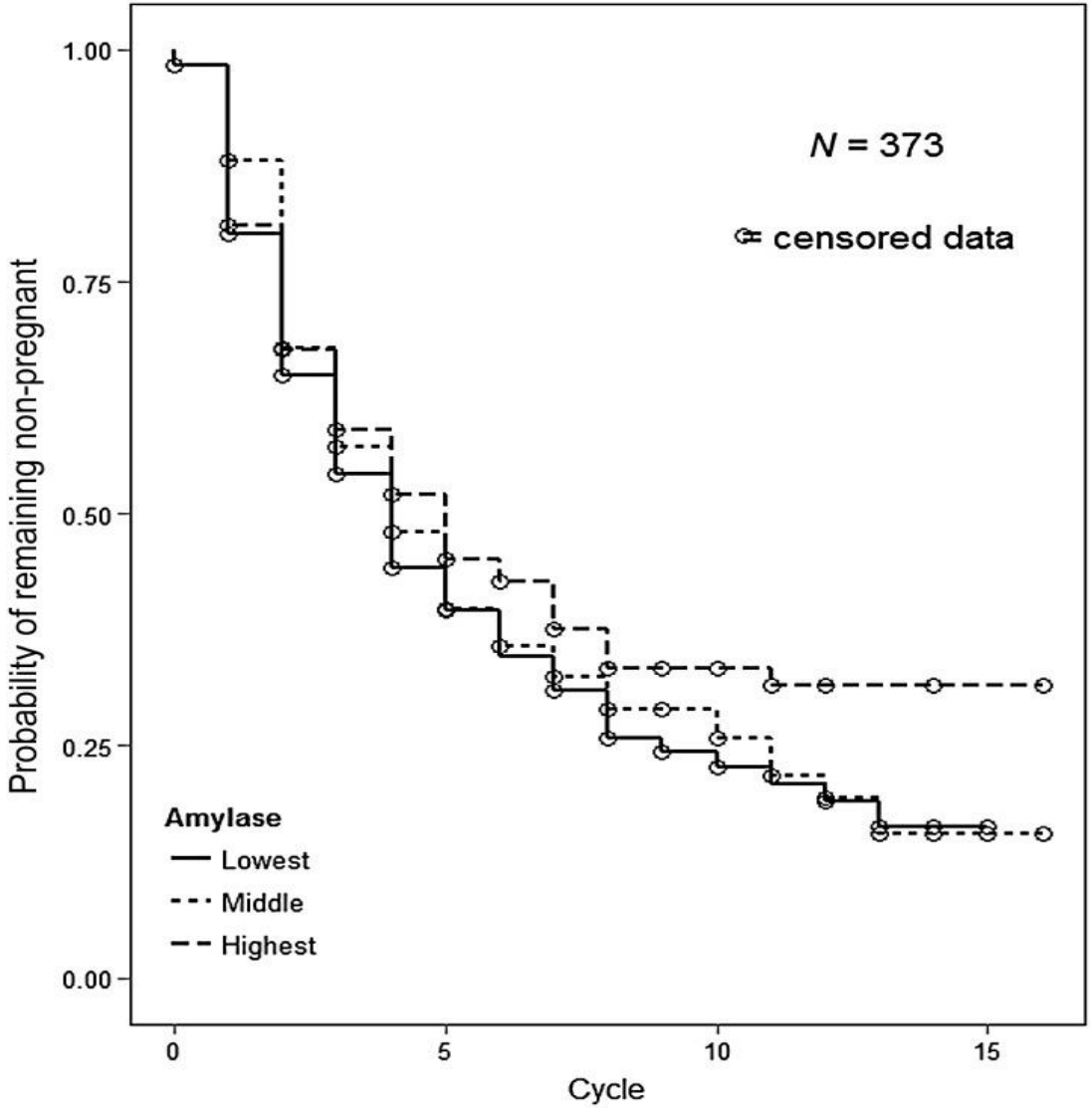
Stress and Fertility

Salivary alpha-amylase

Higher stress= 29% reduction in fecundity (Longer time to pregnancy)

(OR 0.71, CI 0.51, 1.00)

2 fold risk for infertility (RR 2.07; 95% CI 1.04, 4.11)

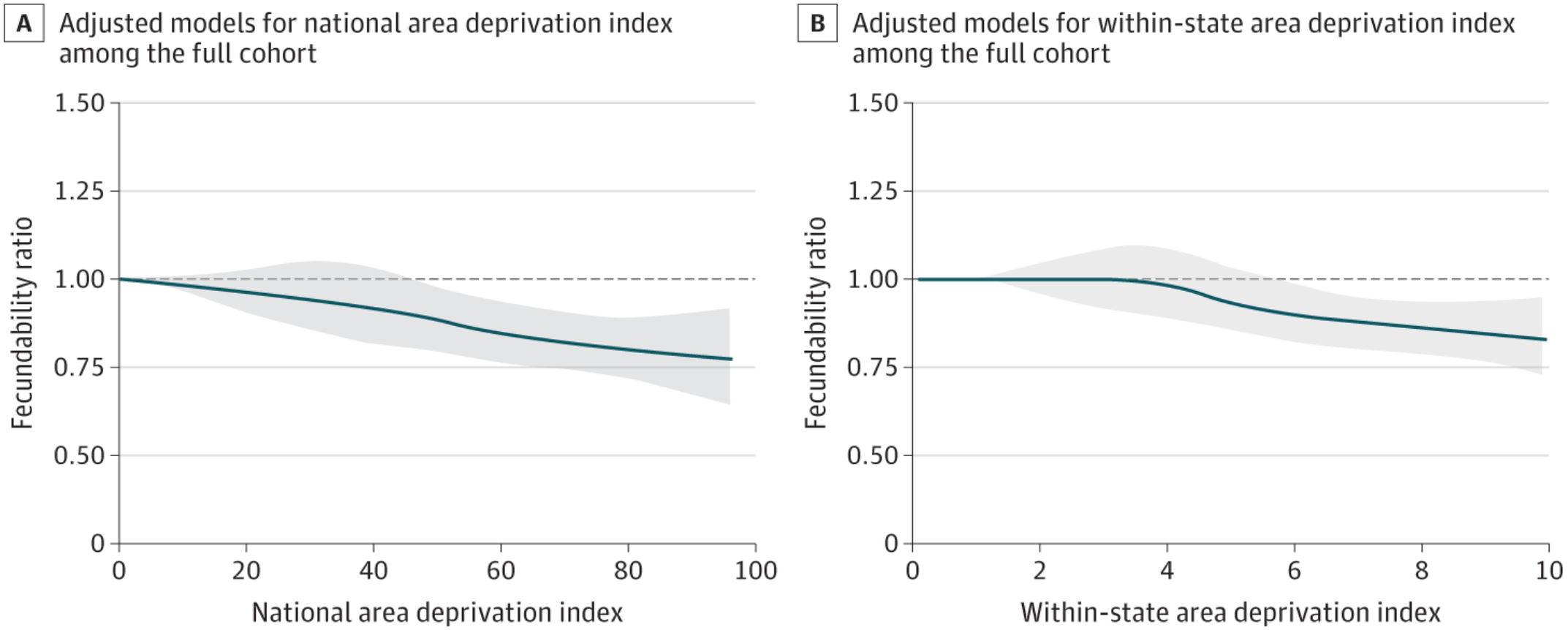


Lynch et al. Human Reproduction. 2014
Louis et al. Fertility and Sterility 2011

Neighborhood Disadvantage and Fecundability

Adjusted fecundability ratios

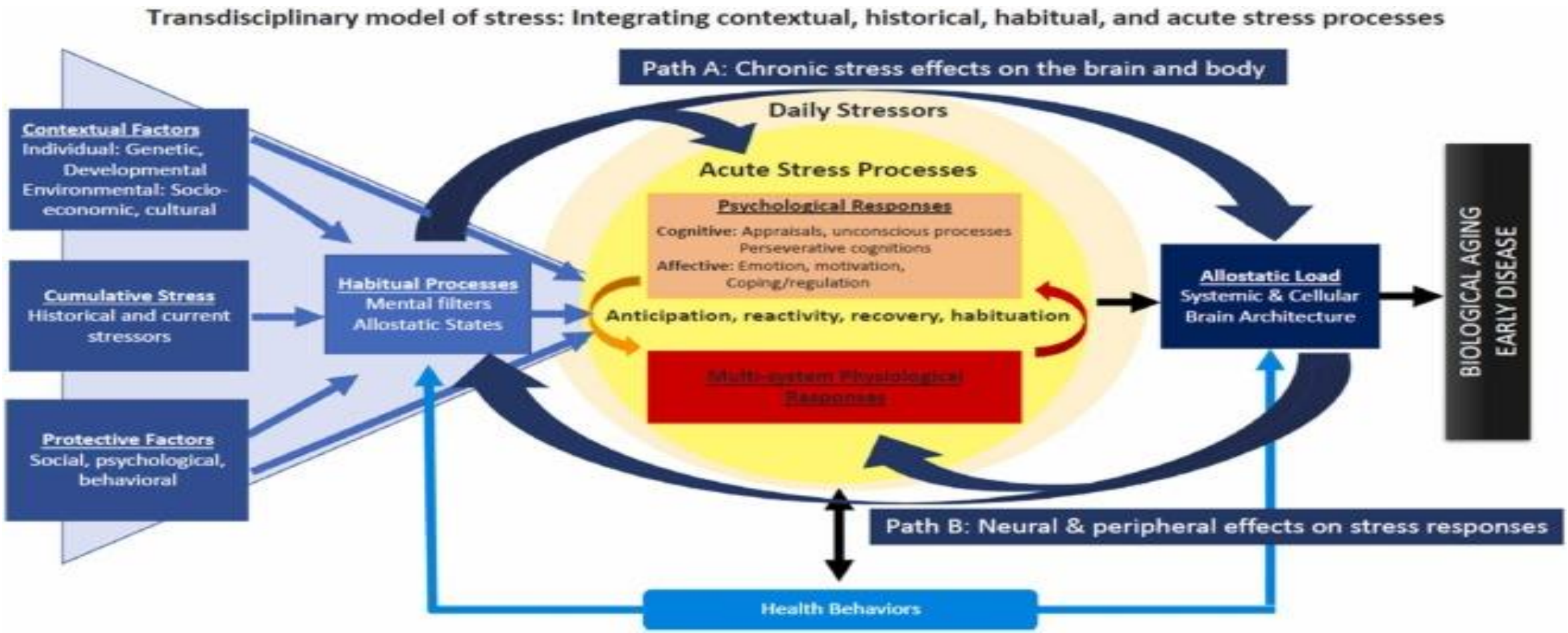
0.79 (95% CI, 0.66-0.96) and 0.77 (95% CI, 0.65-0.92)



Graphs are plots of restricted cubic splines, where the observations are trimmed at the first and 99th percentiles. The reference value is the minimum. The knots are located at 20, 40, 60, and 80 in the national spline and 2, 4, 6, and 8 in within-state spline. The blue line indicates fecundability ratio; the shaded gray area, 95% CI. Adjusted regressions contain covariates for age, daily multivitamin or folic acid intake, parity, intercourse frequency, last method of contraception used before attempting pregnancy, doing something to improve the chances of conception, and year of baseline enrollment

Willis MD et al. *JAMA Netw Open.* 2022

Weathering and Allostatic Load



COMORBIDITIES

Racial Disparity in Gynecologic Disease and Black Maternal Morbidity and Mortality. Connection or Coincidence?

- Cardiovascular disease
- Preeclampsia
- Psychological morbidity
- Structural racism mediated changes to the vaginal microbiome

Yang et al. *Matern Child Health J*. 2015

To what extent these conditions have overlapping inflammatory pathways, risk and protective factors and connections to other gynecologic conditions warrants further study.

Thank you

RACE IS ONLY A PROXY

		Levels of Influence*			
		Individual	**Interpersonal**	**Community**	**Societal**
Domains of Influence *(Over the Lifecourse)*	**Biological**	Biological Vulnerability and Mechanisms	Caregiver–Child Interaction Family Microbiome	Community Illness Exposure Herd Immunity	Sanitation Immunization Pathogen Exposure
	Behavioral	Health Behaviors Coping Strategies	Family Functioning School/Work Functioning	Community Functioning	Policies and Laws
	Physical/Built Environment	Personal Environment	Household Environment School/Work Environment	Community Environment Community Resources	Societal Structure
	Sociocultural Environment	Sociodemographics Limited English Cultural Identity Response to Discrimination	Social Networks Family/Peer Norms Interpersonal Discrimination	Community Norms Local Structural Discrimination	Social Norms Societal Structural Discrimination
	Health Care System	Insurance Coverage Health Literacy Treatment Preferences	Patient–Clinician Relationship Medical Decision-Making	Availability of Services Safety Net Services	Quality of Care Health Care Policies
Health Outcomes		**Individual Health**	**Family/ Organizational Health**	**Community Health**	**Population Health**

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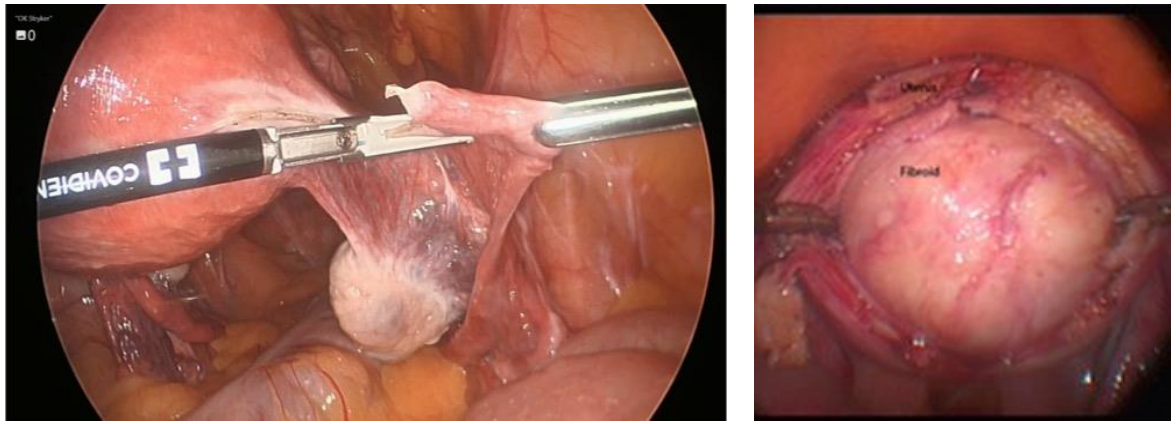
Racial Disparities in Uterine Fibroids

"The Fibroid Factor" in Maternal Mortality

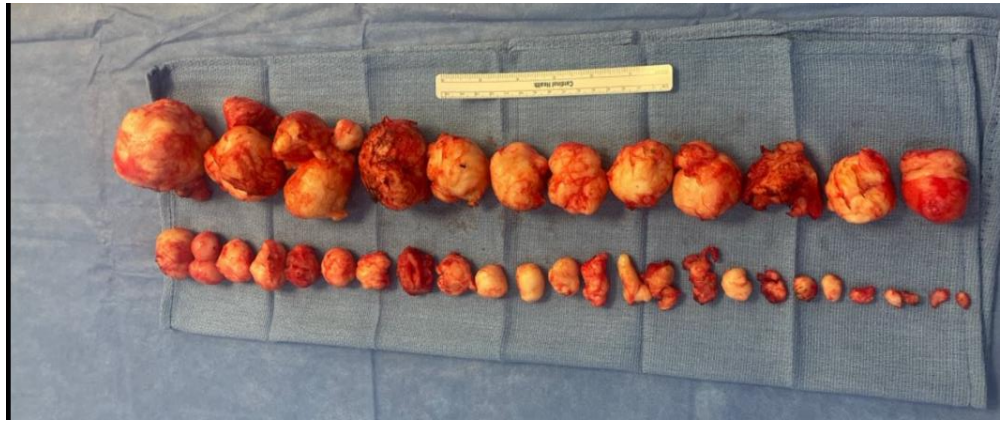
Sandra Madueke-Laveaux, MD, MPH
Associate Professor, Obstetrics & Gynecology
Division of Gynecology & Minimally Invasive Surgery
Director, Center for Advanced Treatment and Research (CATeR) of Uterine Fibroids
University of Chicago Medicine

Uterine Fibroids (UF)

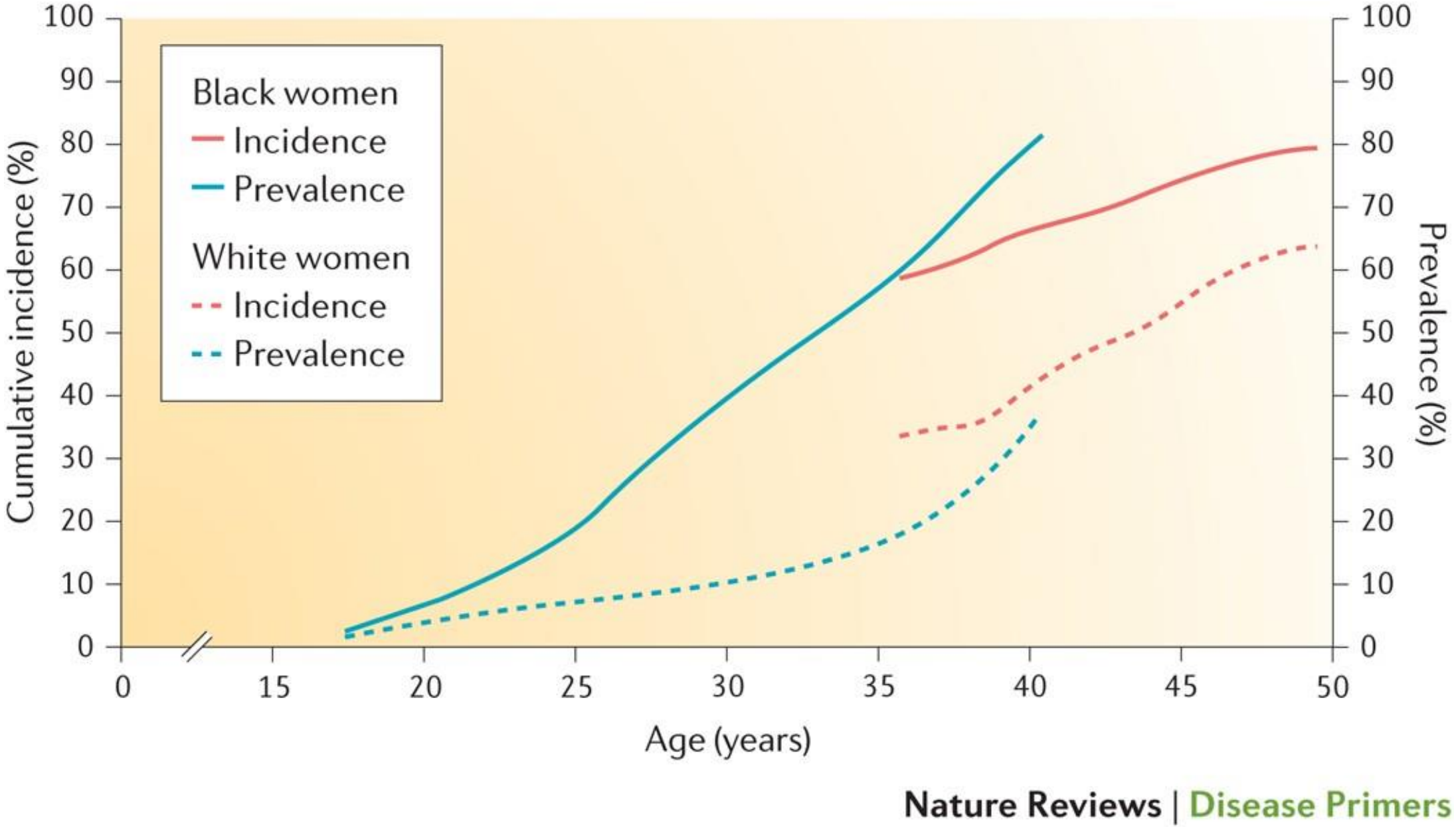
- Benign smooth muscle tumor
- 70-80% prevalence in reproductive age
- Significant source of morbidity
  - leading indication for hysterectomy
  - major cause of gynecologic dysfunction
  - Severe & debilitating symptoms
- **4x more common in Blacks**
  - **More severe disease**
  - **Younger age of onset**



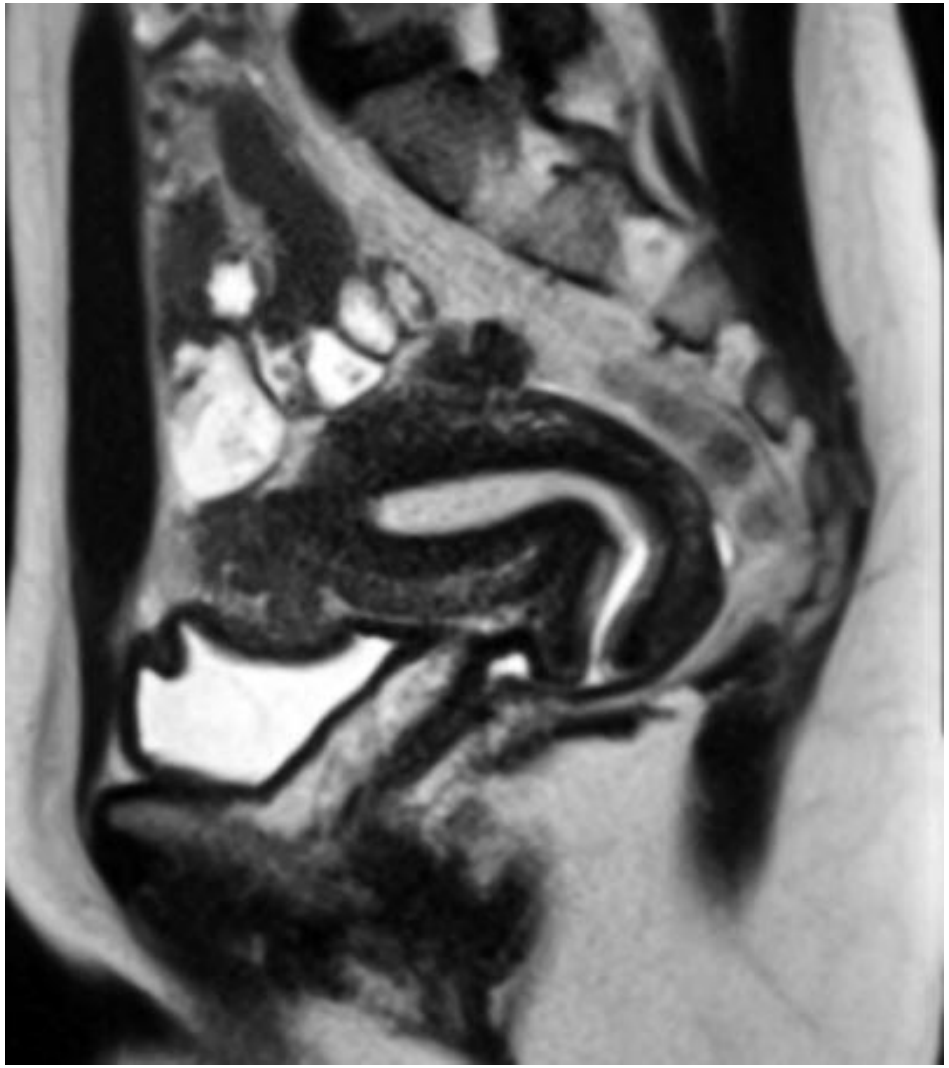
MIS hysterectomy & myomectomy



Yang Q et al,2015, *Reprod Sci*; Yang Q et al 2016 *Front Pharmacol*; Patel et al. *Fertil Steril*, 2014; Stewart, *NEJM*, 2015; Bulun, *NEJM*, 2013, Yang Q et al, Endocrine Reviews, 2021



Stewart et al , Nature Reviews 2016



MRI - Normal Uterus

MRI - Fibroid Uterus

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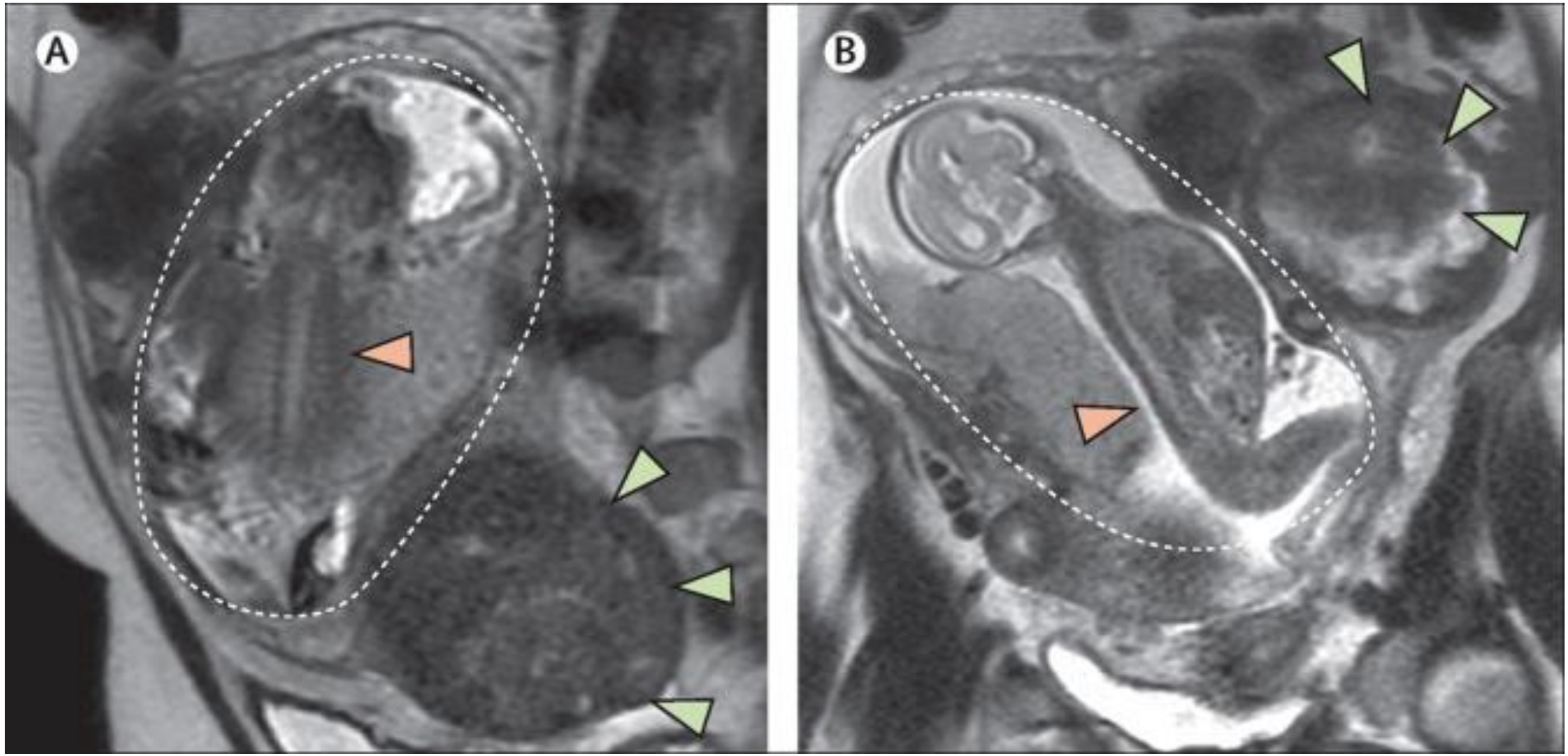

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Lancet 2019

World Health Organization

About 287 000 women died during and following pregnancy and childbirth in 2020. **Most could have been prevented.**

- Sub-Saharan Africa and Southern Asia accounted for around 87% (253 000)
- Sub-Saharan Africa alone accounted for around 70% of maternal deaths (202 000)
- Southern Asia accounted for around 16% (47 000)

World Health Organization

The major complications that account for nearly 75% of all maternal deaths are -

- Severe bleeding (mostly bleeding after childbirth)
- Infections (usually after childbirth)
- High blood pressure during pregnancy (pre-eclampsia and eclampsia)
- Complications from delivery
- Unsafe abortion

The influence of uterine fibroids on adverse outcomes in pregnant women: a meta-analysis

Hong Li, Zhonghua Hu, Yuyan Fan & Yingying Hao

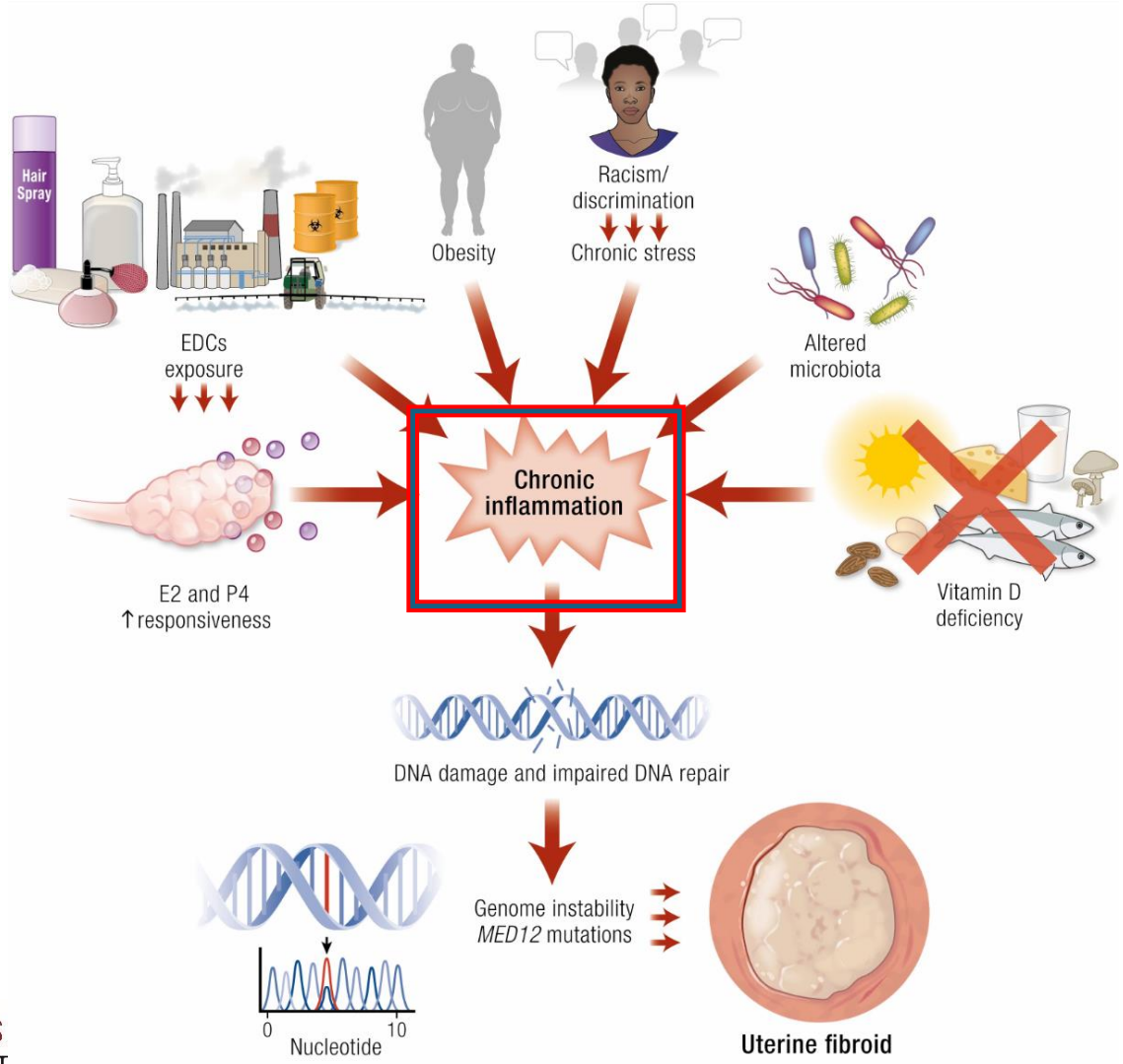
BMC Pregnancy and Childbirth **24**, Article number: 345 (2024) | Cite this article

- Preterm birth
- Cesarean delivery
- Postpartum hemorrhage (PPH)
- Miscarriage
- Preterm premature rupture of membranes (PPROM)
- Placental abruption
- Placenta Previa
- Pre-eclampsia
- Malposition
- Intrauterine fetal death
- Low birth weight
- Breech presentation
- Fetal distress

Overlapping etiologies

Different etiologies affecting the same racial group

Pathogenesis of Uterine Fibroids



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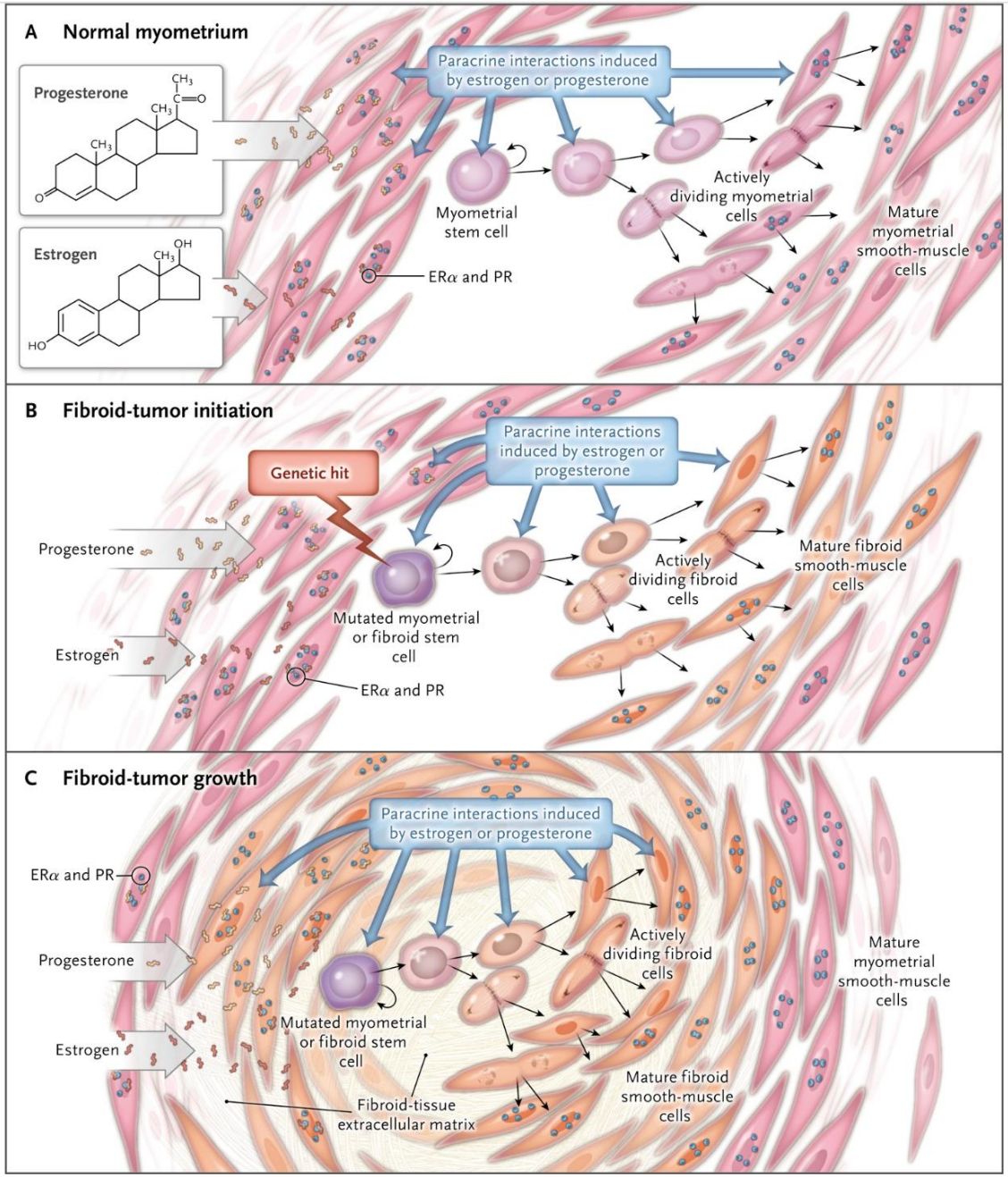
BIOLOGICAL S

Comprehensive Review of Uterine Fibroids: Developmental Origin, Pathogenesis, and Treatment

Qiwei Yang ✉, Michal Ciebiera, Maria Victoria Bariani, Mohamed Ali, Hoda Elkafas, Thomas G Boyer, Ayman Al-Hendy ✉

Endocrine Reviews, Volume 43, Issue 4, August 2022, Pages 678–719, https://doi.org/10.1210/endrev/bnab039

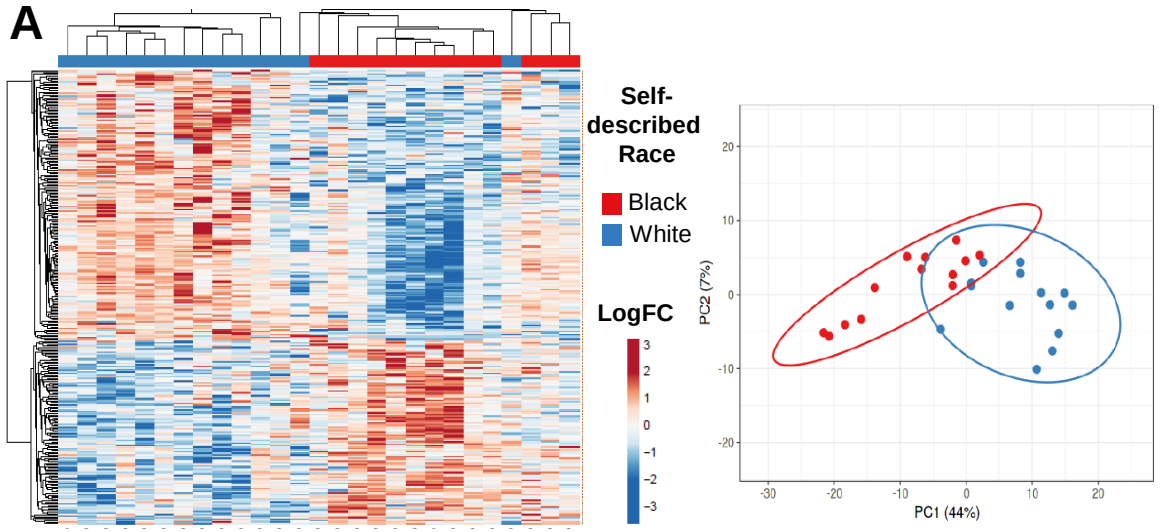


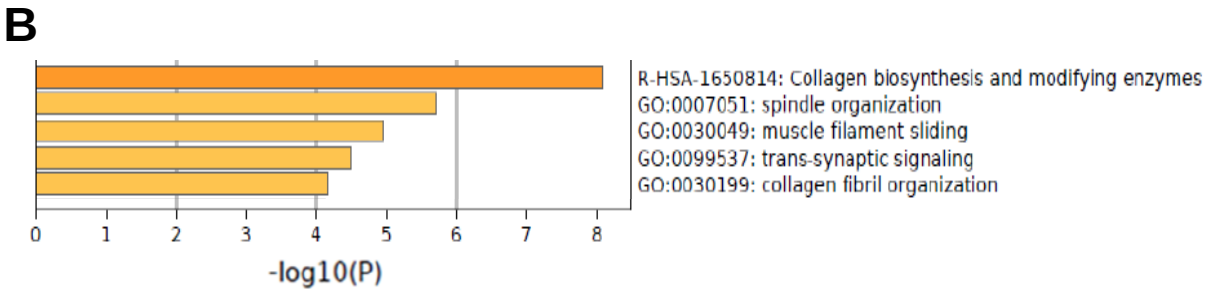
Extracellular Matrix (ECM) correlates to UF stiffness, structure & support

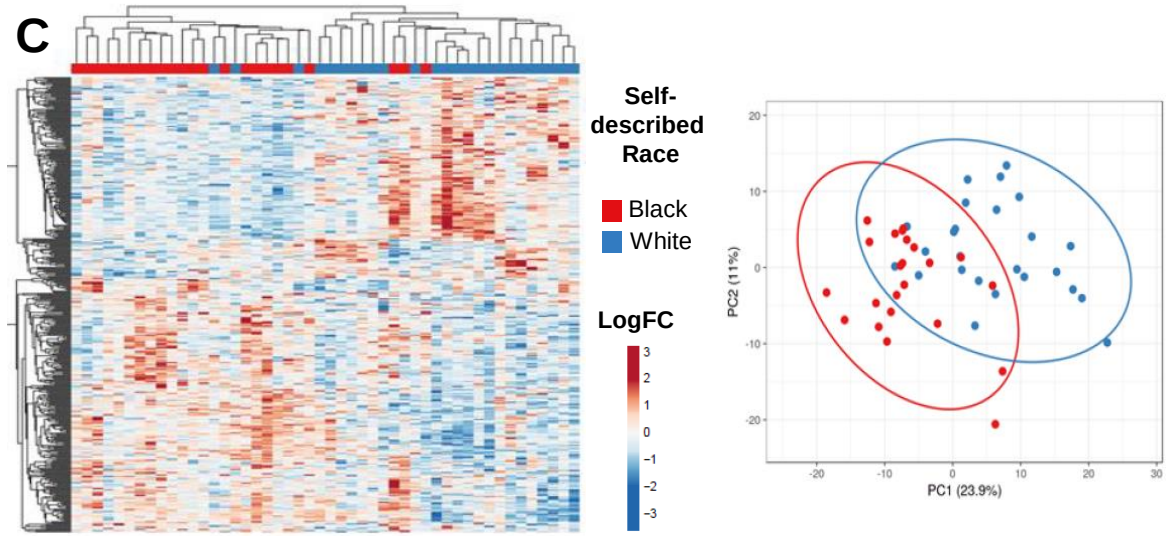
ECM serves as a reservoir of growth factors and bioactive molecules e.g., **TGF-β**

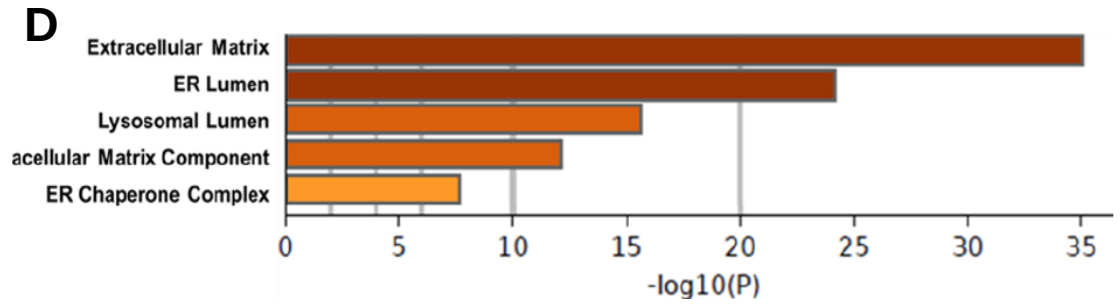
Bulun et al. NEJM , 2013

On a Molecular Level…Enrichment of ECM pathways in Black vs. White



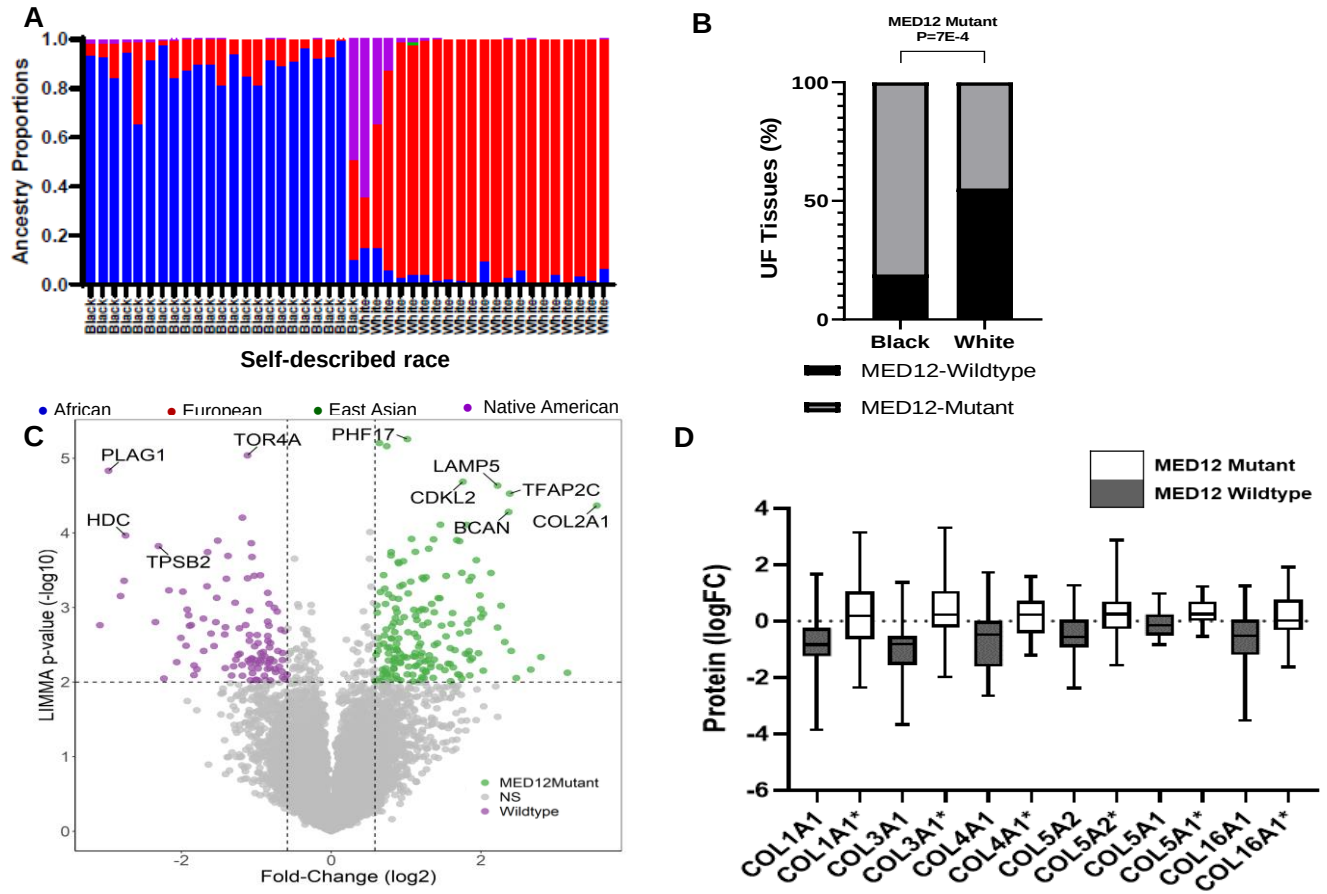






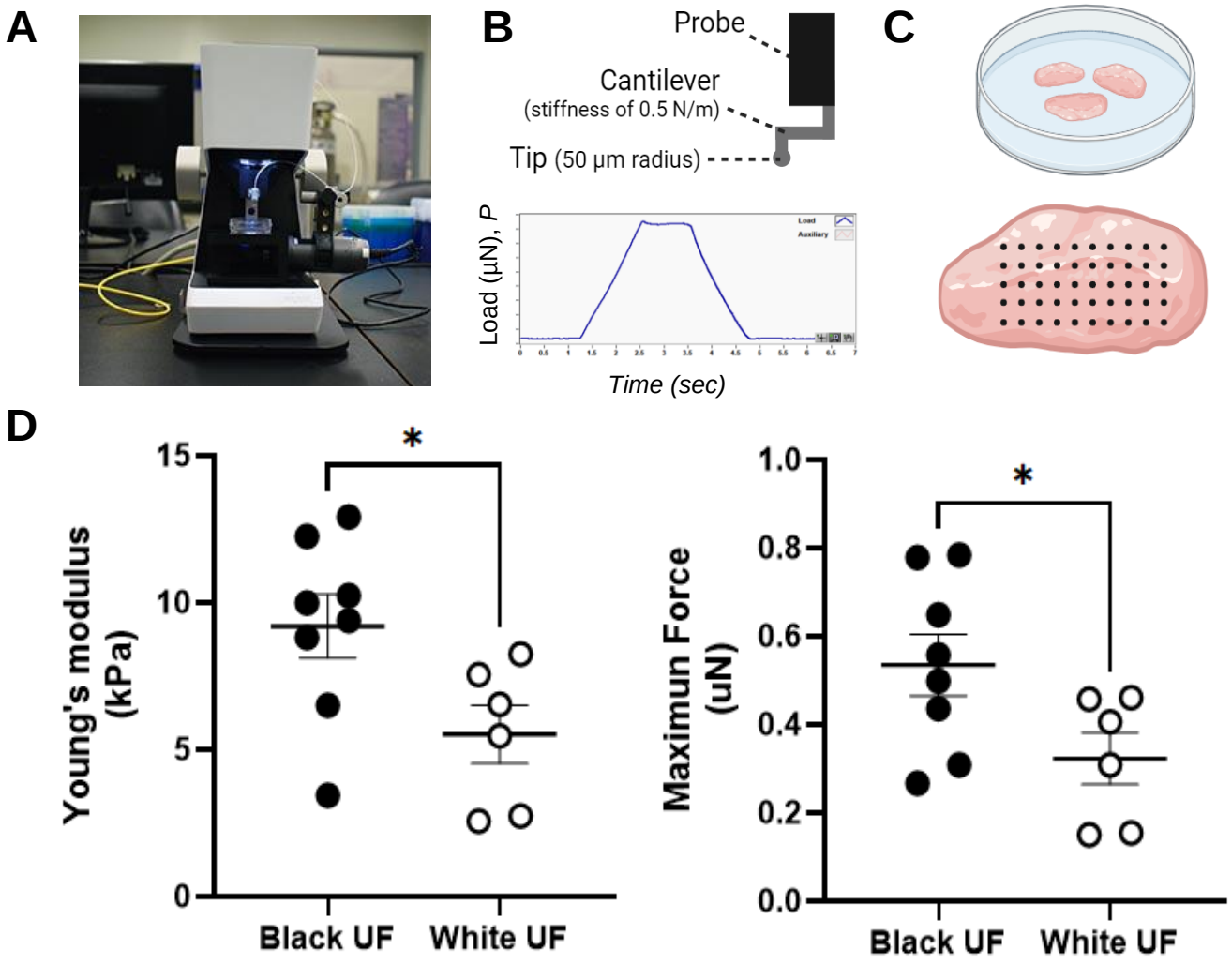
Bateman et al, AJOG 2024

MED 12 mutation..
Link to collagen isoform alteration



Bateman et al. AJOG 2024

Ex-vivo Tissue stiffness measurement



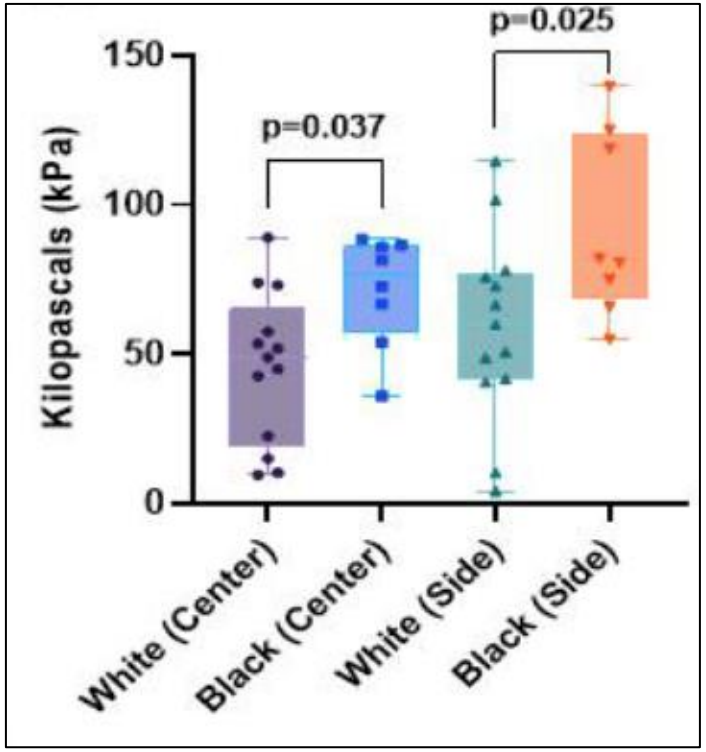
Bariani et al. under review

GYNECOLOGY

Multiomic analysis of uterine leiomyomas in self-described Black and White women: molecular insights into health disparities

SWE to compare UF stiffness in Black vs. White patients

Pilot study Black (n=8) vs White (n=13)



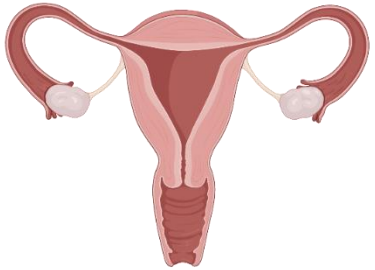
THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Bateman et al, AJOG 2024

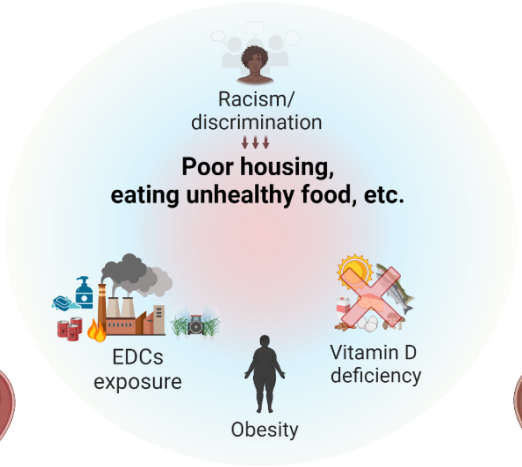
Uterine Tissue Stiffness Contribution to Fibroid Ethnic Disparity

BLACK

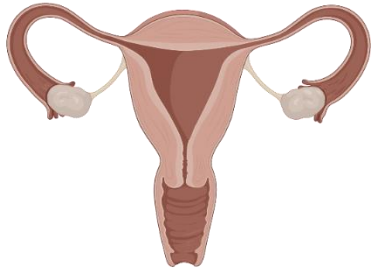
Stiff MyoN due to more ECM anthropologically



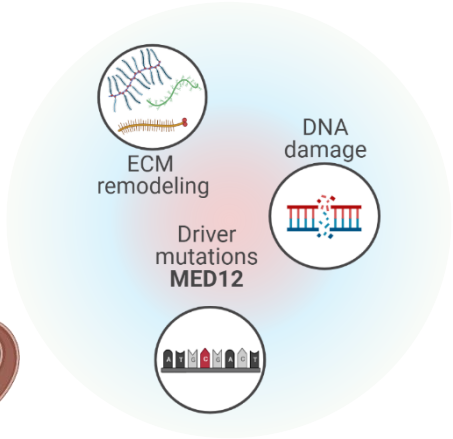
MyoN
(normal myometrium)



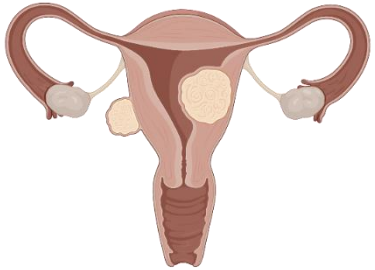
Even **more Stiff MyoF** due to more ECM and more inflammation



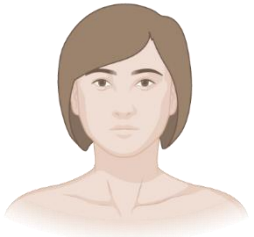
MyoF
(myometrium at-risk)



Large/Early onset fibroid burden with lots of ECM



UF
(myometrium with uterine fibroids)



WHITE

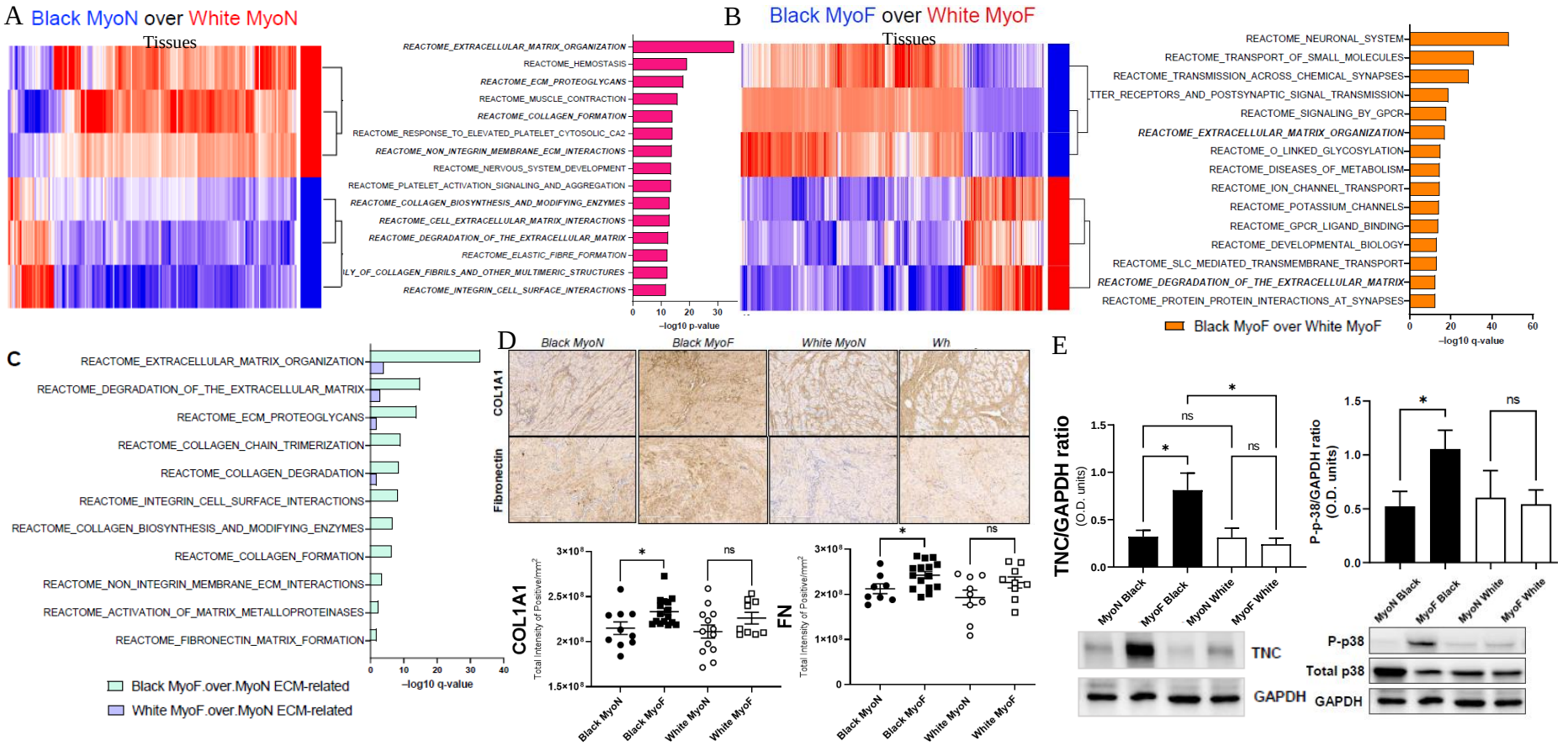
Soft MyoN due to less ECM anthropologically

Slightly stiffer MyoF that MyoN due to more ECM and more inflammation but still way less that blacks

Small/late onset fibroid burden with less ECM

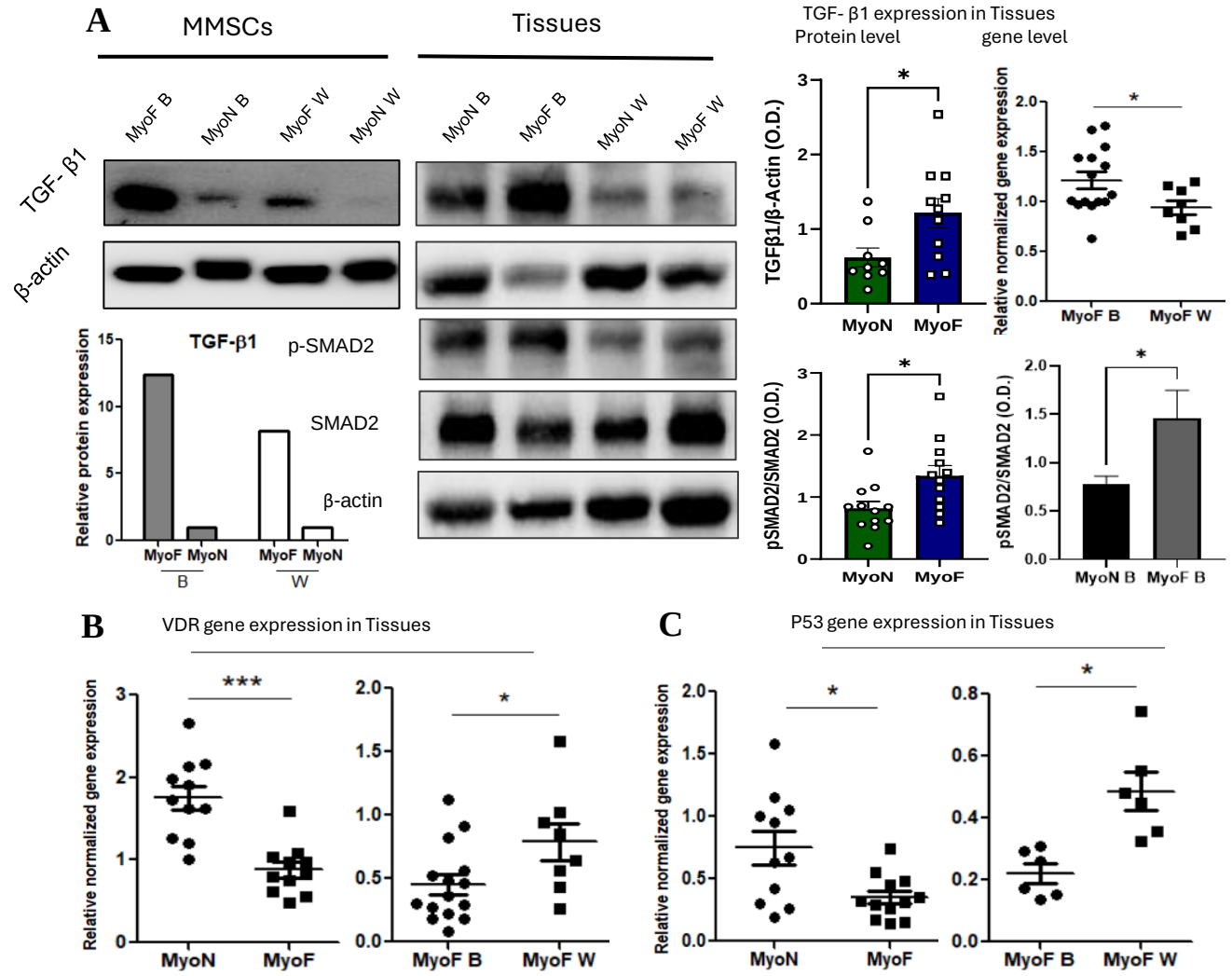
Bariani et al. AJOG, 2024

ECM- related pathways in Black vs. White uterine myometrium (pre-fibroid)



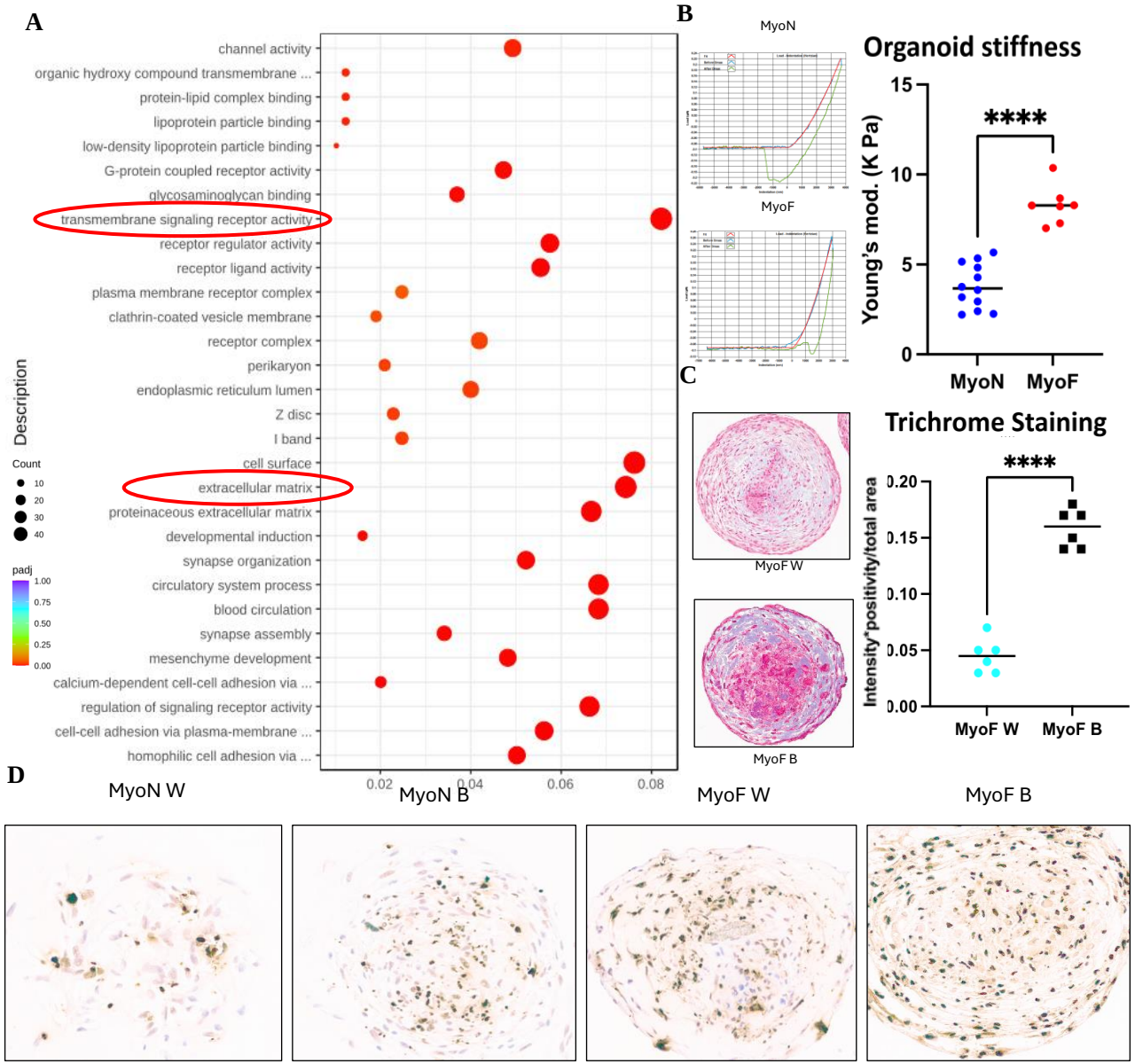
Bariani et al. AJOG 2024

The role of Inflammation in fibroid formation (pre- fibroid)



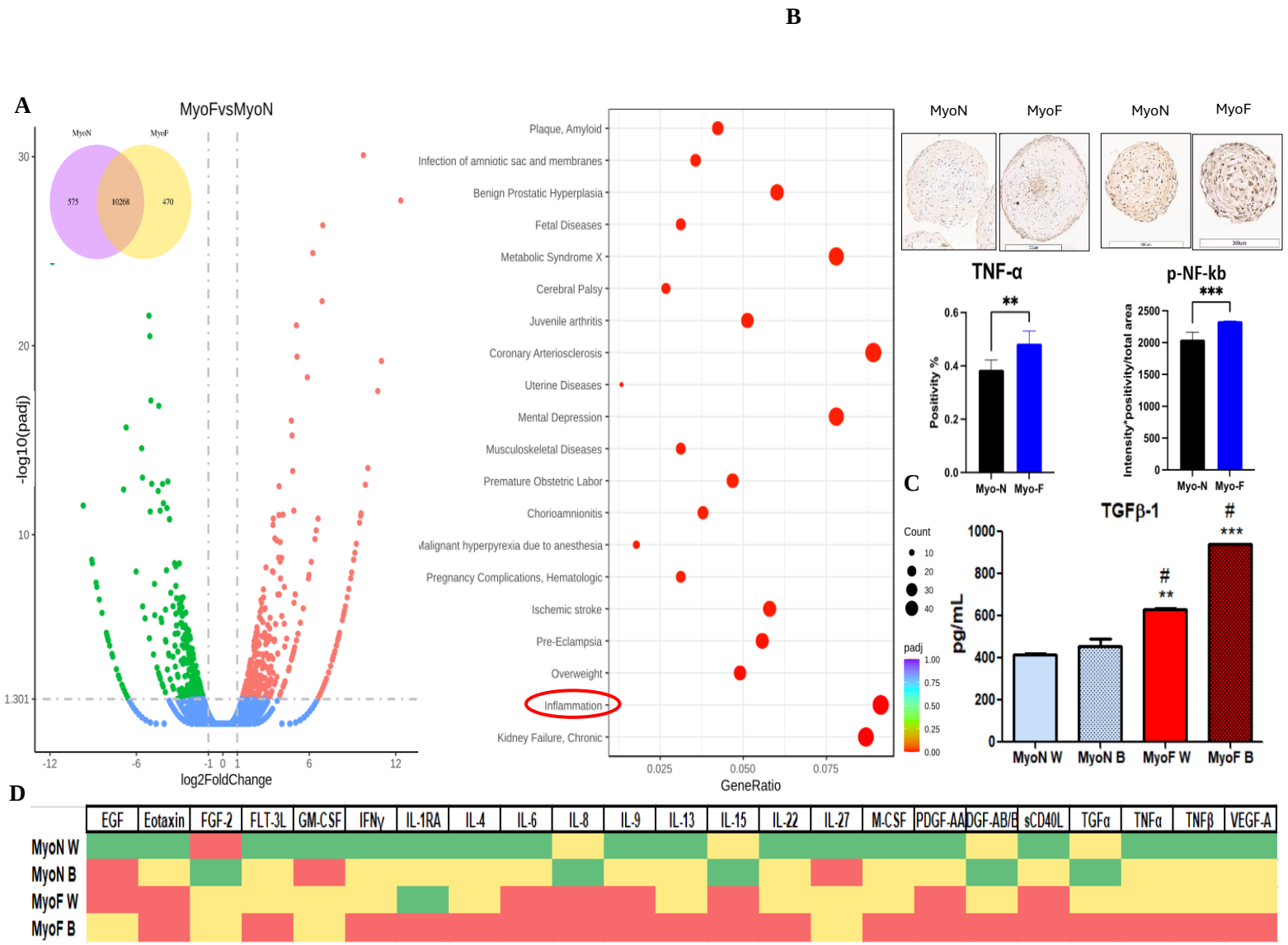
Ali et al. In preparation

3D Organoid (Myometrium) – ECM overexpression



Ali et al. In preparation

3D Organoid (Myometrium) - Inflammation & Angiogenesis



Ali et al. In preparation

The heights by great men reached and kept were not attained by
sudden flight, but they, while their companions slept, were toiling upward in the night.
*- **Henry Wadsworth Longfellow***

Special Thanks
Ayman Al- Hendy MD, PhD
Mohammed Ali PhD
Qiwei Yang PhD
Maria Bariani PhD
Ernst Lengyel MD, PhD
Al-Hendy Lab

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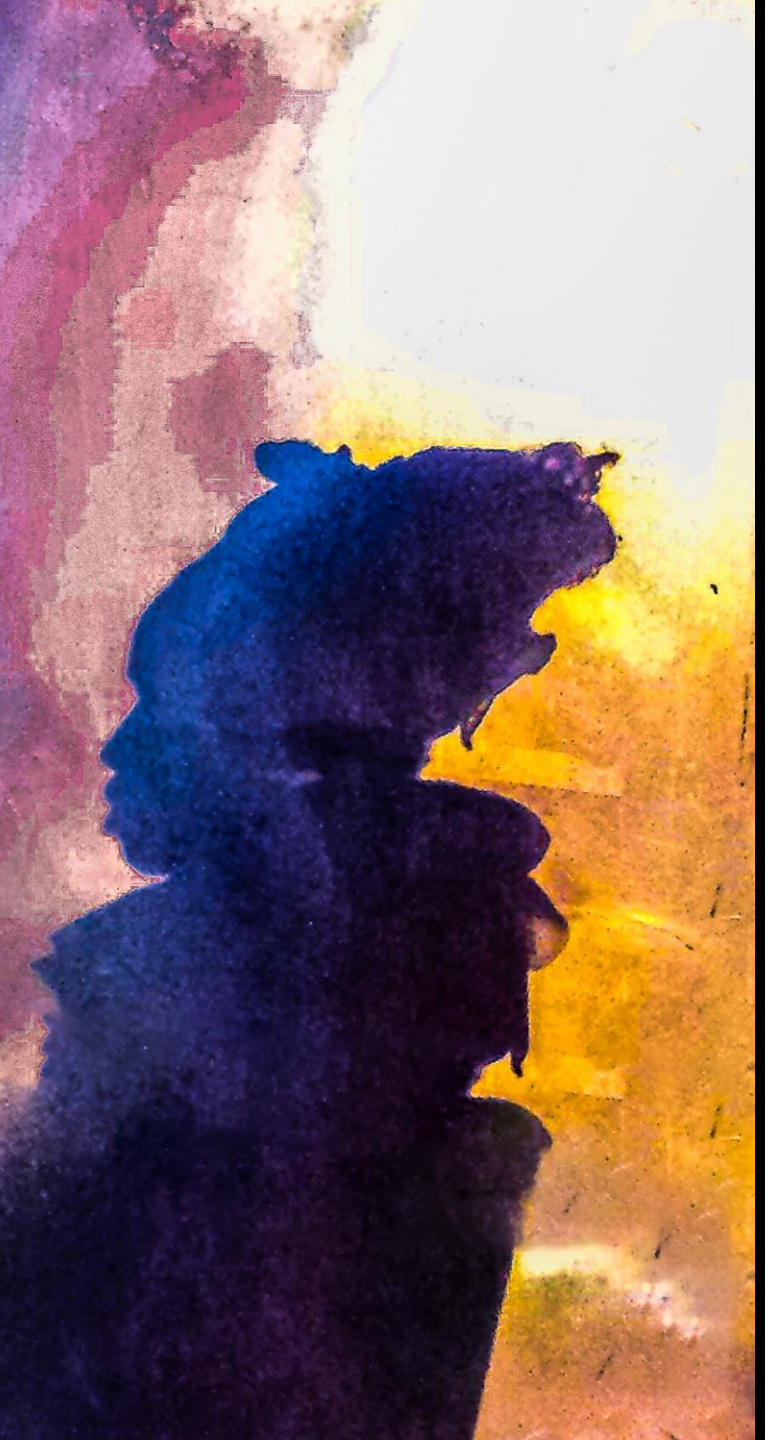


RISE UP 2024

Evolutionary Trajectory of Breast Cancer In Diverse Populations

Funmi Olopade, MBBS, FASCO, OON

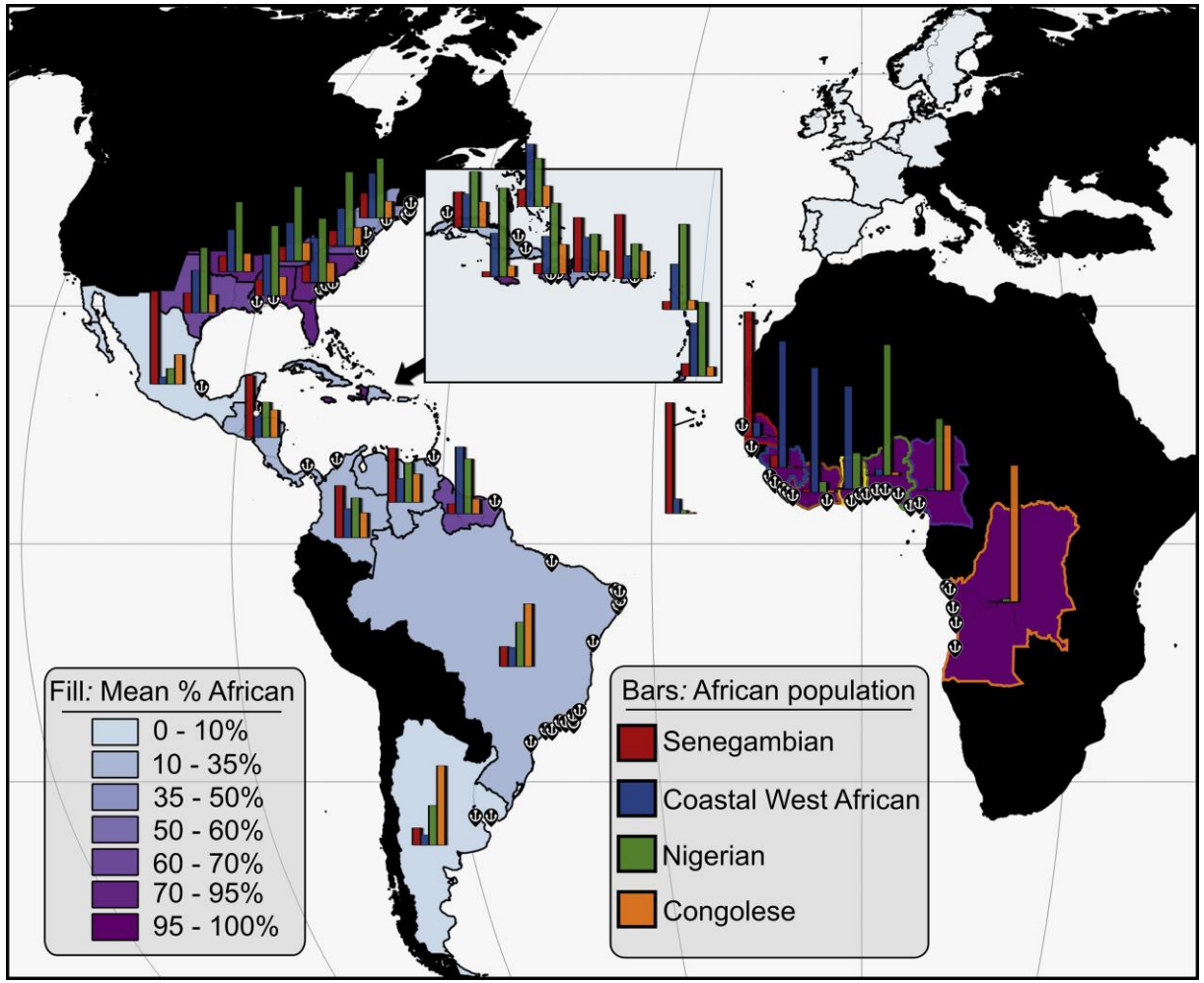
Professor of Medicine & Human Genetics

The University of Chicago

Disclosure Information

Olufunmilayo Olopade, MD, FAACR, OON
I have the following financial relationships to disclose:
Consultant for: none
Speaker's Bureau for: none
Grant/Research support from: Hoffman La Roche, Color Genomics
Stockholder in: CancerIQ, Tempus,
Employee of: The University of Chicago
Board of Trustees: Healthy Life for All Foundation
-and-
I will not discuss off label use and/or investigational use in my presentation.

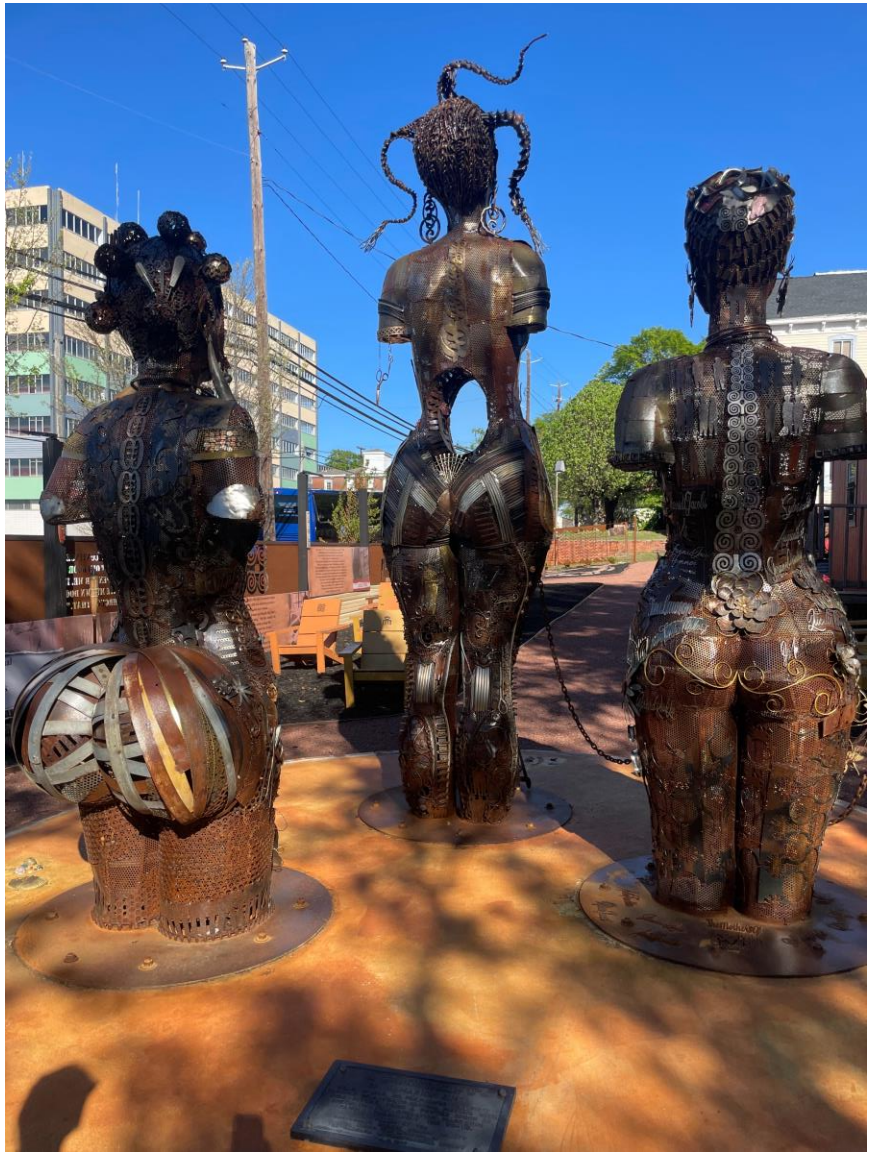
Majority of Black Women in the US, Britain, Europe and Caribbean Islands have Roots in Nigeria and West Africa



Micheletti et al. Genetic consequences of the Transatlantic Slave Trade in the Americas 1
23andMe, Inc., AJHG 107, 265–277, August 6, 2020

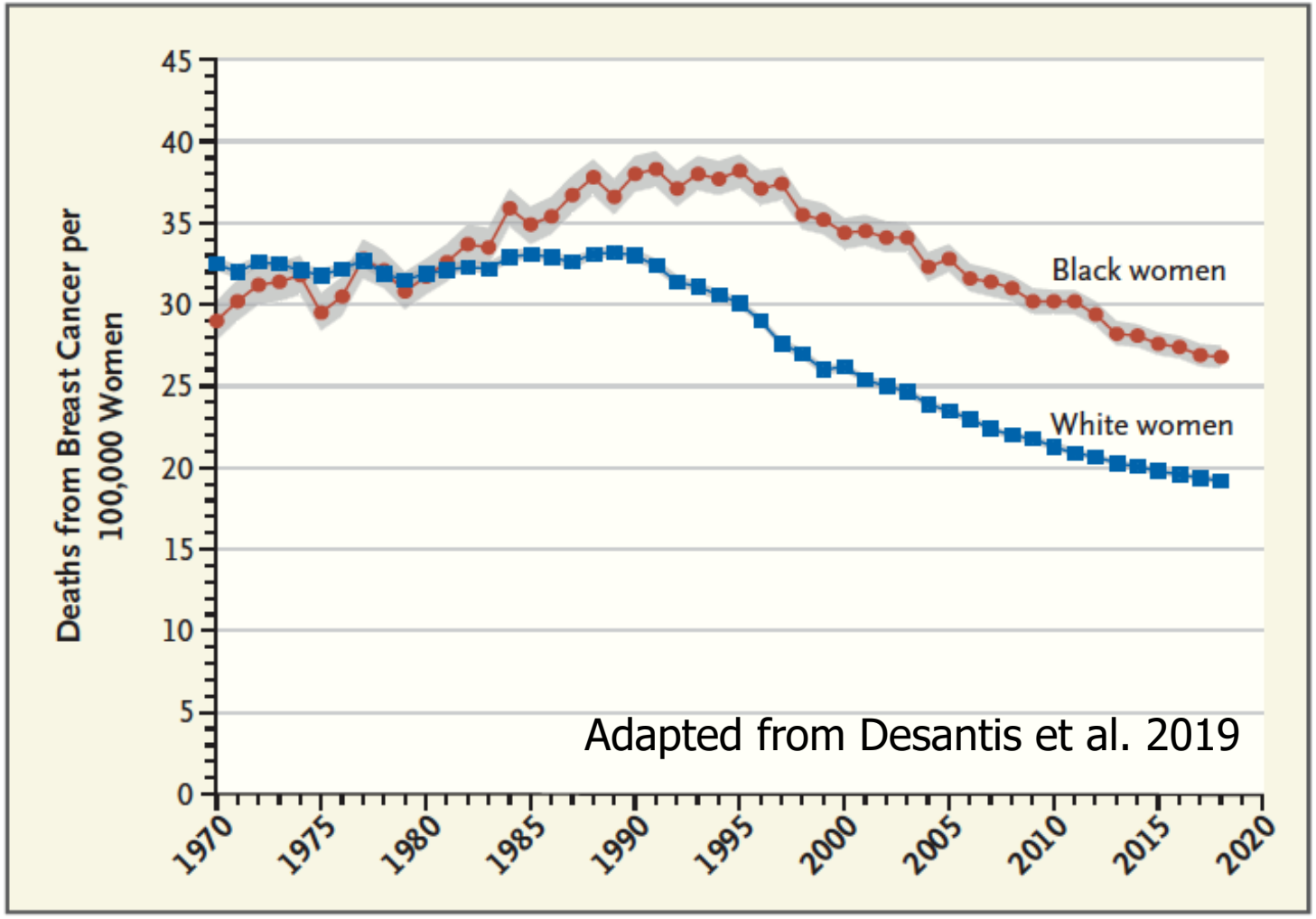
- Forced deportation of over 10 million Africans
- DNA from those who survived live on in Black populations from North, Central, and South America as well as the Caribbean
- Violence on Black and Brown populations shaped the current genetic landscape of African ancestry in the Americas
- Black women have the highest death rate from breast cancer

Legacy of Slavery and Social Injustice



March 2023 visit to Montgomery

Racial Disparity in U.S Breast Cancer Mortality

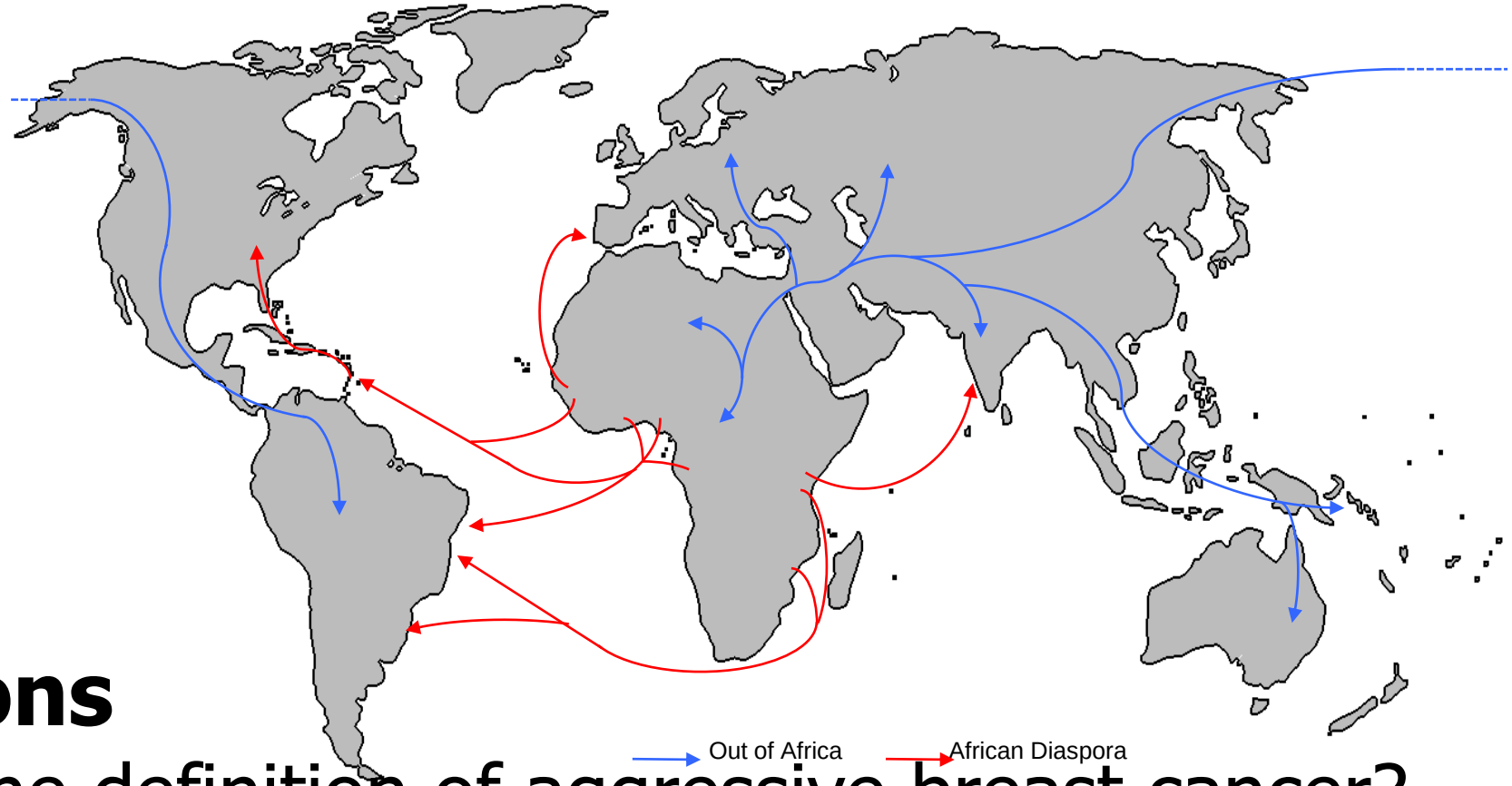


Trends in Breast-Cancer Mortality among Black Women and White Women in the United States, 1970 through 2018.

- Introduction of Mammography
- Adoption of Tamoxifen
- Mortality 19% higher for Black women for HR-positive despite 22% lower incidence
- Mortality for HR-negative twice as high for Black women
- 40% overall mortality gap

Jatoi et al. NEJM 286:25, 2022

“Out of Africa” Theory of Early Migration

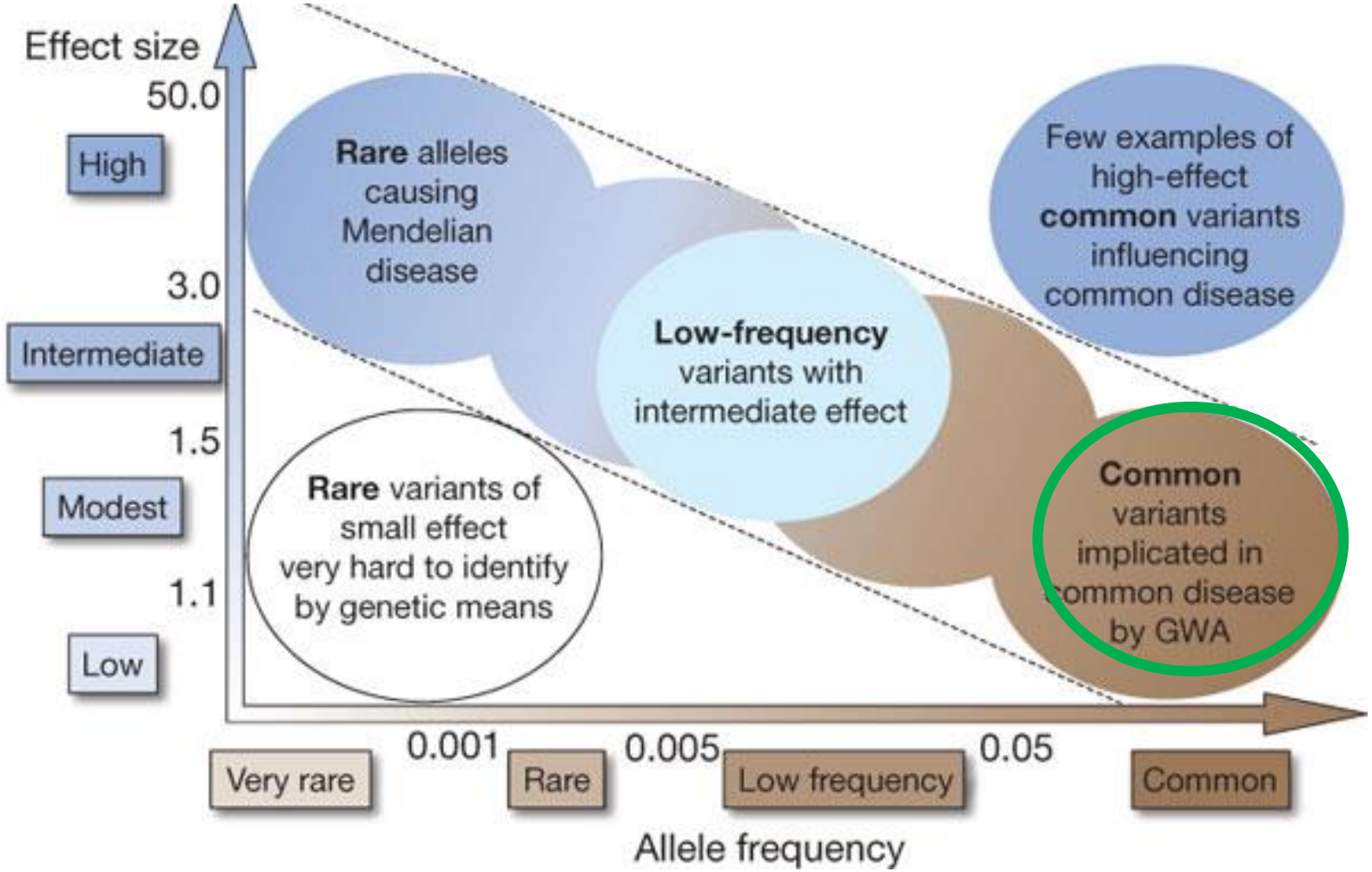


Questions

What is the definition of aggressive breast cancer?

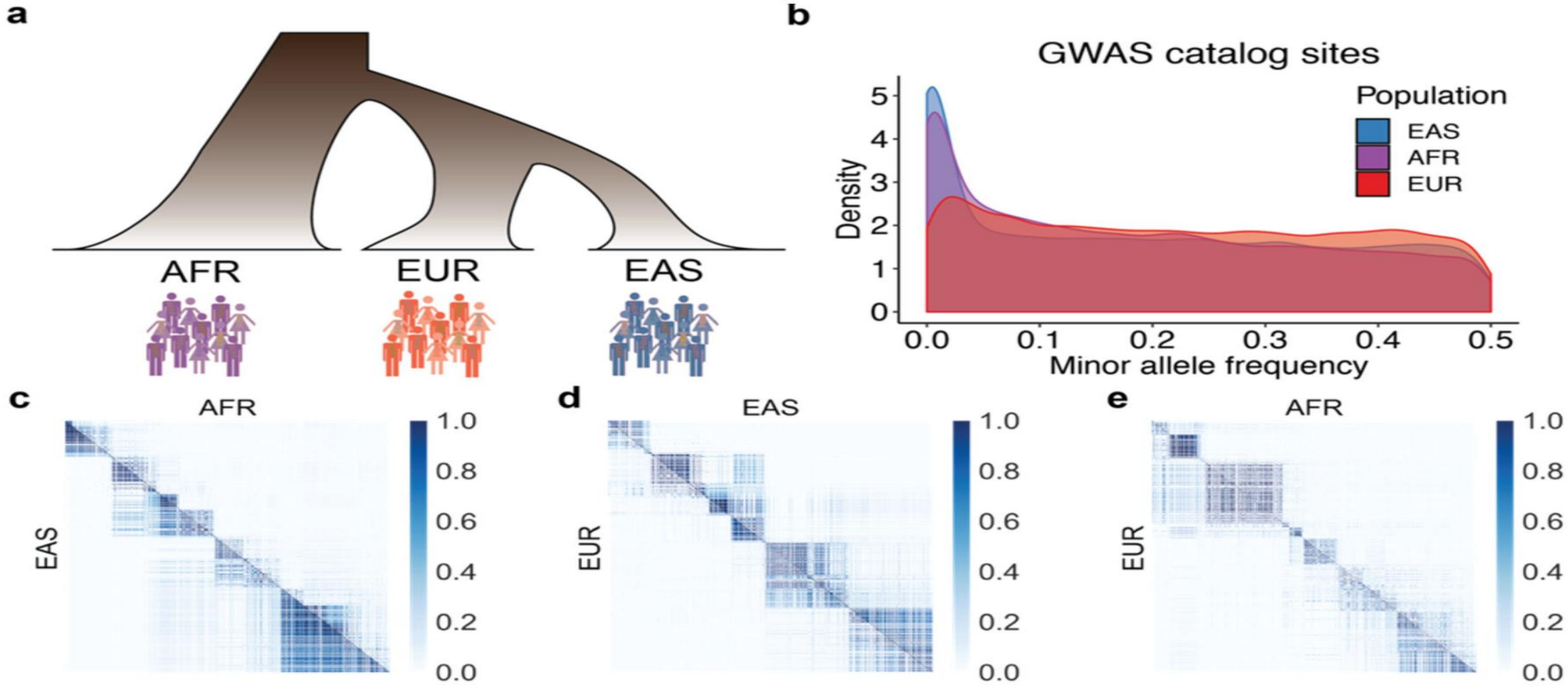
Could the burden of lethal breast cancer in Black women be due to differences in the distribution of lifestyle and genomic risk factors?

Spectrum of genetic variants by allele frequency and strength of effect



TA Manolio *et al. Nature* **461**, 747-753 (2009) doi:10.1038/nature08494

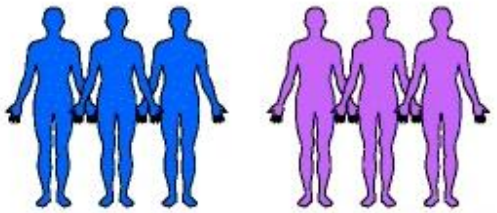
Genetic ancestry may impact cancer evolutionary trajectory – but there is paucity of data



Martin et al Nat Gen 2019

Breast Cancer Common Susceptibility Single Nucleotide Polymorphisms (SNPs) in Women of African Ancestry

Control (n=4,774) Cases (n=4,673)



Meta-analysis

↓

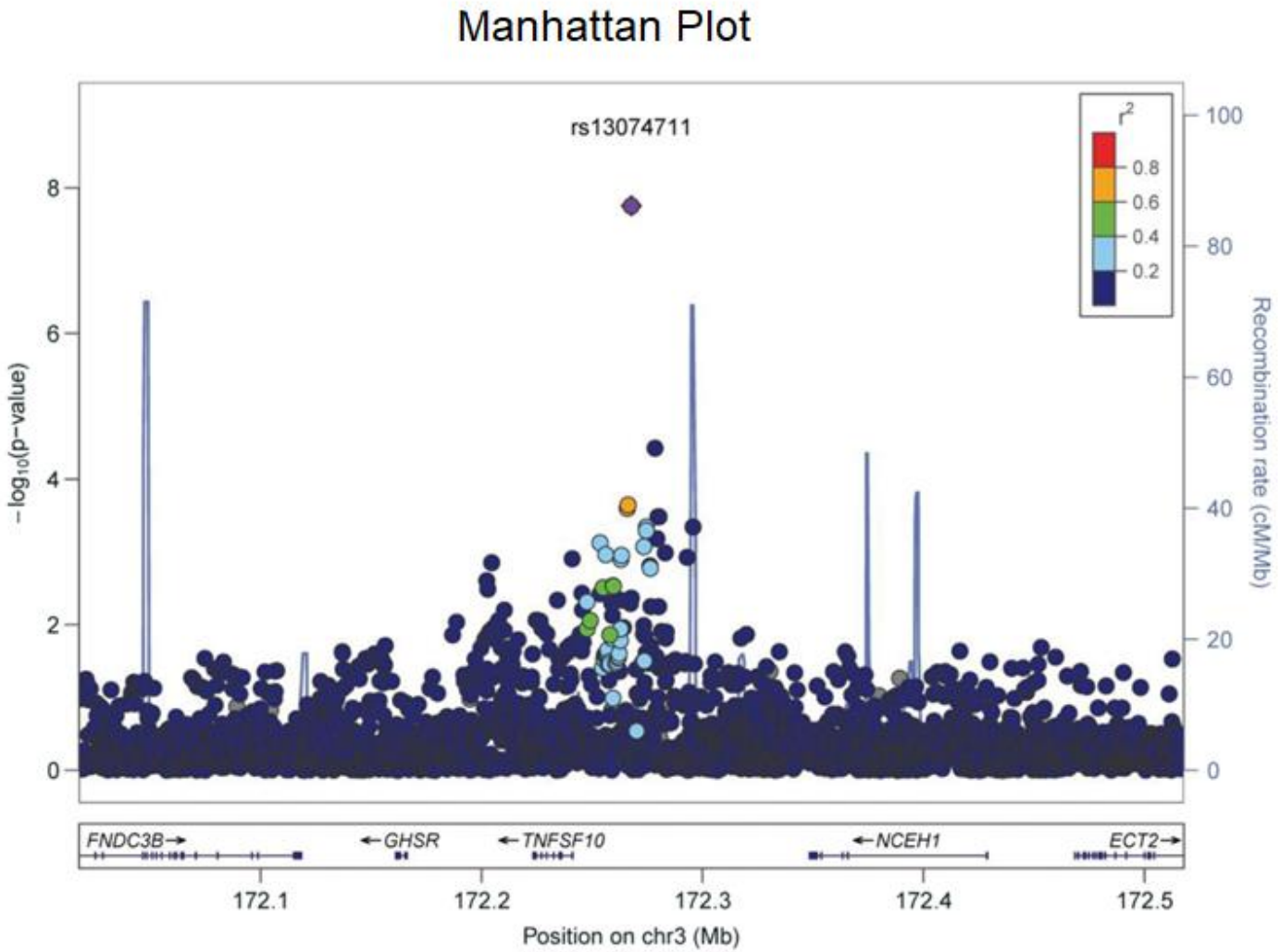
Top 18,376 SNPs for replication

↓

AMBER
1,984 cases
2,939 controls

↓

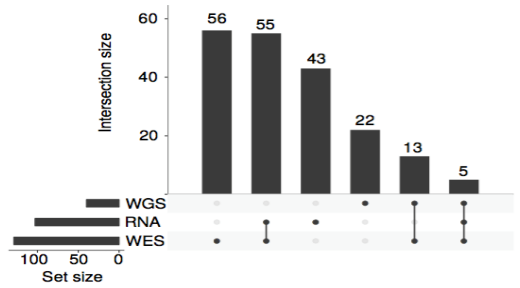
TNFSF10 --Tumor Necrosis Factor Ligand Superfamily Member 10



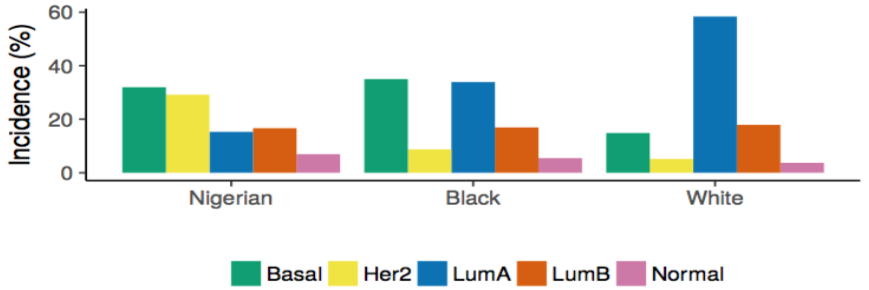
Huo D, *et al*. Hum Mol Genet, 2016

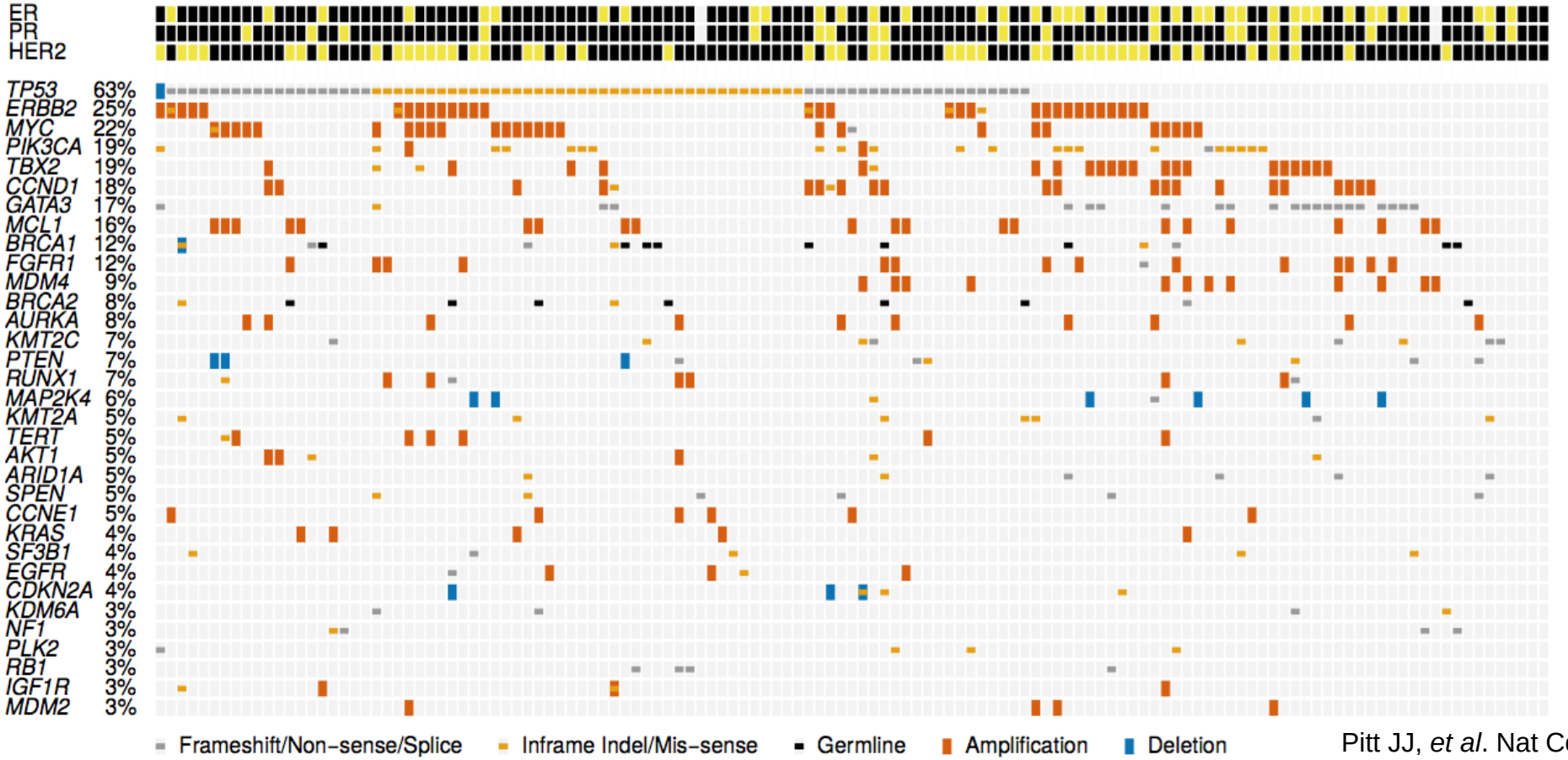
Mutation Landscape in Nigerian Breast Tumors

Samples across Platforms



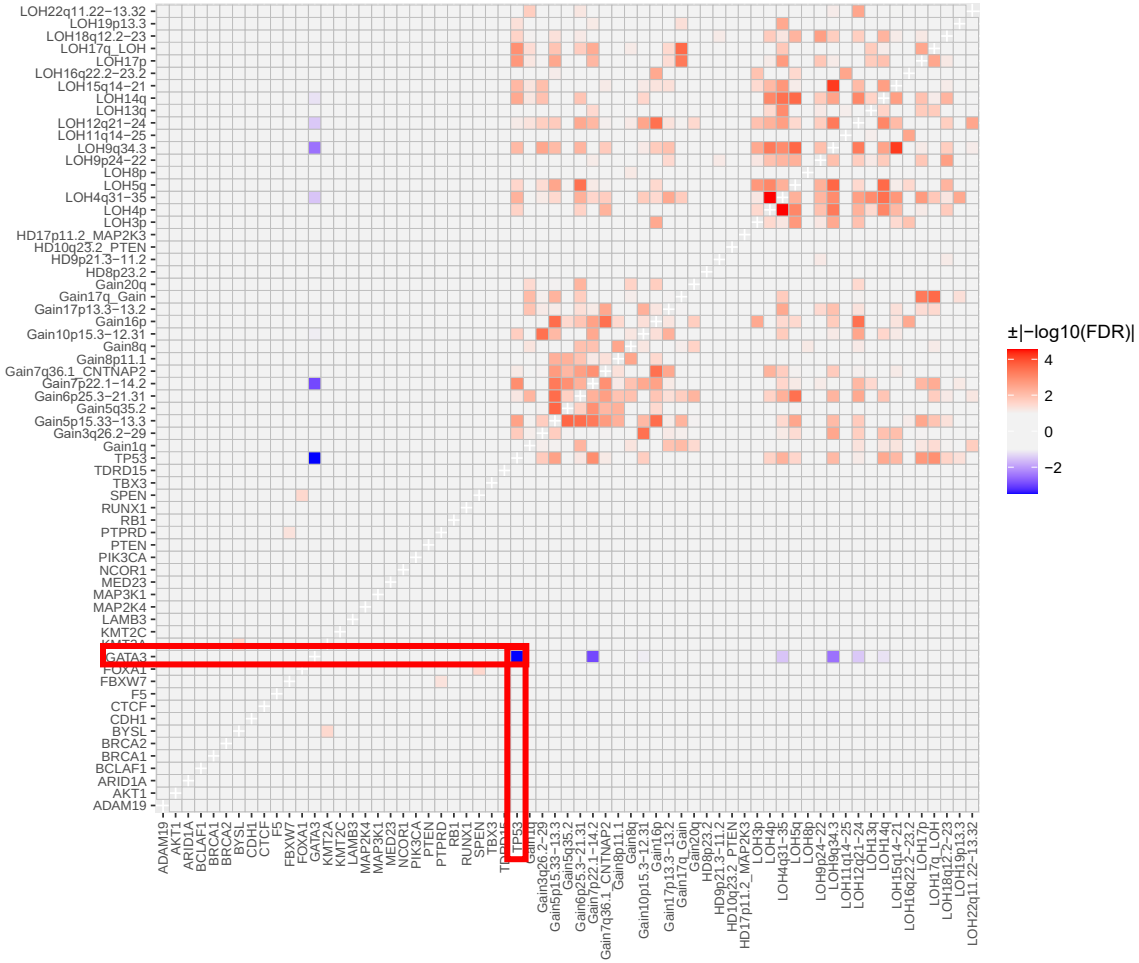
PAM50 Subtypes in Nigerian and TCGA Breast Tumors

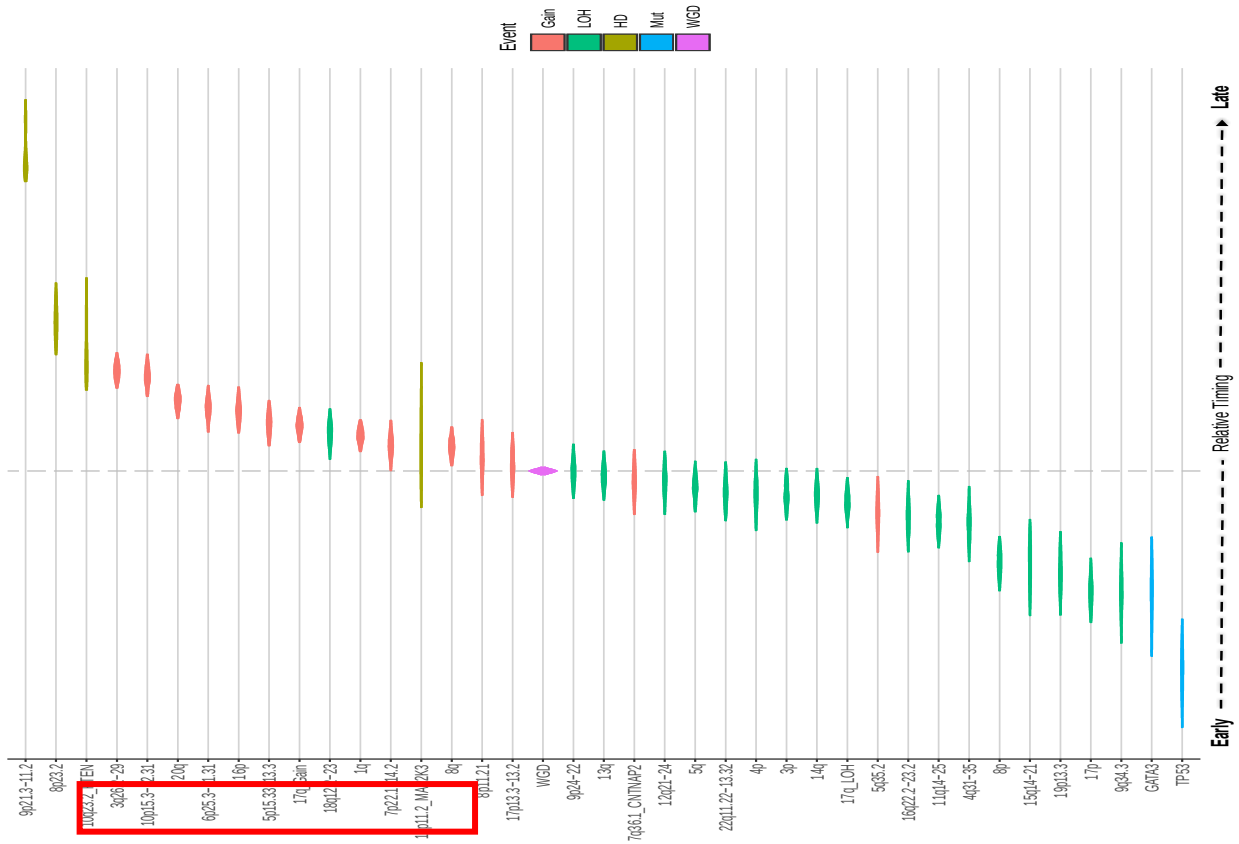




Pitt JJ, *et al*. Nat Commun. Oct 2018

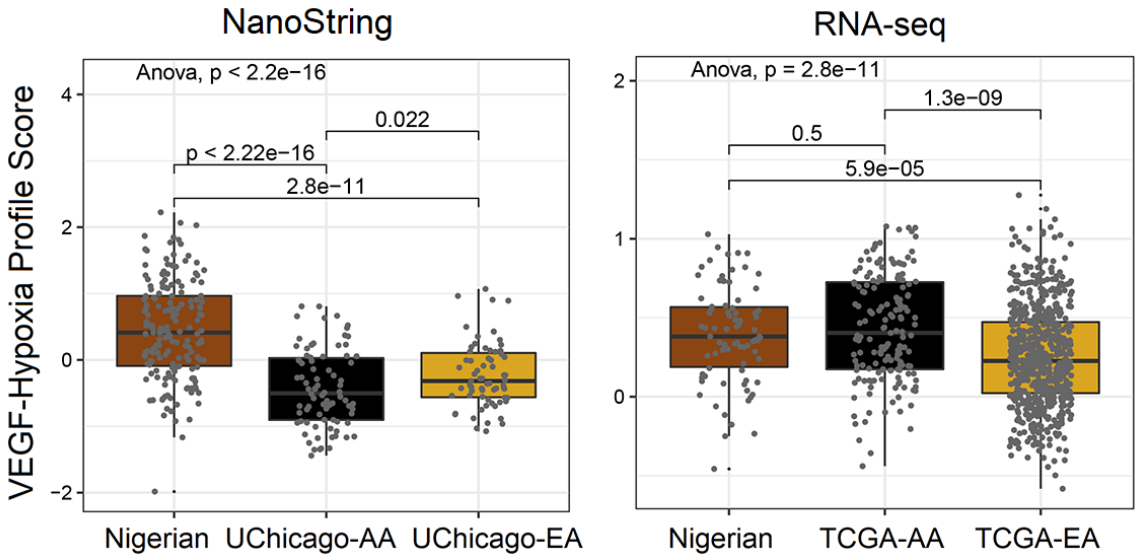
TP53 and *GATA3* Mutations are mutually exclusive and early drivers of breast cancer in Nigerian women

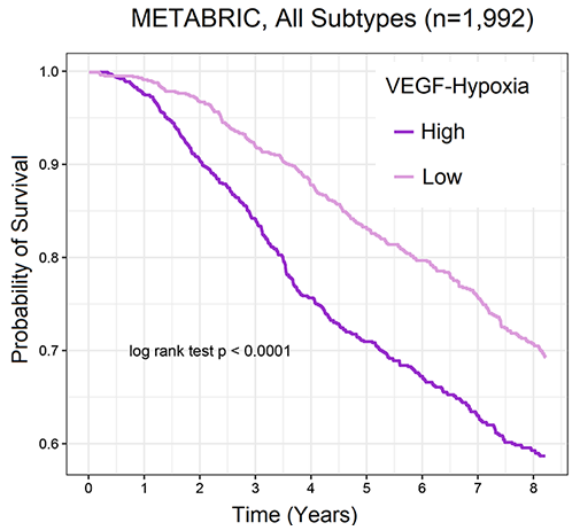




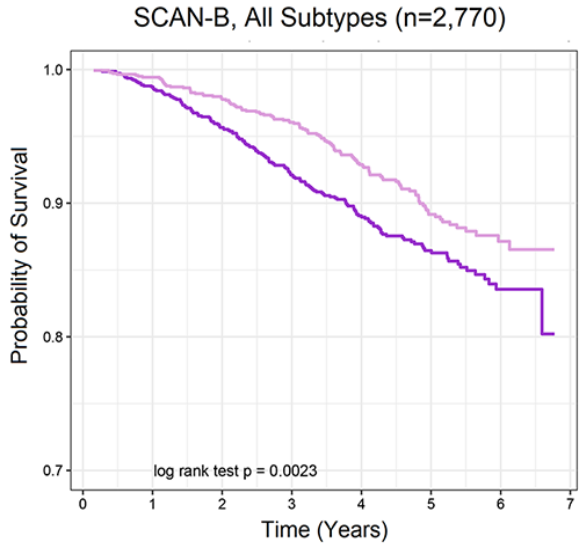
Ansari-Pour N, *et al*. Nat Commun, *2021*

The VEGF-Hypoxia Signature is increased in Breast Tumors from Black women and associated with poor outcomes



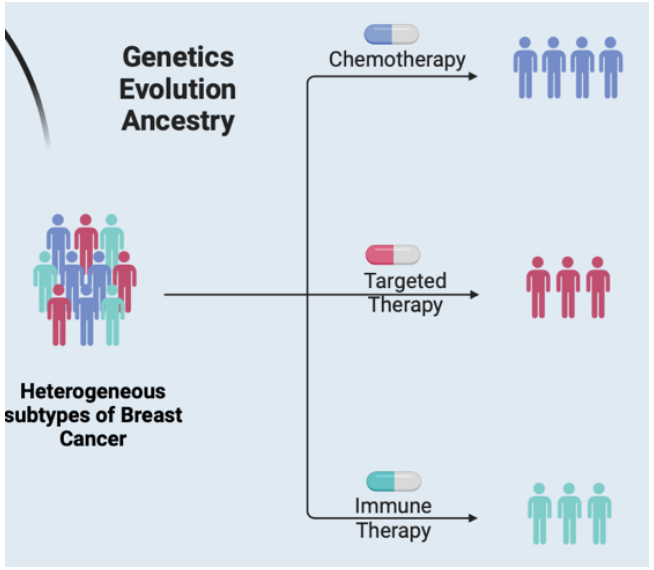


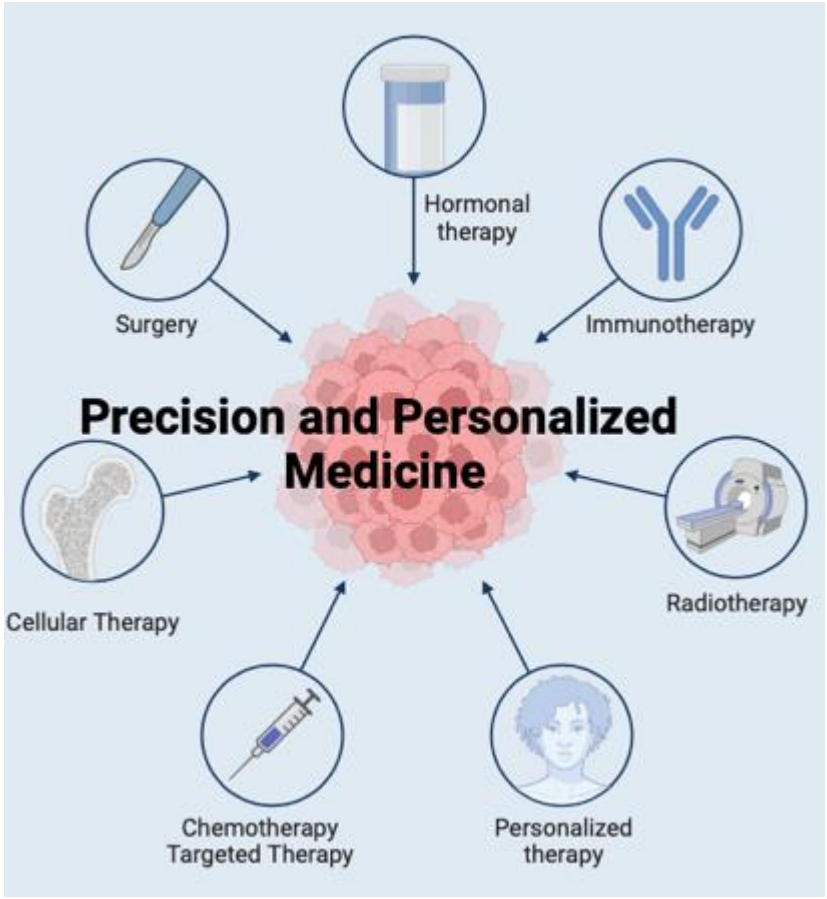
Nigerian Women Breast Cancer Study Group

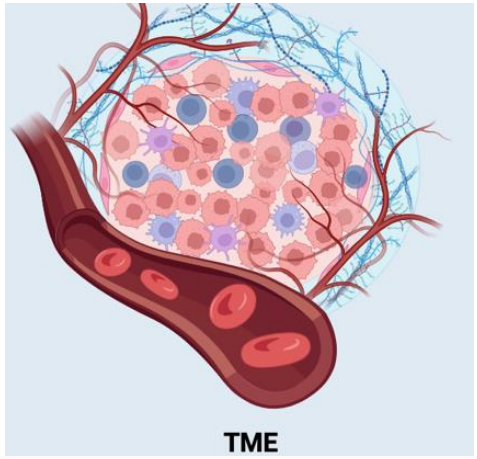


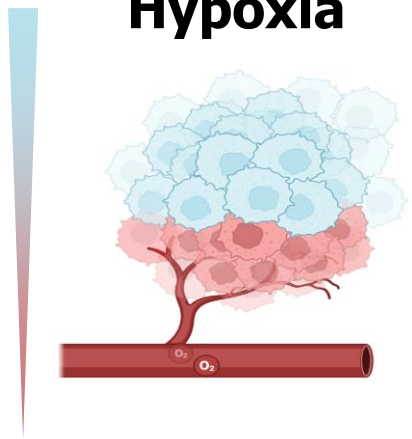
Han *et al*, Clinical Cancer Research, 2024

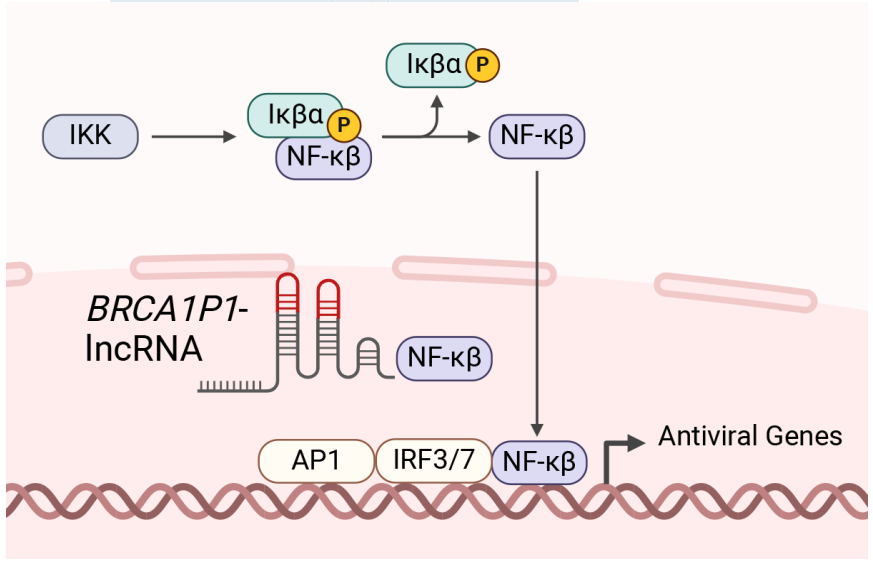
Many Factors Contribute to Breast Tumor Heterogeneity and Progression (Genetic factors, Hypoxia, Tumor Microenviroment, Pseudogene RNAs etc)





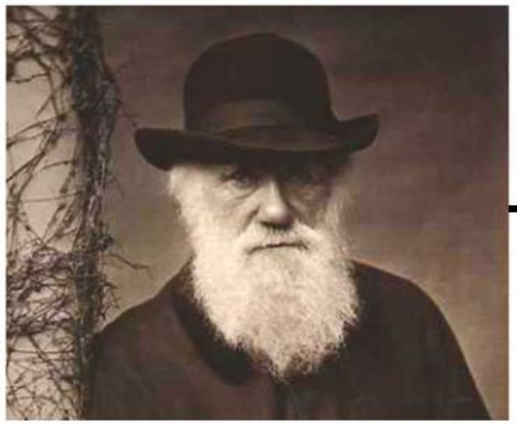


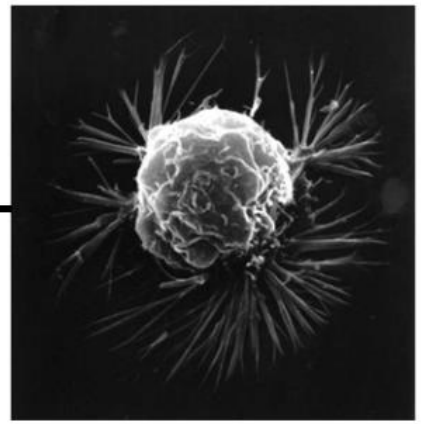




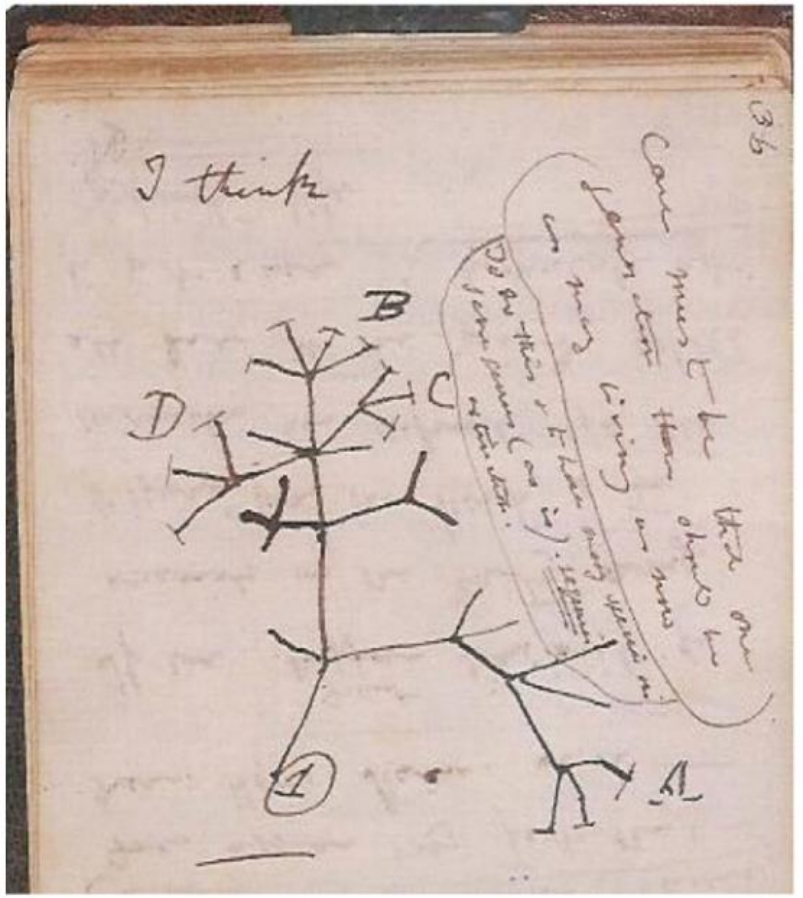
Breast Cancer and Maternal Mortality Disparities in African American Women: Connection or Coincidence?

"Nothing in Cancer Makes Sense Except in the Light of Evolution"





- Evolutionary logic of vulnerability to cancer
- Cancer clone progression by natural selection in tissue ecosystems
- Emergence of drug resistant variants under the selective pressure of therapy



Charles Darwin's iconic 'I think' drawing of a phylogenetic tree from his 1837 Notebook B

Greaves. BMC Biology. 2018

Special Thanks

University of Chicago

Yonglan Zheng
Yoo Jane Han
Toshio Yoshimatsu
Greg Karczmar
Hiroyuki Abe
Anna Woodard
Subomi Omoleye
Alex Pearson
Fred Howard
Ilona
Lise Sveen
Galina Khramtsova
Niu Qun
Jing Zhang
Sola Olopade
Dezheng Huo
Rita Nanda

Funders – ACS, Avon, BCRF, DOD, Doris Duke Foundation EIF, Falk Medical Research Trust, Komen, NCI, NIMH

UCLA
Dennis Slamon

U of Wash
MC King
Tom Walsh

UCSF
Laura Esserman
Elad Ziv
Laura Vant Veer

UNC
Chuck Perou
Melissa Troester

Manchester
David Wedge

Vanderbilt
Wei Zheng

AT THE FOREFRONT
UChicago Medicine

Maternal-fetal Tolerance and Breast Cancer

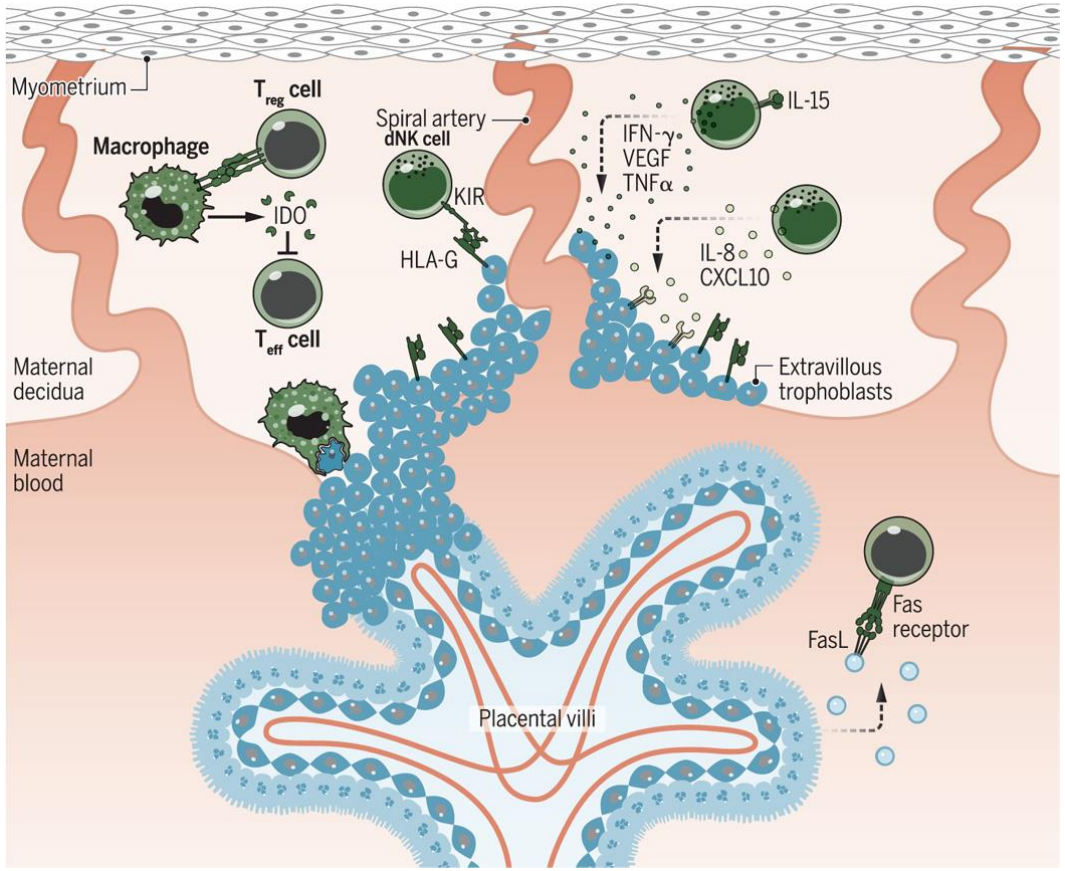
Frederick Howard, MD
Assistant Professor
Department of Medicine
University of Chicago

Disclosures

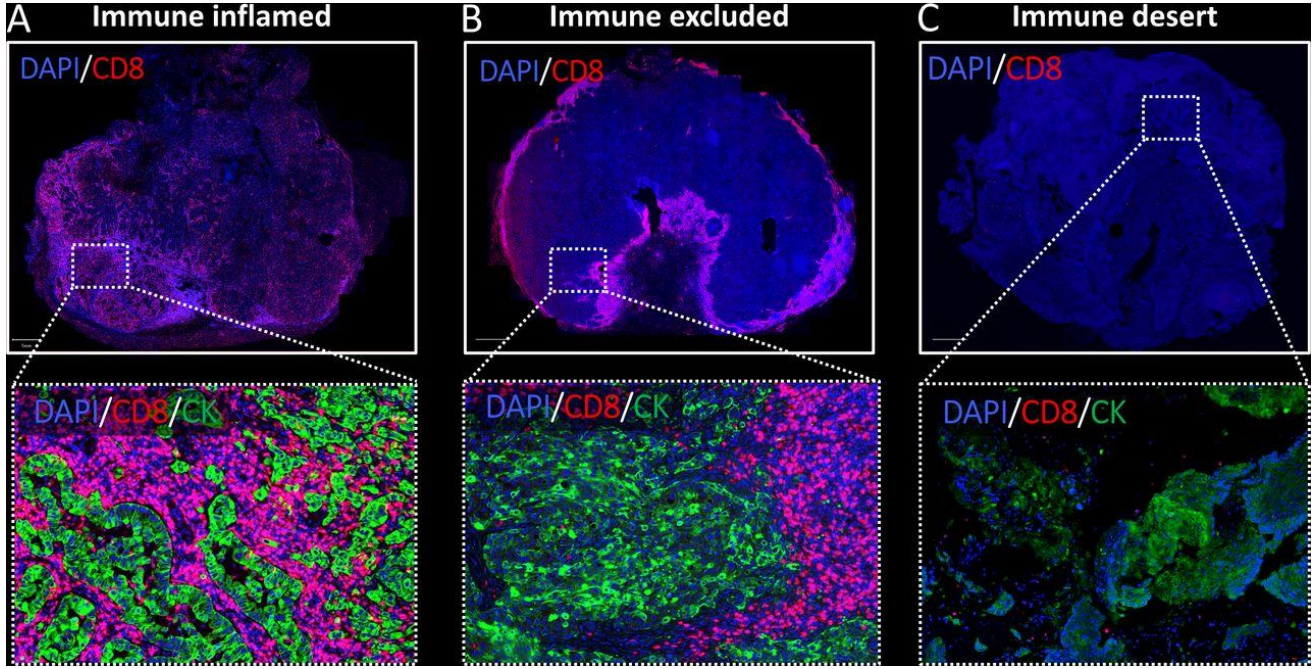
- Consulting fees, Novartis, Leica Biosystems, Veracyte

Immune Tolerance in Pregnancy and Cancer

Immune Tolerance is Essential in Pregnancy



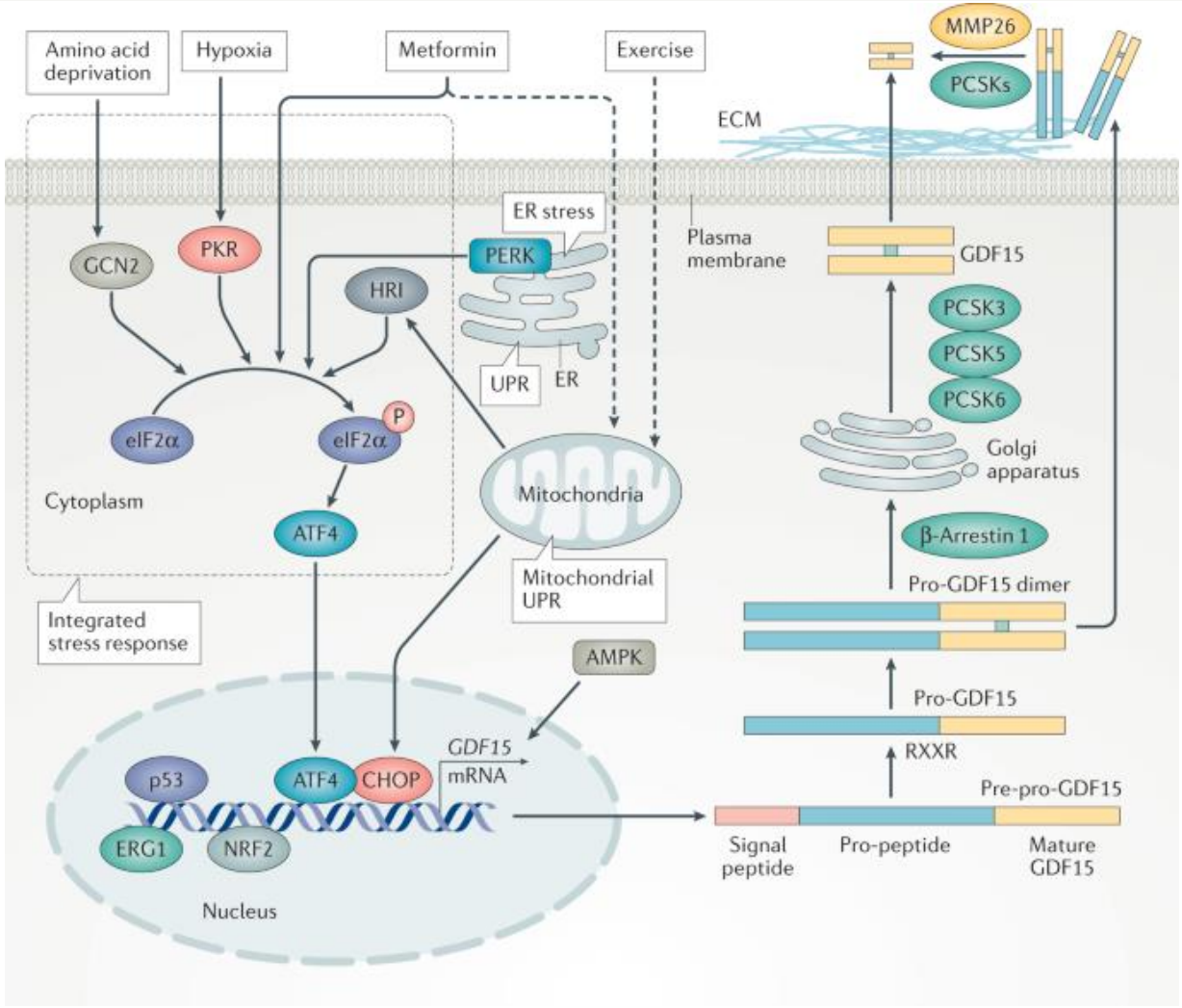
…but Leads to Adverse Outcomes in Cancer



Ander et al, Science Immunology 2019

Clifton et al, JITC 2023

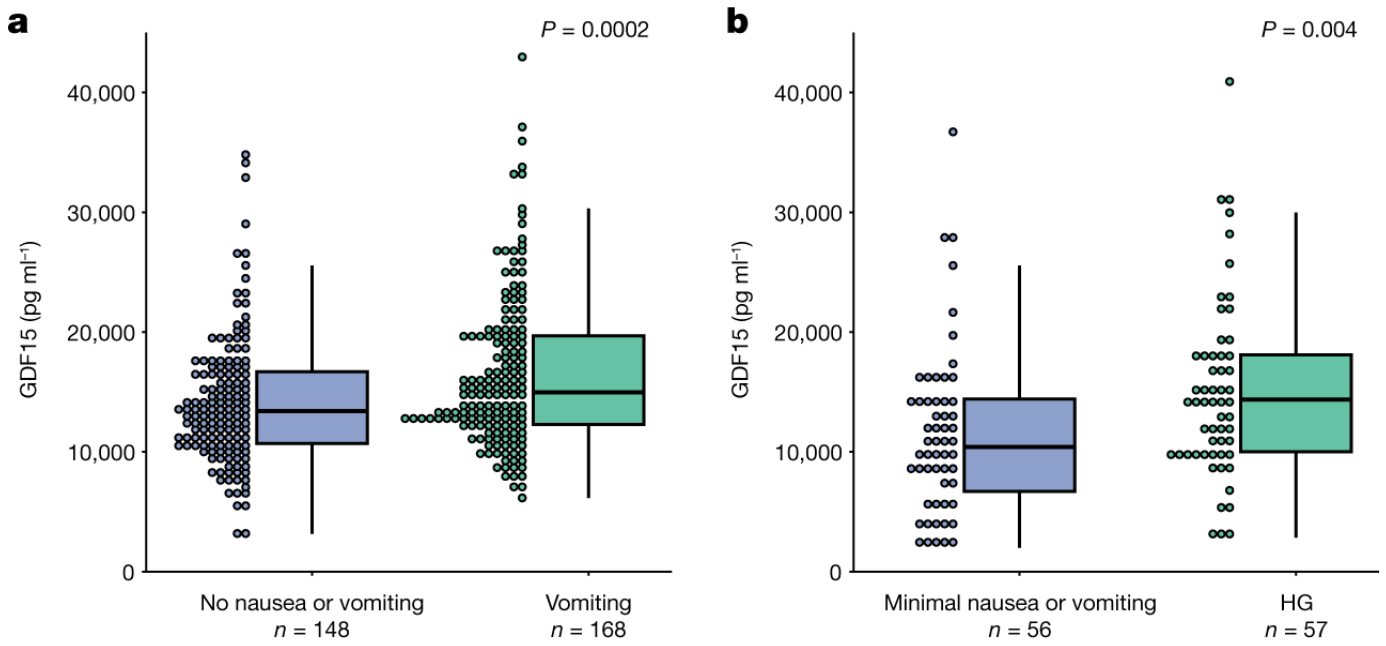
GDF15 physiology and role in disease

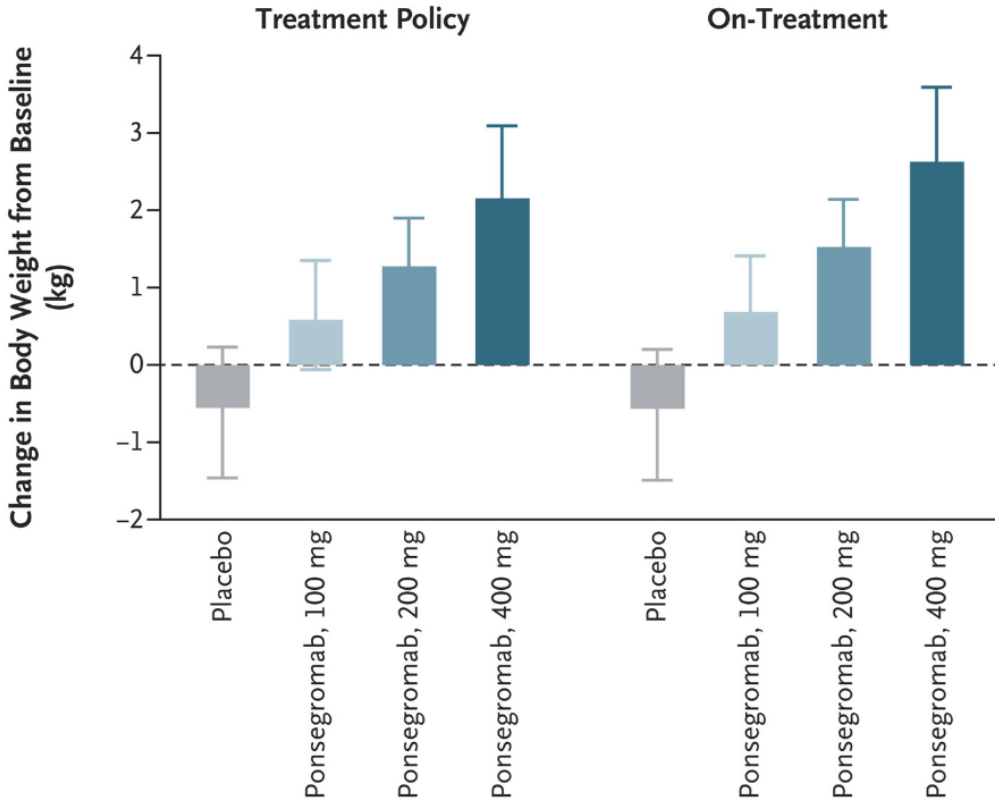


- GDF15 is a member of the TGFβ family and is not expressed in somatic tissue, but is abundant in placenta, leading to hypothesized role in feto-maternal tolerance
- Early preclinical studies found an significant inhibitory effect on macrophages, although a wide range of immunomodulatory effects have now been demonstrated

Wang et al, Nature Reviews Endocrinology

GDF15 Linked to Nausea/Vomiting In Pregnancy

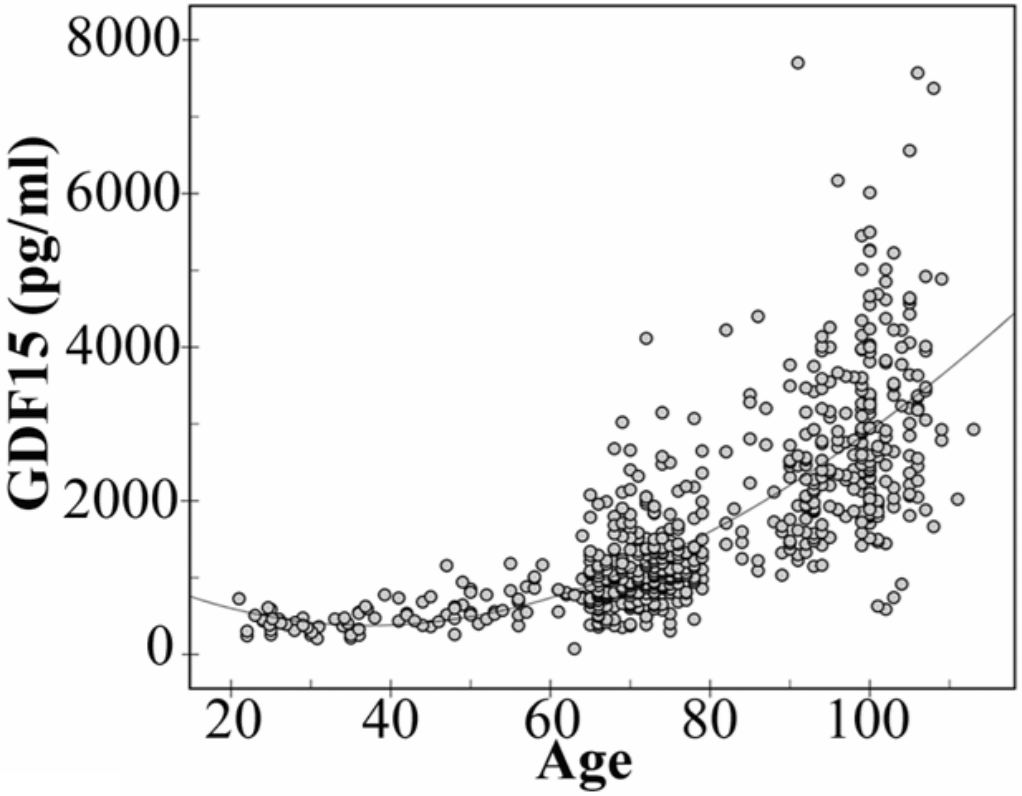




Similarly – elevated GDF15 in cancer leads to cancer induced anorexia / cachexia

Determinants of GDF15

GDF15 Rises with Age



GDF15 Increase with Race and Socioeconomic Stress

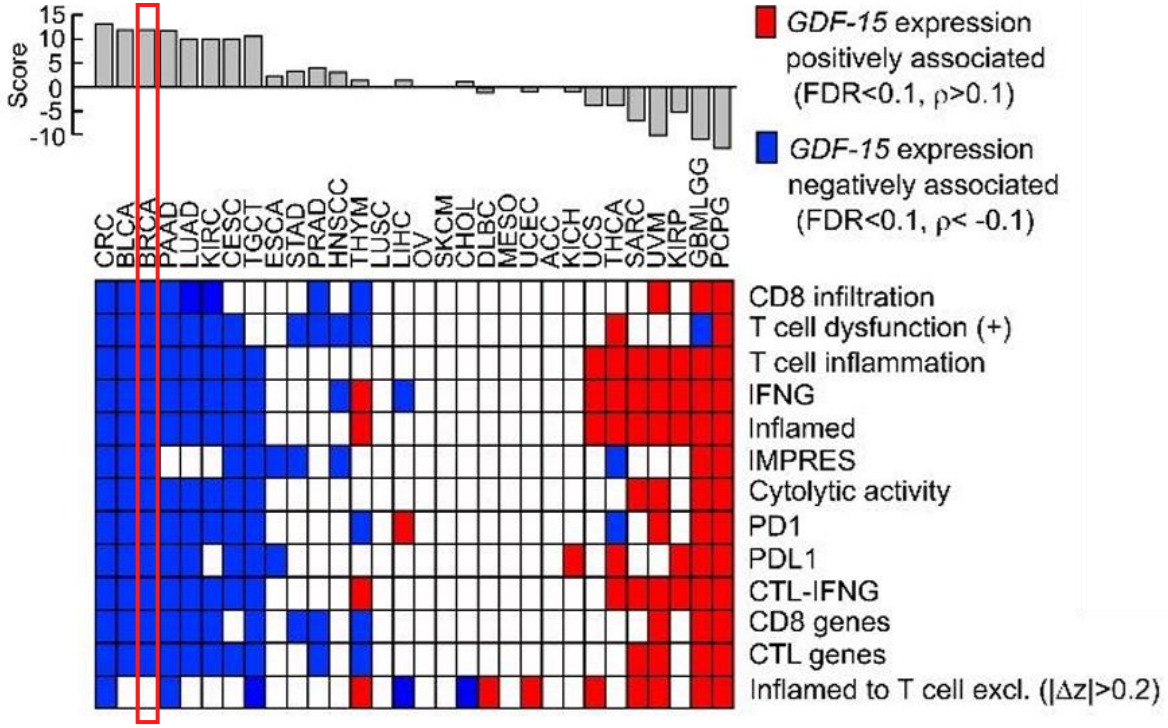
	Growth differentiating factor-15 (pg/ml)		
	1st Quartile (n = 338)	4th Quartile (n = 297)	p-trend
GDF-15 (pg/ml)	219 (215; 222)	521 (513; 530)	**< 0.0001**
Age (years)	24.2 ± 3.02	25.0 ± 3.14	**0.010**
Sex, male, n (%)	156 (46.2)	140 (47.1)	0.32
Ethnicity, black, n (%)	146 (43.2)	173 (58.2)	**< 0.0001**
Socio-economic score	21.4 ± 5.59	19.8 ± 6.46	**0.014**
Body height (m)	1.69 ± 0.097	1.68 ± 0.091	0.13
Body weight (kg)	71.3 ± 15.9	69.9 ± 20.1	0.26
Waist-to-hip ratio (cm)	0.78 ± 0.084	0.78 ± 0.075	**0.044**
Body mass index (kg/m^2)	24.9 ± 4.89	24.8 ± 6.66	0.089

Conte et al, FJ Gerontol A Biol Sci Med Sci, 2019

Vermeulen et al, Nutrition, Metabolism, and Cardiovascular Disease 2020

Rationale for Evaluation in Breast Cancer

GDF15 Expression Negatively Associated with Immune Markers in TCGA-BRCA Cohort



Associations with Biomarkers, Race, and pCR/DRFS

	pCR (Logistic Regression)						DRFS			
	Coef	LCI	UCI	Waldp	LRp	exp	LCI (exp)	UCI (exp)	Waldp	LRp
B_cells	-0.33	-1.18	0.53	0.451	0.707	0.66	0.25	1.79	0.420	0.397
CD274	0.78	-0.09	1.67	0.082	**0.003**	1.49	0.59	3.76	0.405	0.443
CD68	0.11	-0.83	1.05	0.814	0.574	0.53	0.17	1.63	0.269	0.504
CD8_T_cells	-0.32	-1.20	0.54	0.466	0.675	1.86	0.75	4.62	0.178	0.386
Chemokine12	-0.01	-0.87	0.87	0.986	0.697	1.18	0.45	3.07	0.736	0.822
Cytotoxic_cells	0.52	-0.36	1.41	0.248	0.295	1.24	0.45	3.40	0.674	0.552
Dendritic_cells	0.03	-0.84	0.89	0.952	0.817	1.31	0.54	3.19	0.548	0.800
ER_PGR_avg	-0.74	-2.63	0.61	0.350	0.583	1.31	0.46	3.73	0.616	0.534
Mod7_ERBB2	-0.25	-1.14	0.62	0.576	0.852	0.59	0.21	1.69	0.326	0.594
Module3_IFN_score	0.54	-0.31	1.41	0.218	0.258	0.88	0.38	2.03	0.761	0.498
Module4_TcellBcell	-0.13	-0.99	0.73	0.763	0.776	0.96	0.35	2.62	0.936	0.970
Neutrophils	0.21	-0.66	1.08	0.632	0.578	1.83	0.79	4.28	0.161	0.336
NK_CD56dim_cells	-0.59	-1.48	0.28	0.189	0.406	1.06	0.44	2.55	0.903	0.740
NK_cells	0.24	-0.62	1.11	0.586	0.794	1.47	0.57	3.76	0.422	0.478
PDCD1	0.15	-0.71	1.04	0.728	0.798	2.05	0.80	5.24	0.135	0.333
STAT1_19272155	0.99	0.11	1.91	0.031	0.089	0.76	0.29	1.95	0.565	0.519
T_cells	0.13	-0.74	1.01	0.764	0.830	1.47	0.56	3.85	0.434	0.736
TGFB_score	-1.13	-2.17	-0.18	**0.024**	**0.041**	2.73	1.16	6.41	**0.021**	**0.024**
Th1_cells	-0.24	-1.12	0.64	0.593	0.853	1.69	0.61	4.72	0.313	0.437
TILs										0.901
TIS_2865										0.343
Treg	-0.07	-0.95	0.78	0.867	0.840	1.03	0.45	2.39	0.937	0.888

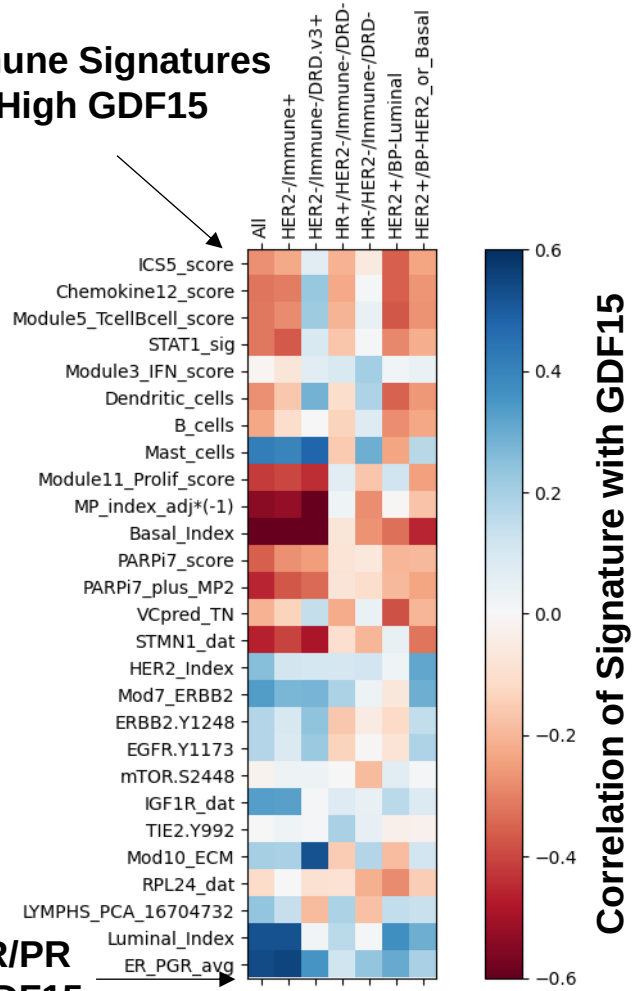
Interaction term for biomarker x black race

Melero et al, Research Square 2024

Kyalwazi et al, JAMA Network Open 2023

GDF15 in ISPY2 990 Cohort

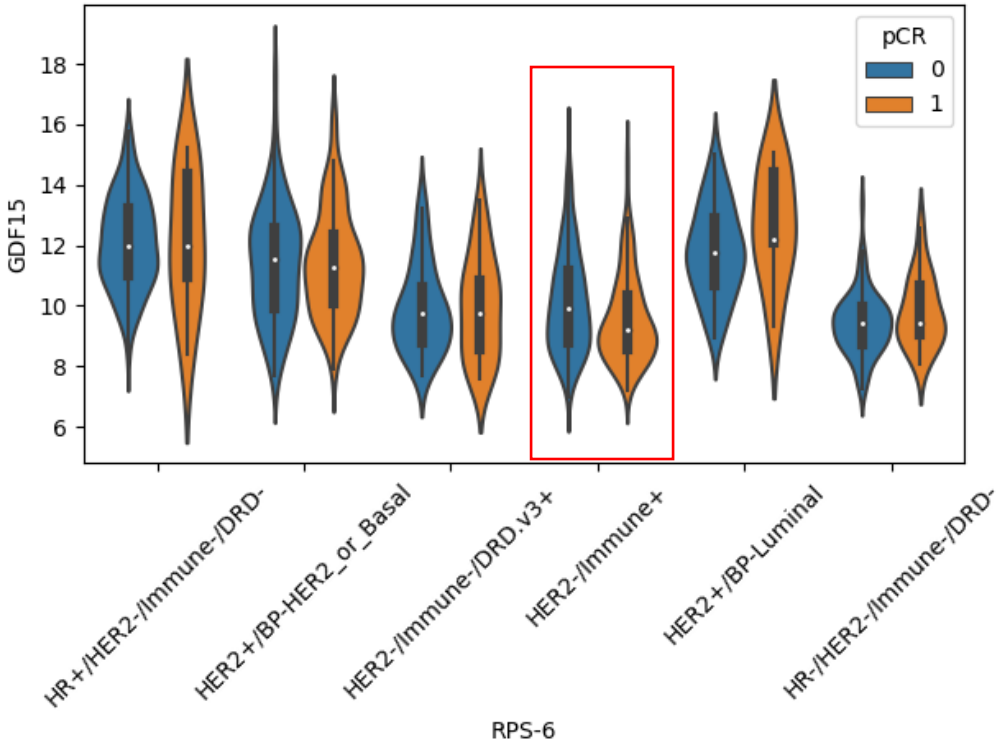
Low Immune Signatures With High GDF15



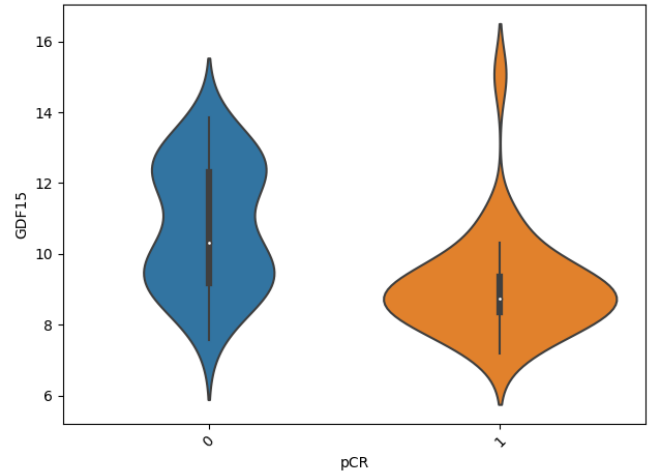
Correlation of Signature with GDF15

But High ER/PR With High GDF15

Possible Association with Better pCR Rates in HER2- Immune+



Higher pCR in Pembro4 Arm with low GDF15?



Phase I Dose Escalation Trial of Visugromab

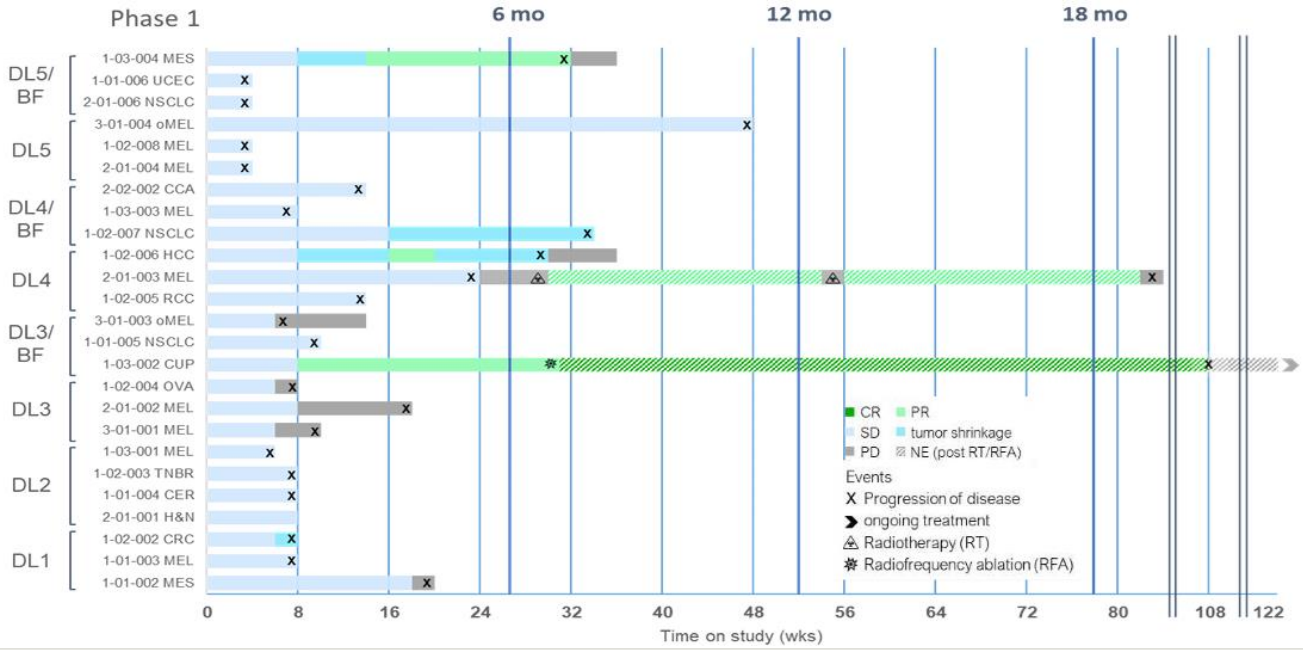
Baseline Biopsy → **D14 Biopsy** → **D28 Biopsy**

Mixed solid tumors
Refractory/relapsed to ICI
Median of 4 lines prior therapy

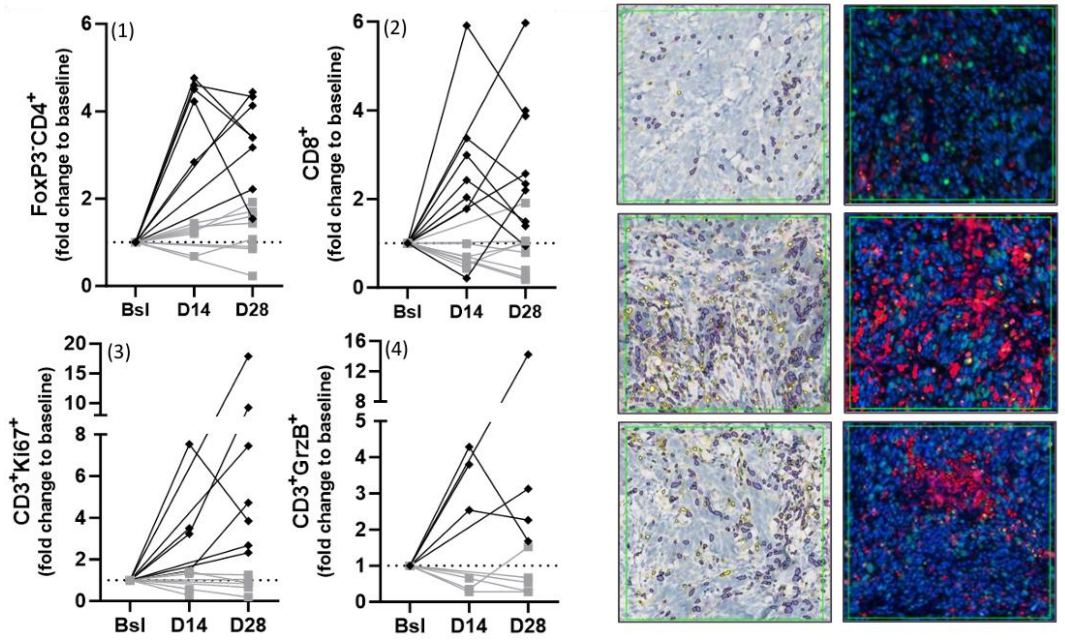
→ **Visugromab** q2w x 1 dose (0.3/1.0/3.0/10/20 mg/kg)

→ **Visugromab** q2 week + **Nivolumab** 240mg q2 week →

Phase I Swimmer's Plot



Increase in CD8 and GrzB+ CD3+ Cells



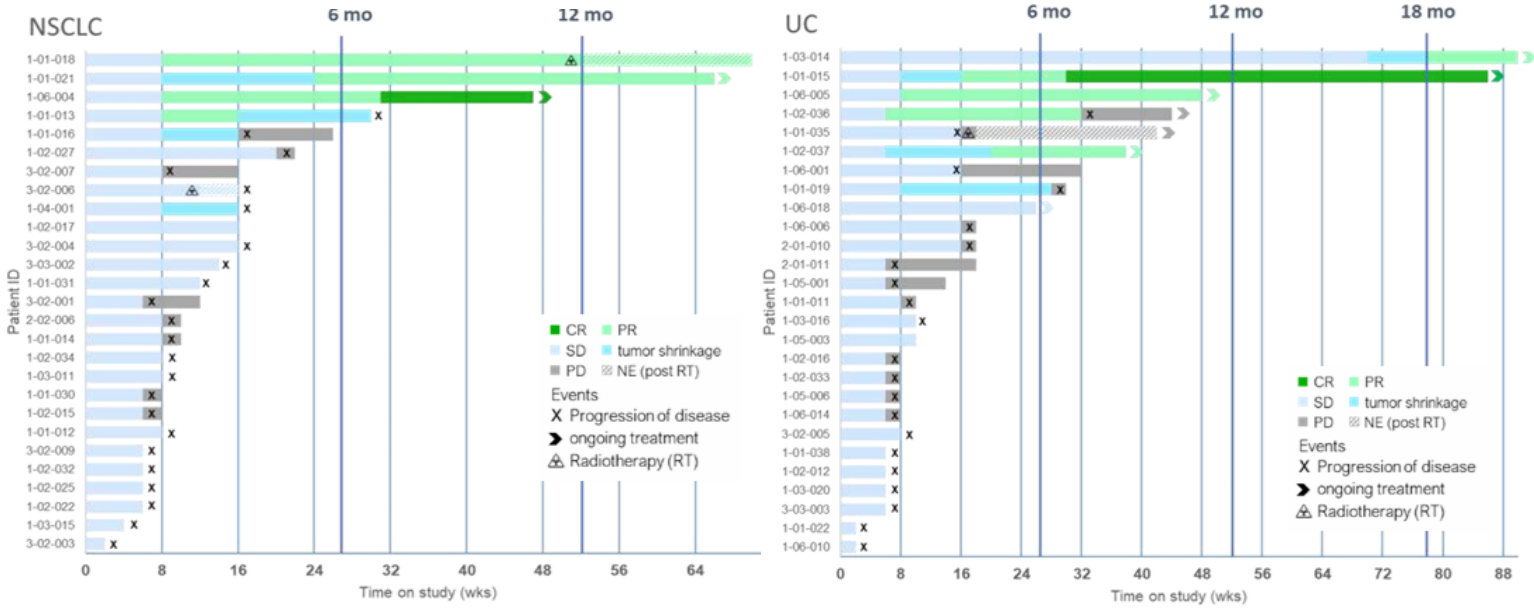
Melero et al, Research Square 2024

Phase IIa Study Expansion

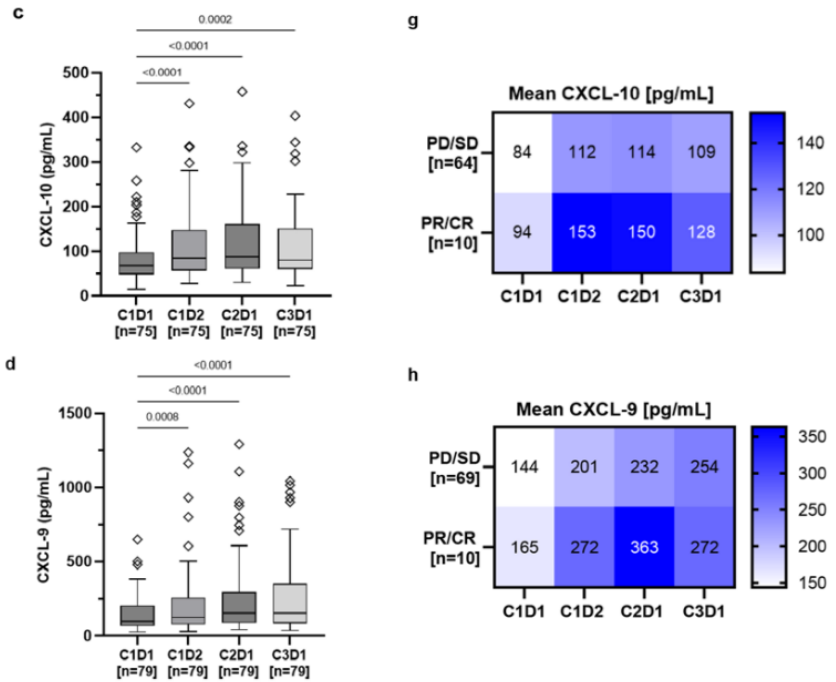
27 each NSCLC and UC
Refractory to anti-PD(L)1
Median 3 prior lines

→ **Visugromab** 10mg/kg q2w
Nivolumab 240mg q2 week →

NSCLC / UC Swimmers Plot



Visugromab Induces Interferon Signaling



Melero et al, Research Square 2024

Safety Profile

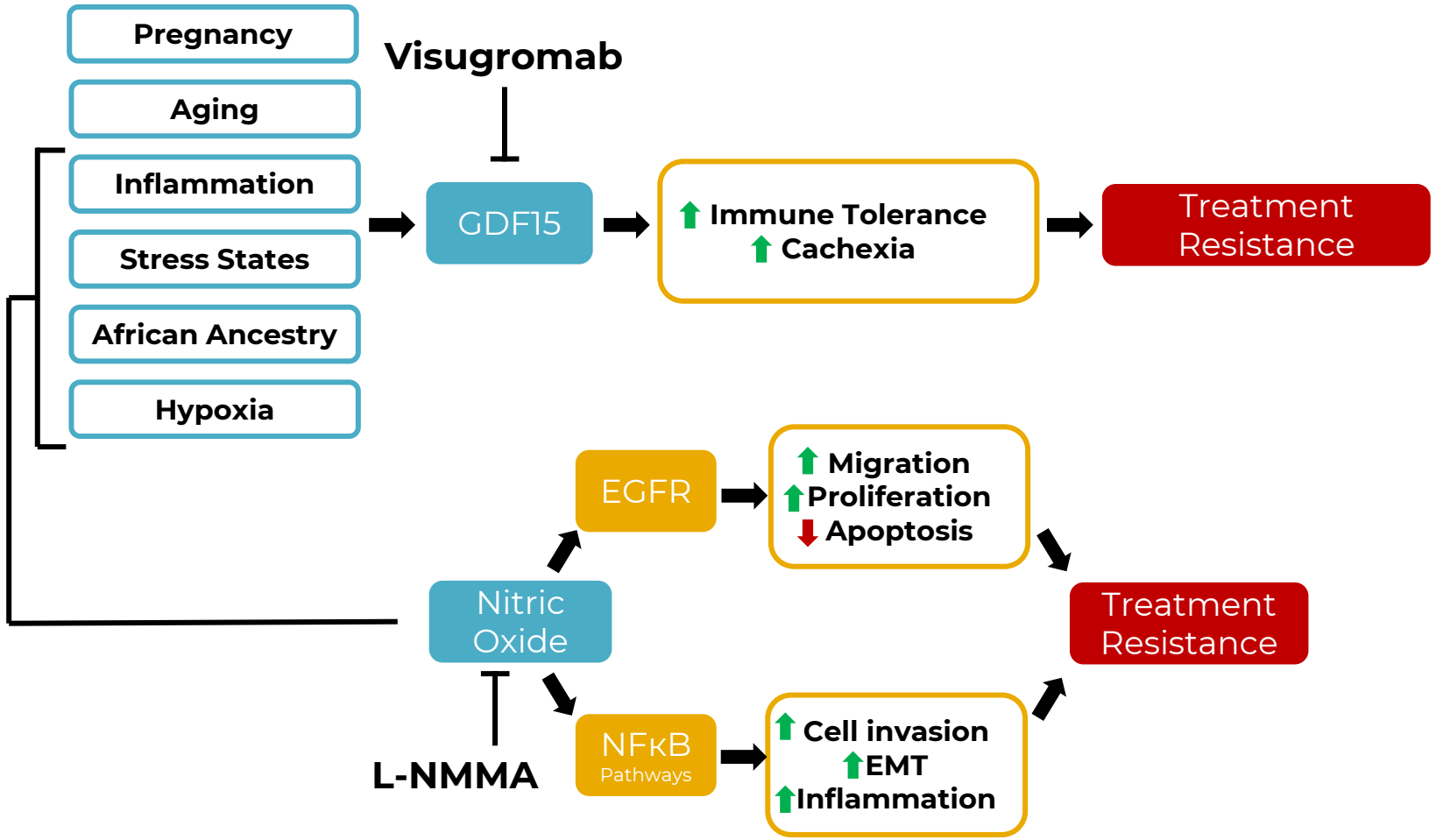
Visugromab

- Phase II NSCLC cohort (n = 27)
  - Grade 3 TRAEs included diarrhea in 1 patient, laboratory abnormalities (elevated AST and hypokalemia) in 1 patient
  - 1 patient with grade 4 hepatic failure and acute kidney injury -> death due to organ dysfunction
- Phase II Urothelial cohort (n = 27)
  - Two grade 3 TRAEs - pneumonitis in one, HTN and platelet count decrease in another
  - No grade 4/5

Ponsegromab (142 with treatment vs 45 placebo)

- Similar rates of TRAE in treatment / placebo groups – two SAEs considered treatment related (dyspnea, abdominal pain)

Summary


Pregnancy
Aging
Inflammation
Stress States
African Ancestry
Hypoxia
Visugromab
GDF15
↑ Immune Tolerance
↑ Cachexia
Treatment Resistance
EGFR
↑ Migration
↑ Proliferation
↓ Apoptosis
Nitric Oxide
L-NMMA
NFκB Pathways
↑ Cell invasion
↑ EMT
↑ Inflammation
Treatment Resistance

Clinical Trial Participation Needs to be Commensurate with the Burden of Disease!

Why Don’t **BLACK WOMEN** Participate in Clinical Trials?

Doctors don’t invite Black women to clinical trials.

When the patient brings up the conversation, they still walk away not sufficiently informed.

Since we have negative history, and minimal awareness/understanding of clinical trials and research, Black women fear the unknown.

“Don’t do a clinical trial! You will get the sugar pill and die.”
Metastatic Patient

WHEN we Trial

COMMUNITY EVENTS

When We Tri(al): Reaching, Motivating, & Effectively Engaging Black Women In Breast Cancer Clinical Trial Research

Authors: Ricki Fairley, MBA; Emily Powers; Hayley Brown; TOUCH, The Black Breast Cancer Alliance

SAN ANTONIO BREAST CANCER SYMPOSIUM® - DECEMBER 5-9, 2023 | For more information: 610-883-1177 | whenwetrial.org | Contact: Ricki Fairley, CEO: ricki@touchbbca.org

SURVEY FINDINGS

FOLLOWING EXPOSURE TO WWT >>>

34.5% of respondents reported an increase in their understanding of how breast cancer clinical trials work

31.9% reported an increase in their understanding of standard of care in breast cancer clinical trials

40.7% reported an increased understanding of why clinical trials are important for Black women

32.7% of survey respondents ***were more likely*** to consider participating in a clinical trial after interacting with the WWT movement.

After interacting with the movement, 31% of respondents took active steps to participate in a clinical trial—specified as searching for clinical trials in a portal, asking about clinical trial options, talking to a doctor about clinical trials, etc. Another 17.7% of respondents reported supporting a loved one in taking steps to participate in a clinical trial only after interacting with WWT.

The majority of respondents reported first hearing about WWT through social media **(59.2%)**, followed by "Other" (the majority of write-in responses named Google or a friend) **(19.5%)**. Respondents reported that the most convincing WWT messages were delivered via social media **(26.6%)** and in-person conversations **(20.4%)**.

SOCIAL MEDIA, WEBSITE, AND ADS METRICS: CUMULATIVE & COMPREHENSIVE

01.26.22 - 09.30.24

WHEN WE TRI(AL) CAMPAIGN

WEBSITE VISITS
166,078

UNIQUE WEBSITE VISITS
50,503

WEBSITE SIGN-UPS
1,825

CLINICAL TRIALS SEARCH
20,039

SOCIAL IMPRESSIONS / VIEWS
1,042,838

- **FACEBOOK ORGANIC:** 4,310
- **INSTAGRAM ORGANIC:** 20,286
- **INSTAGRAM PAID:** 0
- **TWITTER:** NA

SOCIAL INTERACTIONS
447,933

- **FACEBOOK:** 151
- **INSTAGRAM:** 1,321
- **TWITTER:** NA

SOCIAL CONVERSIONS
119,622

- **FACEBOOK ORGANIC & PAID:** 980
- **INSTAGRAM:** 666

SOCIAL CONVERSION RATE
42%

TOUCH Care

To facilitate the clinical trial process for Black women, TOUCH is providing a Nurse Navigator Service to assist patients with securing trials, the application process, managing the informed consent process and providing coaching and counseling throughout the trial.

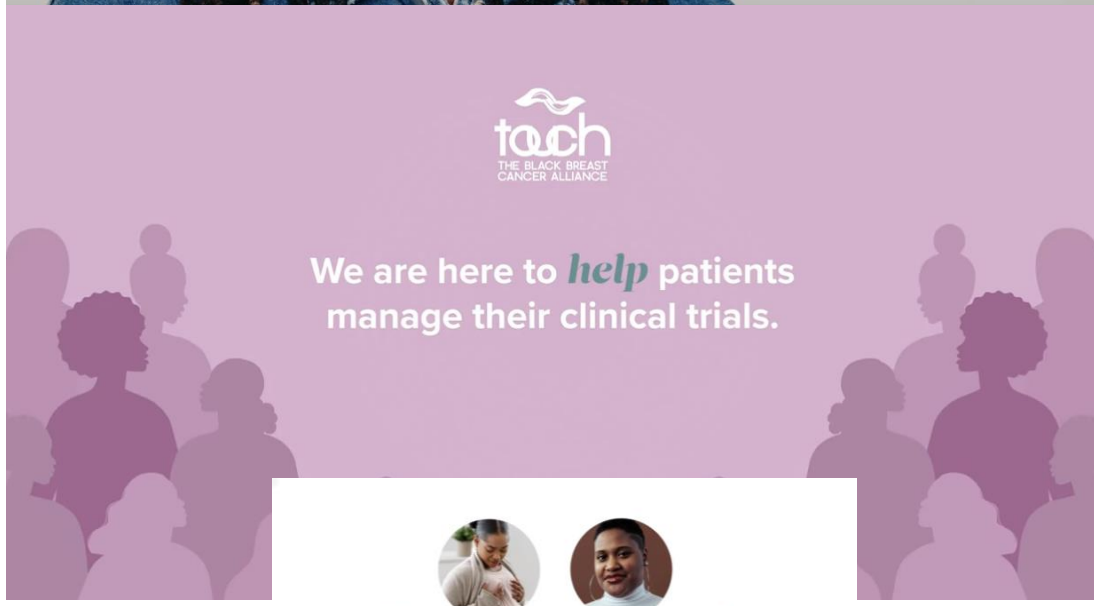
PATIENT NAVIGATION

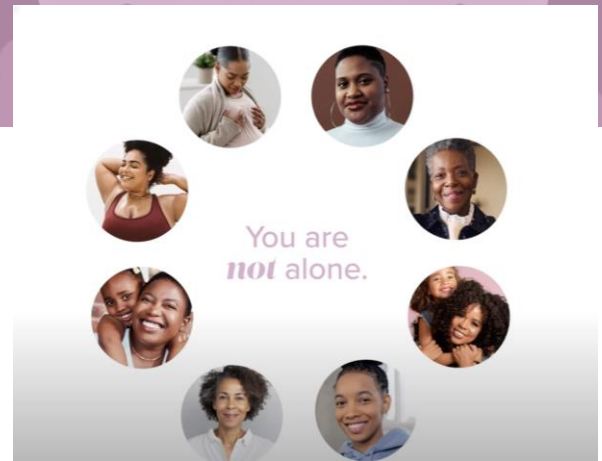
A navigation program that addressed insurance, food, housing, transportation, language, health literacy, social and clinical needs **increased participation in clinical research**:

	Before Navigation*	After Navigation*
Rural	19%	40%
Black	13%	41%
Hispanic	5%	33%

* Participation (% of patients)

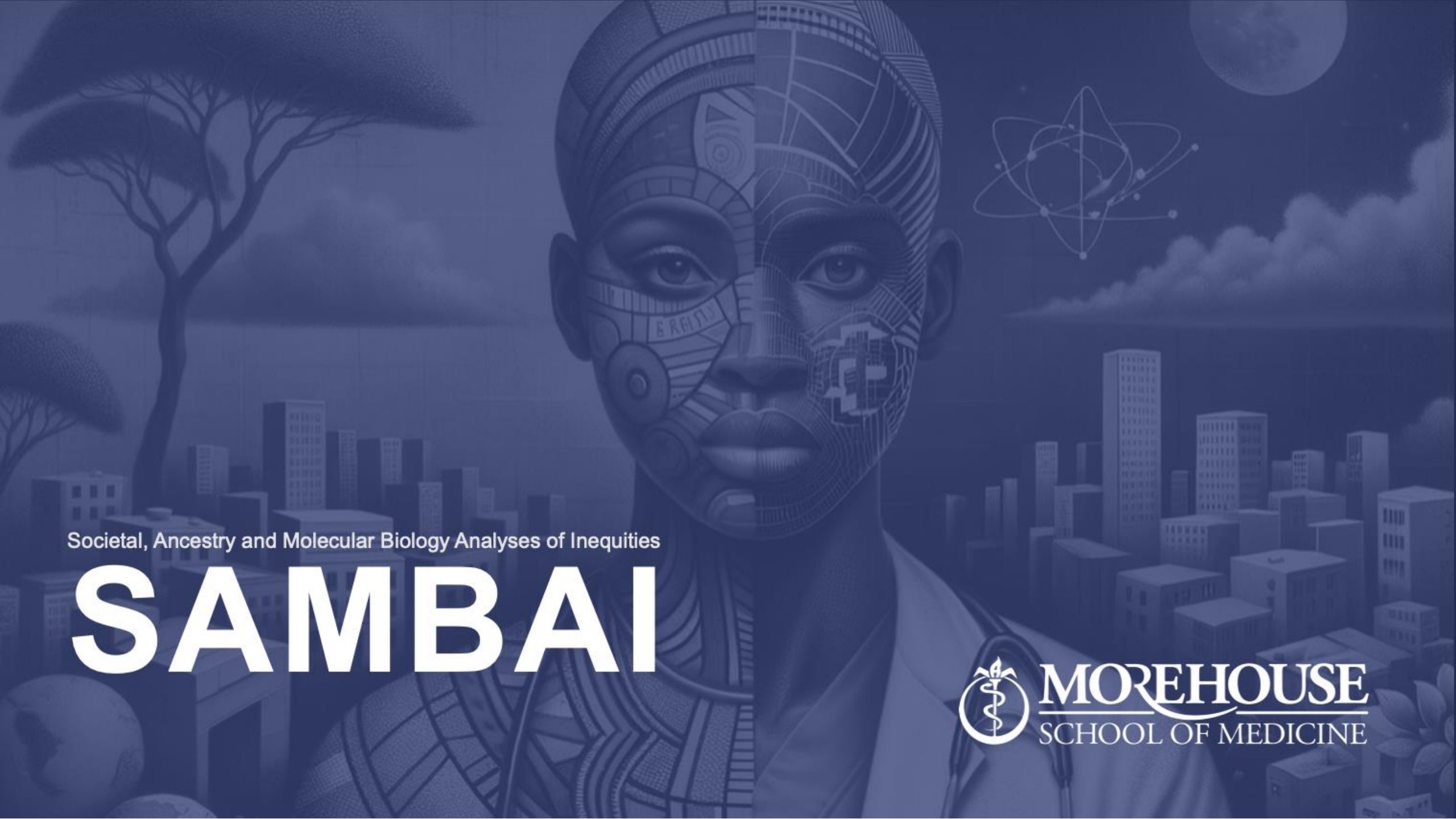
AACR Cancer Disparities Progress Report 2024






careforHER


Ricki’s Ideal Clinical Research Scenario


Societal, Ancestry and Molecular Biology Analyses of Inequities
SAMBAI
MOREHOUSE
SCHOOL OF MEDICINE

Patient ~~engagement~~ INVOLVEMENT

More than mere engagement, genuine partnership!

Genetic Ancestry

SAMBAI

Patient Partnership & Advocacy

The Golden Rule

Treat others the way YOU want to be treated.