BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University

Racial Disparities in Lung Cancer Risk and Outcomes

Ann G. Schwartz, PhD, MPH

January 18, 2023

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

A Short and Winding Road

BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University

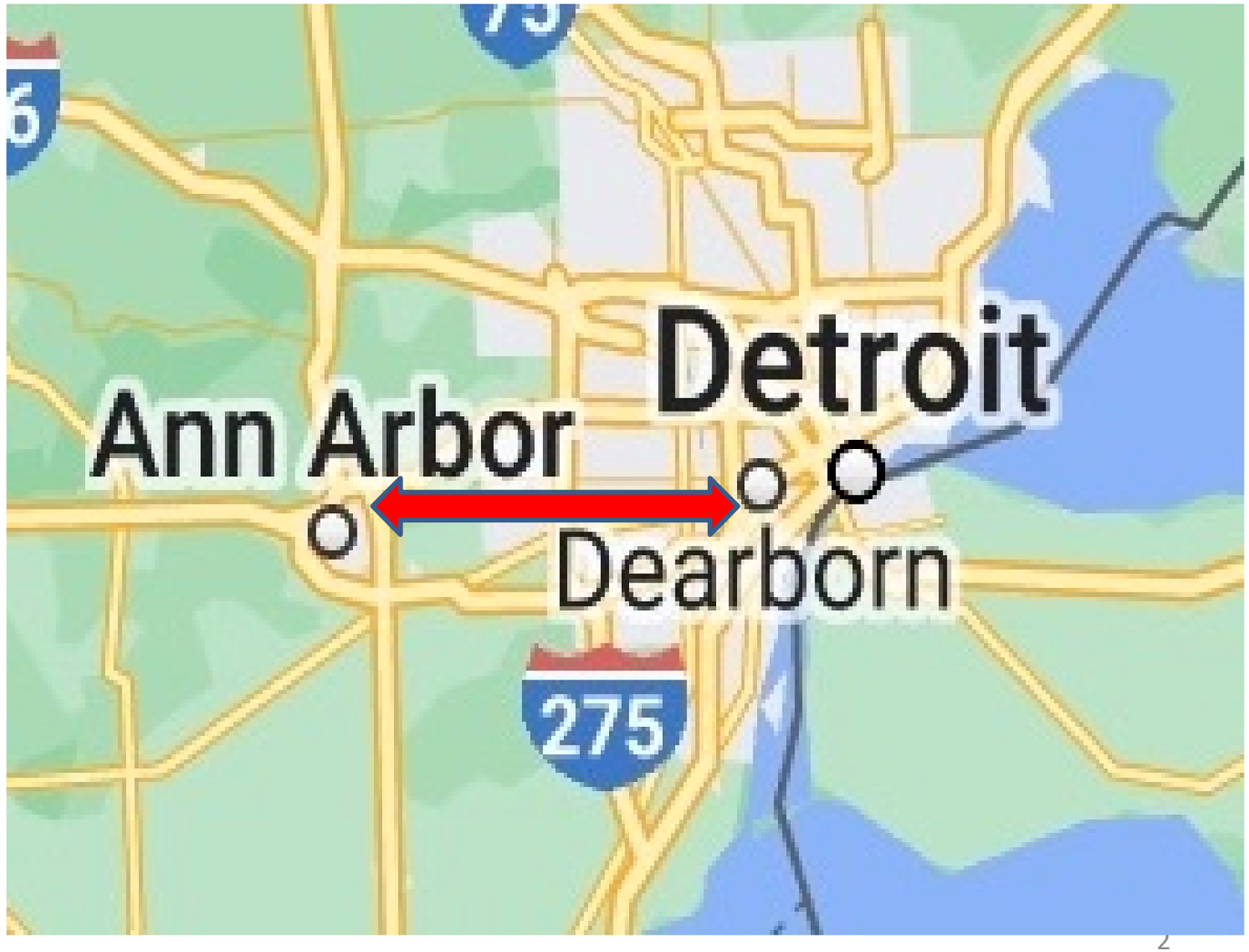
<u>Education</u>

BS, Zoology, University of Michigan

MS, Biophysics, WSU

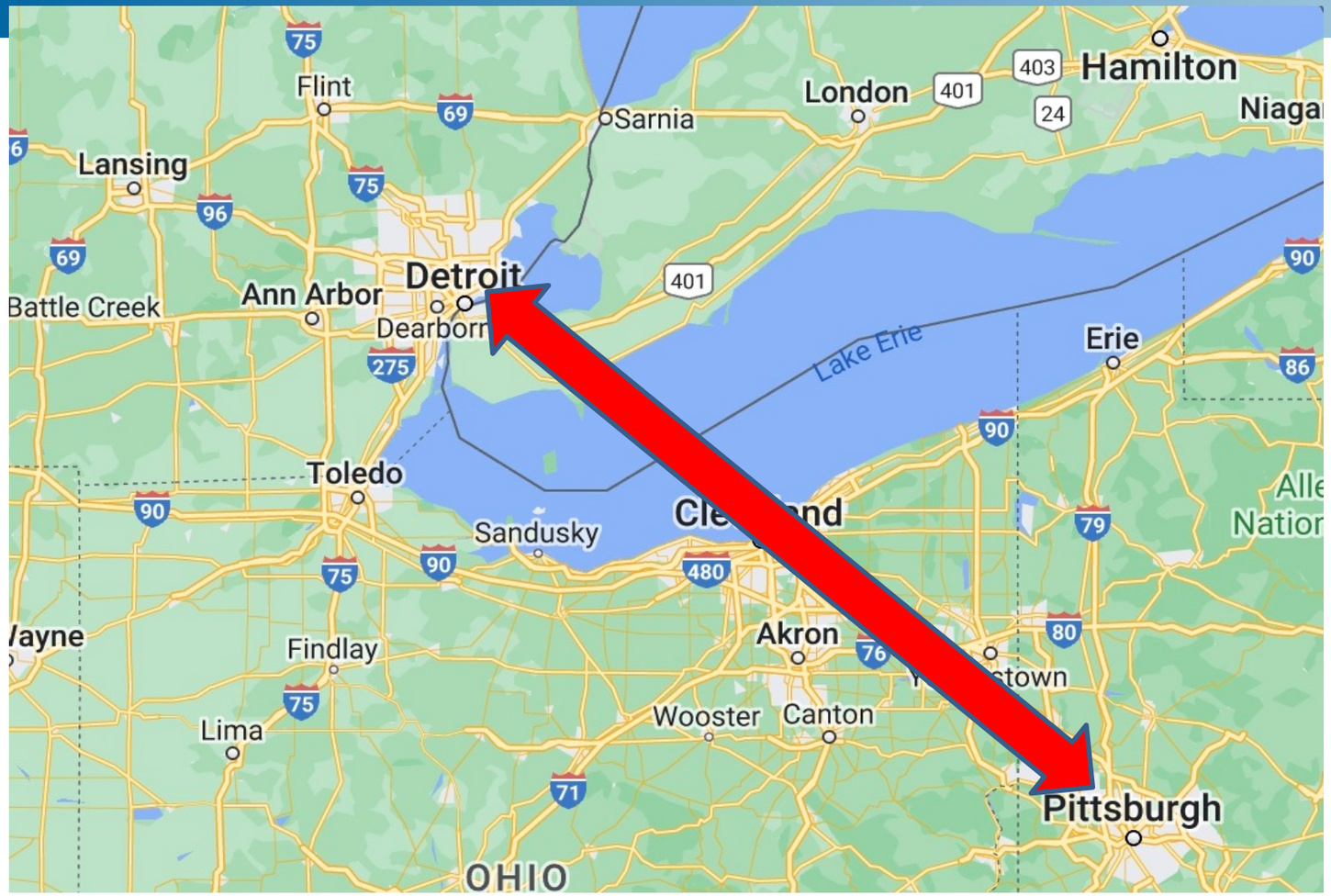
MPH, Environmental Health, University of Michigan

PhD, Epidemiology, University of Michigan (while working at the Michigan Cancer Foundation)



NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

A Longer Road Back to the Beginning



Barbara Ann Karmanos Cancer Institute
Wayne State University

Academic Appointments

Michigan Cancer Foundation

University of Pittsburgh

Allegheny Health Sciences

WSU/Karmanos Cancer Institute
Deputy Center Director
Assoc. Chair, Oncology
Professor

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Cancer Continuum

BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University

Prevention & Risk Reduction

- *Tobacco Use*
- Diet
- Physical Activity
- Environmental Exposures
- Alcohol Use
- Immunization

Risk Profiles/ Screening

- *Risk/Screening*
  - Age
  - Race
  - Gender
  - Smoking
  - Family Hx
  - COPD
- Genetic Testing

Diagnosis

- Biopsy
- Pathology
- Staging
- *Biomarkers*
- *Molecular Profiling*

Treatment

- Systemic Therapy
- Radiation
- Surgery

- *Personalized Treatments*

Survivorship

- CIPN
- *COVID-19*
- Surveillance
- Screening for second primary cancers
- *Tobacco Use*
- *Physical Activity*
- *Mental Health*

End of Life

- Advanced care
- Hospice care
- Bereavement care

Care Planning Psychosocial Support
Palliative Care Family and Caregiver Support
Prevention and Management of Long Term and Late Effects

Crosscutting Areas

Health Communication, Epidemiology, *HEALTH DISPARITIES*, Surveillance, Implementation Science, Healthcare Delivery

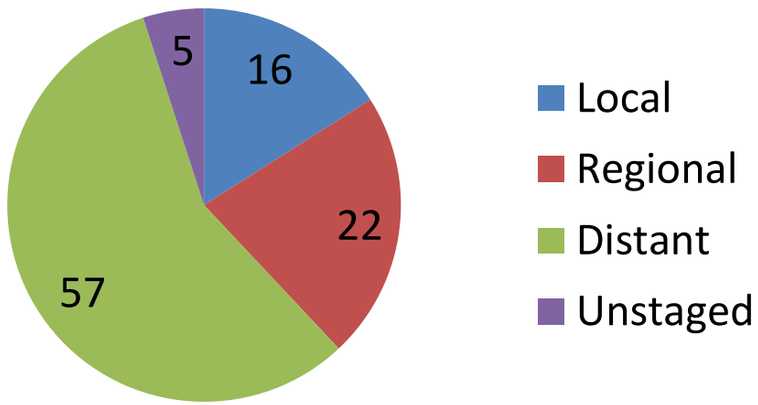
NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Lung Cancer in the US

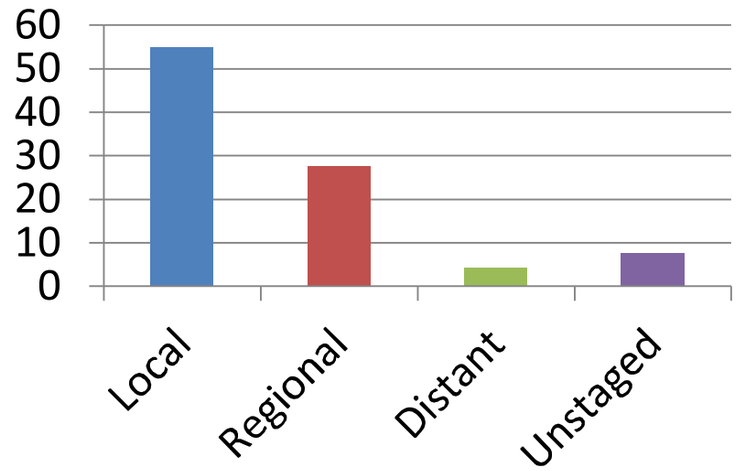
BARBARA ANN Karmanos CANCER INSTITUTE Wayne State University

Lung Cancer Statistics	
Estimated number of new cases annually	228,000
Estimated deaths annually	136,000
% surviving 5 years	19%
% of lung cancer cases who are ever smokers	~80%

Stage at Diagnosis

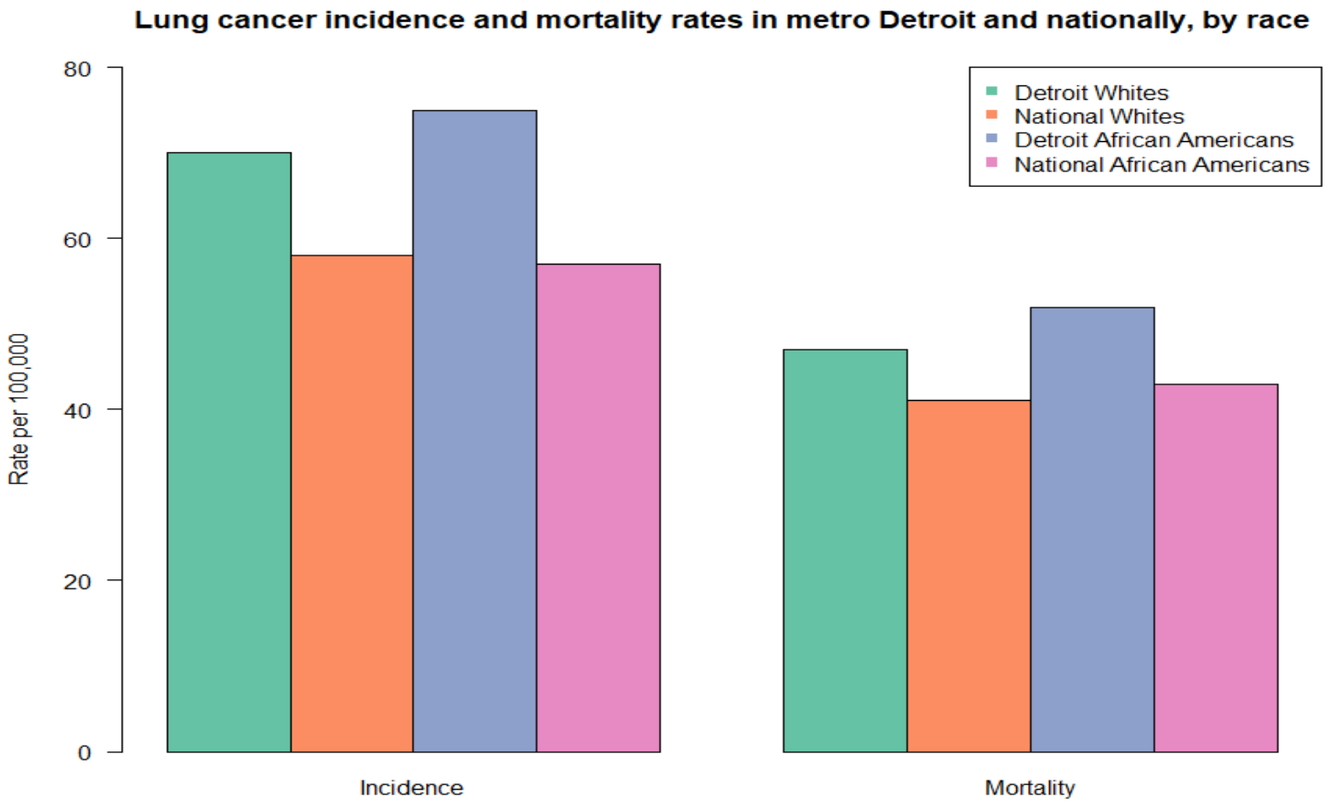


5-Yr Survival %



NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Racial Disparities in Lung Cancer



African Americans, as compared to whites, tend to have:

- Fewer pack-years of cigarette exposure
- Higher risk associated with family history *(Cote et al, JAMA 2005)*
- Lower risk associated with COPD

Self-reported history of COPD as a risk factor for lung cancer

BARBARA ANN Karmanos CANCER INSTITUTE Wayne State University

	White OR* (95% CI)	African American OR* (95% CI)
COPD	1.9 (1.2-2.8)	1.1 (0.5-2.5)
Emphysema	3.8 (1.7-8.3)	1.9 (0.4-8.2)
Chronic Bronchitis	1.8 (1.1-2.9)	1.4 (0.6-3.4)

** Adjusted for pack-years, age, race, sex, family history of lung cancer, education, BMI and regular aspirin use*

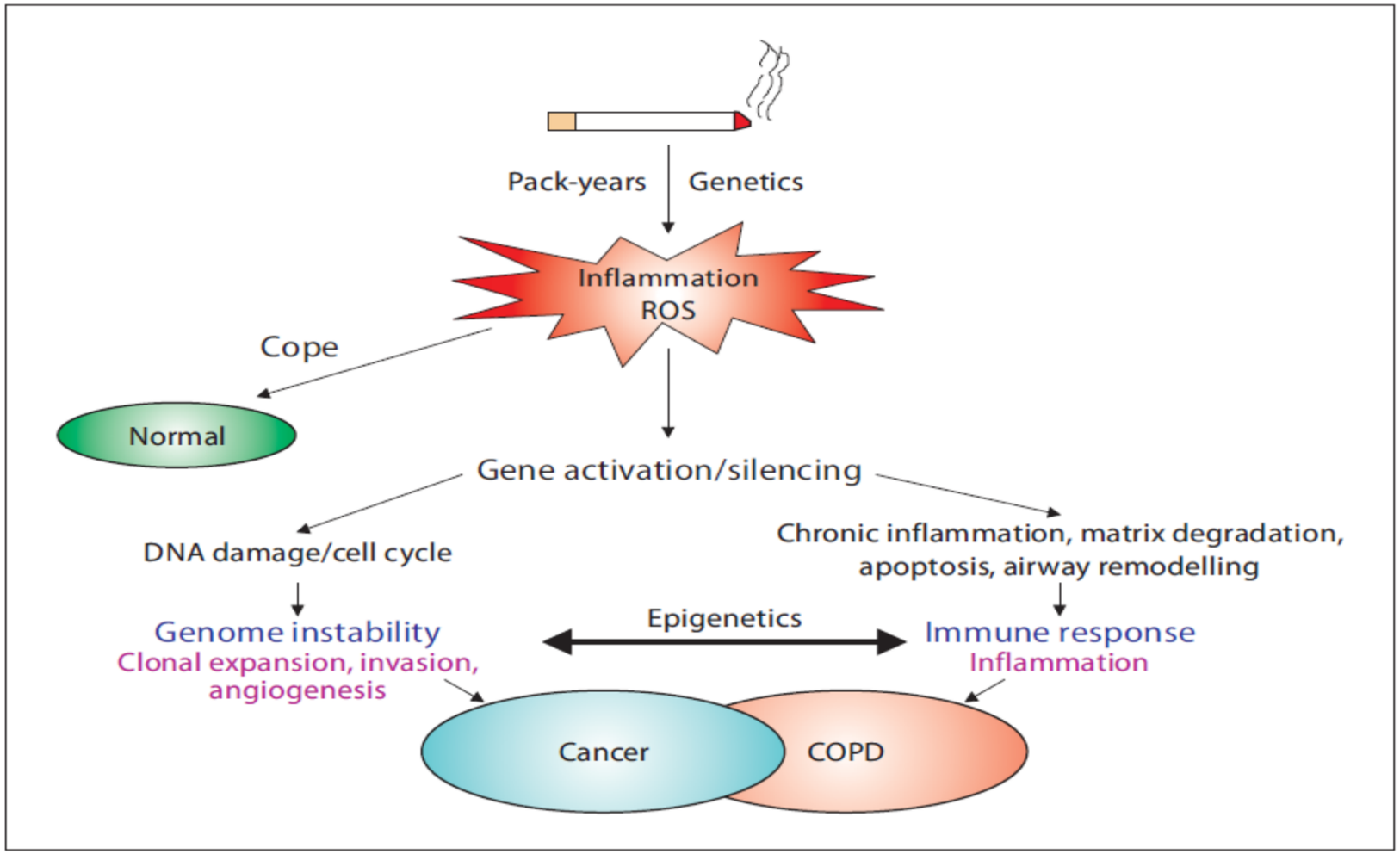
Schwartz et al, J Thoracic Oncol, 2009

78% of African Americans with lung cancer self-reported NO history of COPD, but had spirometry or CT evidence of COPD suggesting severe under-reporting or under-diagnosing of COPD in African Americans.

Mina et al, Clin Lung Cancer, 2012

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Pathogenesis in lung cancer and COPD



Adcock et al, Respiration, 2011

The INHALE Study

BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University

Define the role of specific COPD phenotypes and inflammatory/immune pathway genes in the development of lung cancer by race.

- 1,560 Hospital-based lung cancer cases: 30% African American, 9.5% never smokers
- 1,760 Volunteer controls without lung cancer: 41% African American, 13% never smokers

- ***Interview*** to collect smoking history, family cancer history and other risk factor data
- ***Blood draw/saliva*** collection for germline DNA
- ***Spirometry*** to measure lung function, COPD diagnosis
- ***Low Dose Chest CT*** for quantitative imaging studies
- ***Tumor and adjacent normal tissue*** collection to measure tumor characteristics and gene expression

Schwartz, R01CA141769

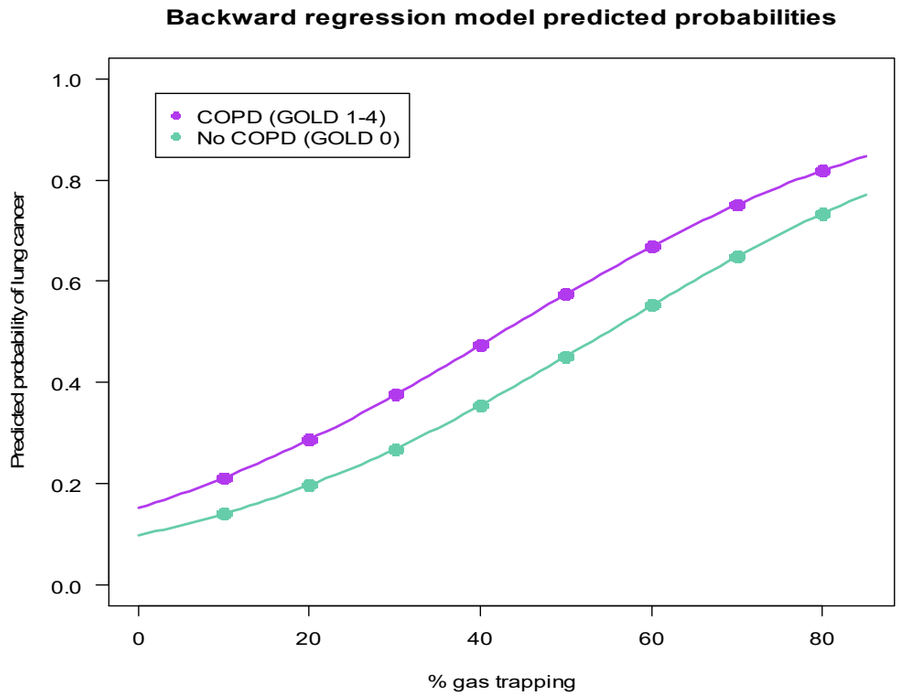
NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Quantitative Imaging Markers of Lung Function on Risk of Lung Cancer

BARBARA ANN Karmanos CANCER INSTITUTE Wayne State University

Measure	OR (95% CI)	p-value
% gas trapping	1.04 (1.03, 1.06)	<0.001
Spirometry ($FEV_1/FVC < 0.70$)	1.64 (1.13, 2.37)	0.009

- Quantitative image analysis measured:
  - % emphysema as % total lung voxels < -950 HU in inspiration across both lungs
  - % air trapping quantified as % voxels < -856 HU on expiratory scans
- Spirometry measured FEV_1/FVC
- Models adjusted for age, race, gender, pack years, scanner and total lung volume (inspiratory and expiratory)



NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Schwartz et al., CEBP 2016
Lusk et al, CEBP, 2019

Defining a "Lung Health" Profile

Hierarchical clustering of INHALE current/former smoking controls with qCT and spirometry (N=1179)

			Cluster		
Variable	1	2	3	4	5
N	64	232	73	609	201
Pack years	47.5 (24.1)	38.4 (31.4)	26.0 (18.7)	34.2 (20.9)	22.5 (19.6)
Quit years	2.6 (4.9)	1.1 (3.1)	6.2 (10.1)	1.8 (3.6)	25.9 (9.9)
FEV_1/FVC	0.53 (0.11)	0.69 (0.10)	0.47 (0.11)	0.77 (0.07)	0.77 (0.07)
% predicted FEV_1	53.9 (18.6)	67.0 (16.6)	49.1 (16.2)	83.5 (16.9)	86.5 (17.6)
qCT % emphysema[a]	16.3 (7.3)	2.6 (2.4)	1.5 (1.6)	1.2 (1.4)	2.4 (2.5)
qCT % air trapping[b]	51.3 (13.6)	30.6 (16.9)	11.2 (9.6)	7.1 (6.7)	14.9 (13.5)
qCT MLD ratio[c]	0.94 (0.04)	0.95 (0.05)	0.86 (0.06)	0.84 (0.05)	0.86 (0.06)

[a]Percent lung voxels < -950 HU on inspiration across both lungs.
[b]Percent lung voxels < -856 HU on expiration across both lungs.
[c]Mean lung density (MLD) ratio = expiratory MLD / inspiratory MLD

Lusk et al., CEBP, 2019

Lung Health

BARBARA ANN Karmanos CANCER INSTITUTE Wayne State University

Most detrimental → Least detrimental

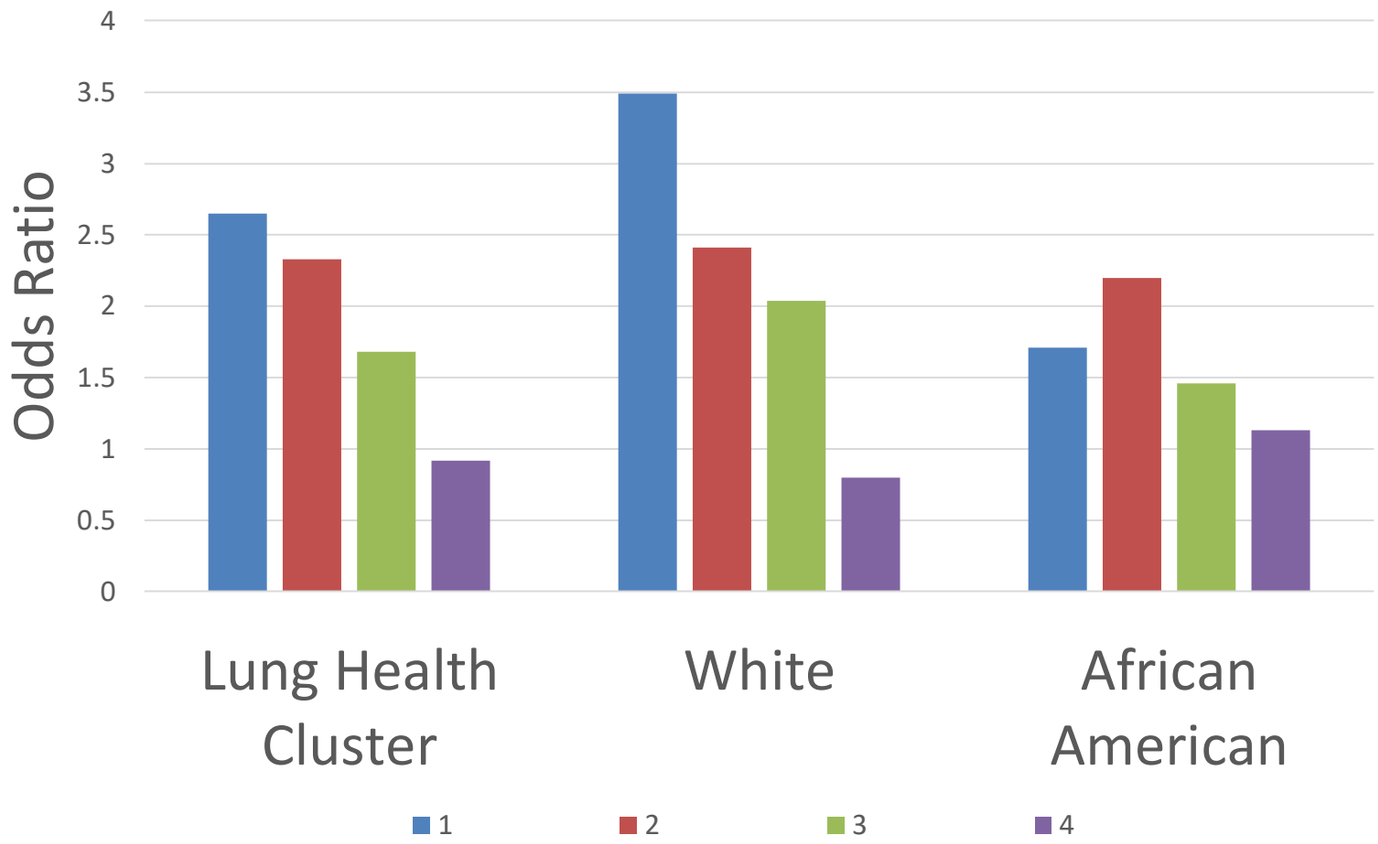
	Cluster	1	2	3	4	5
Smoking history	Pack years	↑	↑	↓	--	↓
	Quit years	↓	↓	--	↓	↑↑
Spirometry	FEV1/FVC	↓↓	↓	↓↓	↑	↑
	% predicted FEV1	↓↓	↓	↓↓	↑	↑
qCT	% emphysema	↑↑↑	--	↓	↓	--
	% air trapping	↑↑↑	↑	↓	↓	--
	MLD ratio	↑	↑↑	--	↓	↓

Figure 1. Mean trends are shown for variables used in clustering. Arrows indicate standardized group means for particular variables, relative to the overall mean (μ = 1), as follows: ↑/↓ = 0.2-1 SD above/below overall mean, ↑↑/↓↓ = 1-1.9 SDs above/below overall mean, ↑↑↑/↓↓↓ > 2 SDs above/below overall mean, -- = within 0.1 SDs above/below mean. Red indicates negative mean trend; blue indicates beneficial mean trend.

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Lung health clusters and lung cancer risk

- ORs comparing odds of lung cancer in each cluster to odds of lung cancer in cluster 5, adjusted for age, race, sex, and BMI
- Odds of lung cancer are significantly ($p<0.05$) elevated in each cluster except in cluster 4 in total sample and for Whites, but only cluster 2 is significantly associated with the odds of lung cancer in African Americans



Summary of smoking, COPD, and imaging markers of lung cancer risk

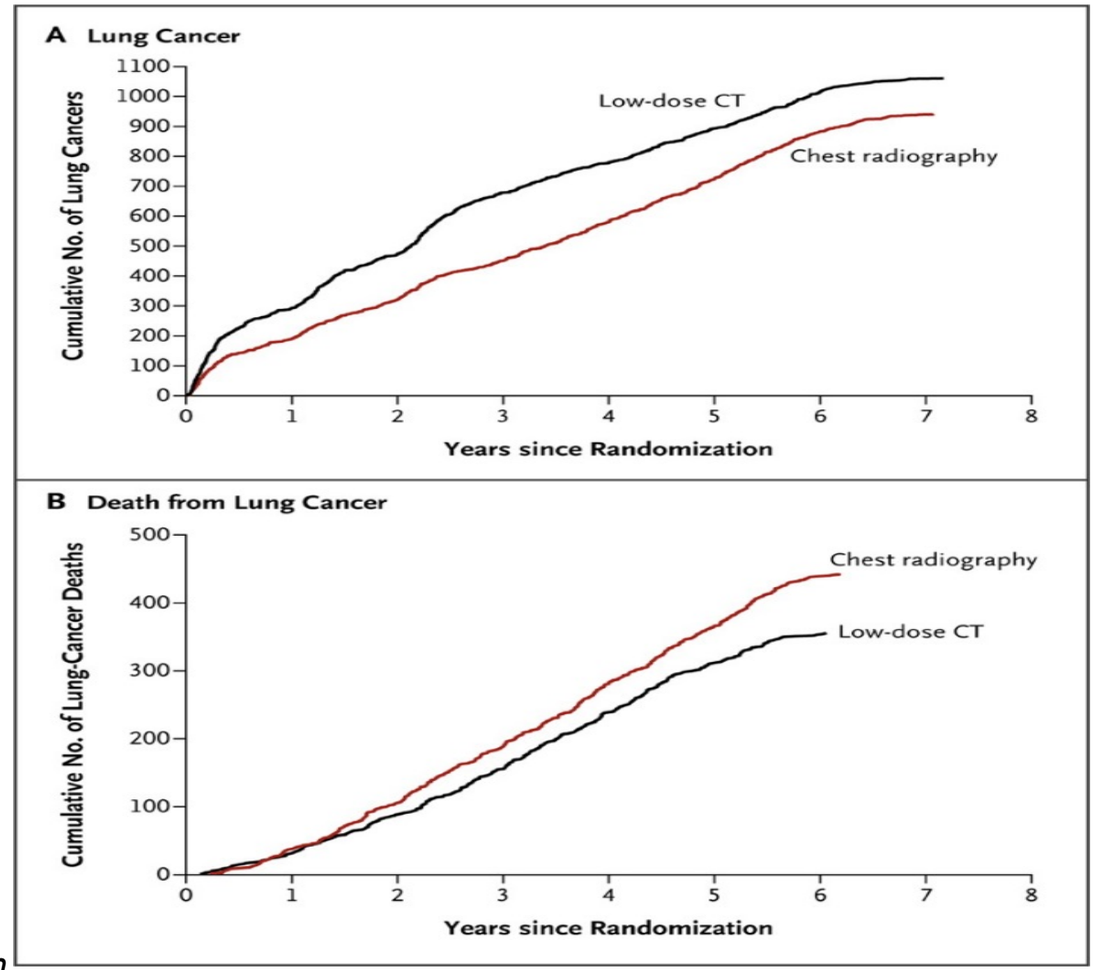
- African Americans were significantly more likely to fall into a risk “cluster” characterized by younger age, lower smoking exposure, poorer FEV_1/FVC, but lower quantitative CT measures of emphysema and air trapping.
- Measures of lung function, and subsequent lung cancer risk, vary considerably among smokers and are not fully explained by smoking intensity.
- Combining spirometry and radiologic measures of COPD aid in defining a spectrum of lung disease that predicts lung cancer risk differentially among patient clusters.

Lung cancer screening

National Lung Cancer Screening Trial (NLST)

BARBARA ANN Karmanos CANCER INSTITUTE Wayne State University

- Prospective randomized trial comparing low dose helical computed tomography (CT) to chest radiograph (X-ray), annual scan, 3 years
- Eligibility: ages 55-74, current or former smoker (quit within 15 years), ≥30 pack years of smoking, 41% female
- Results: a relative reduction in the rate of death from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004)



NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

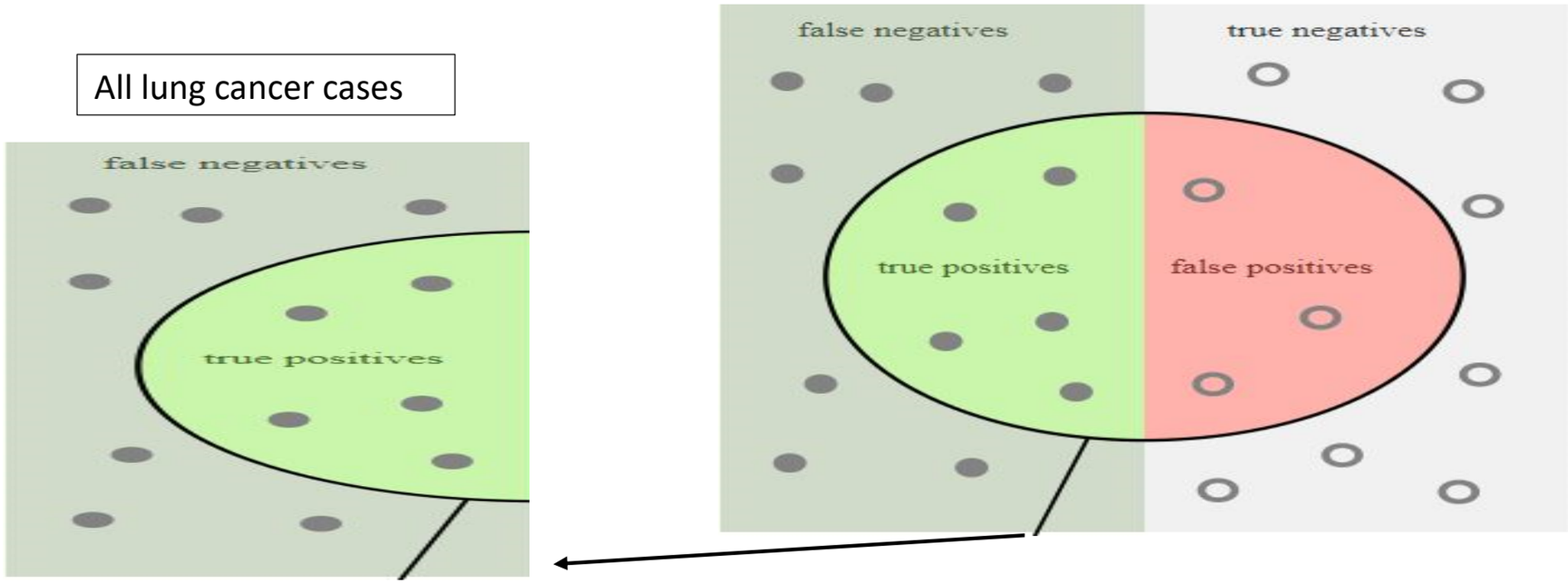
The National Lung Screening Trial Research Team. N Engl J Med 2011;365:395-409

Lung Screening Guidelines

BARBARA ANN Karmanos CANCER INSTITUTE Wayne State University

NLST/NCCN group 1	USPSTF 2013	NCCN group 2	USPSTF 2021	PLCOm2012
Age 55 - 74 years ≥ 30 pack-year smoking history Smoking cessation < 15 years.	Age 55 -80 years ≥ 30 pack-year smoking history Smoking cessation < 15 years.	Age ≥ 50 years ≥ 20 pack-year smoking history 1 additional risk factor (other than secondhand smoke). --cancer history --family history of lung cancer --radon exposure --occupational exposure to silica, cadmium, asbestos, arsenic, beryllium, chromium (VI), diesel fumes, and nickel. --chronic obstructive pulmonary disease (COPD) --pulmonary fibrosis	Age ≥ 50 years ≥ 20 pack-year smoking history Smoking cessation < 15 years	Age Race Education BMI COPD Personal history of cancer Family history of cancer Smoking status Smoking intensity Duration of smoking Smoking quit time Risk ≥ 1.51% is used as cut off for screening eligibility

Sensitivity of lung cancer screening eligibility criteria in INHALE



Sensitivity= Cases included by criteria / All lung cancer cases

Pu et al., JAMA Oncol, 2022

Sensitivity of screening eligibility in INHALE lung cancer cases

BARBARA ANN Karmanos CANCER INSTITUTE Wayne State University

Screening Eligibility Guidelines	White n=625	African American n=287	White vs African American	
			RR (95% CI)	p-value
NLST	47.7%	39.7%	1.2 (1.0,1.4)	0.03
USPSTF 2013	51.8%	42.2%	1.2 (1.1,1.4)	<0.01
NCCN group 2	66.7%	50.9%	1.3 (1.2,1.4)	<0.01
USPSTF 2021	65.3%	63.4%	1.0 (0.9,1.1)	0.6
PLCOm2012 ≥ 1.51%	68.4%	66.9%	1.0 (0.9,1.1)	0.7

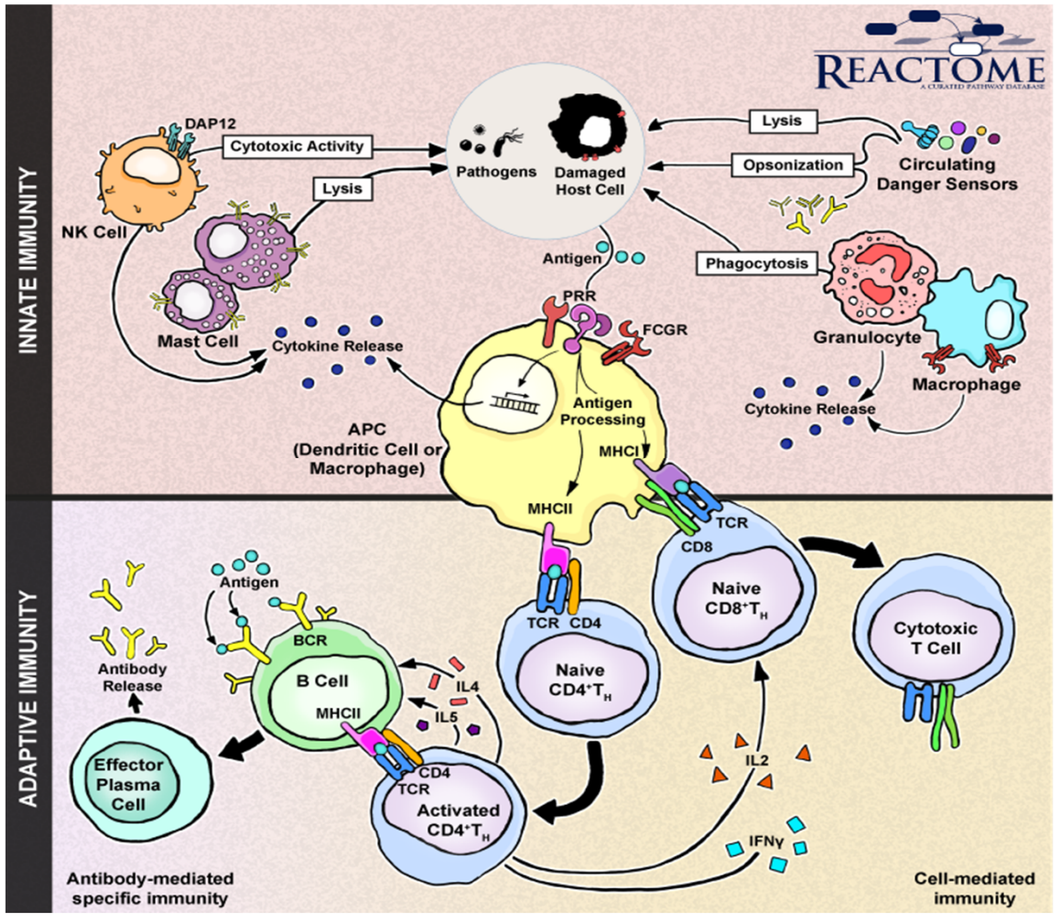
NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Screening conclusions

- African American lung cancer patients are significantly under-represented under USPSTF 2013 and NCCN grp 2 criteria
- USPSTF 2021 and PLCOm2012 guidelines improve on earlier, fixed screening criteria for lung cancer, broadening eligibility and reducing the racial disparity in access to screening
- There are still barriers to screening uptake, with heightened need to increase awareness among primary care physicians and the community

Immune Pathway Gene Expression Signatures in Lung Tumor Tissue

BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University



Is overall survival related to differential gene expression of immune pathways genes? Are there differences by race?

48 Immune-centric Pathways including 8 Major Pathways:
- Adaptive Immunity
- Innate Immunity
- Cytokine Signaling
- Adhesion-Extravasation-Migration
- Programmed Cell Death
- Reactive Oxygen/Nitrogen Generation
- Immune Signaling

~2,253 immune related genes

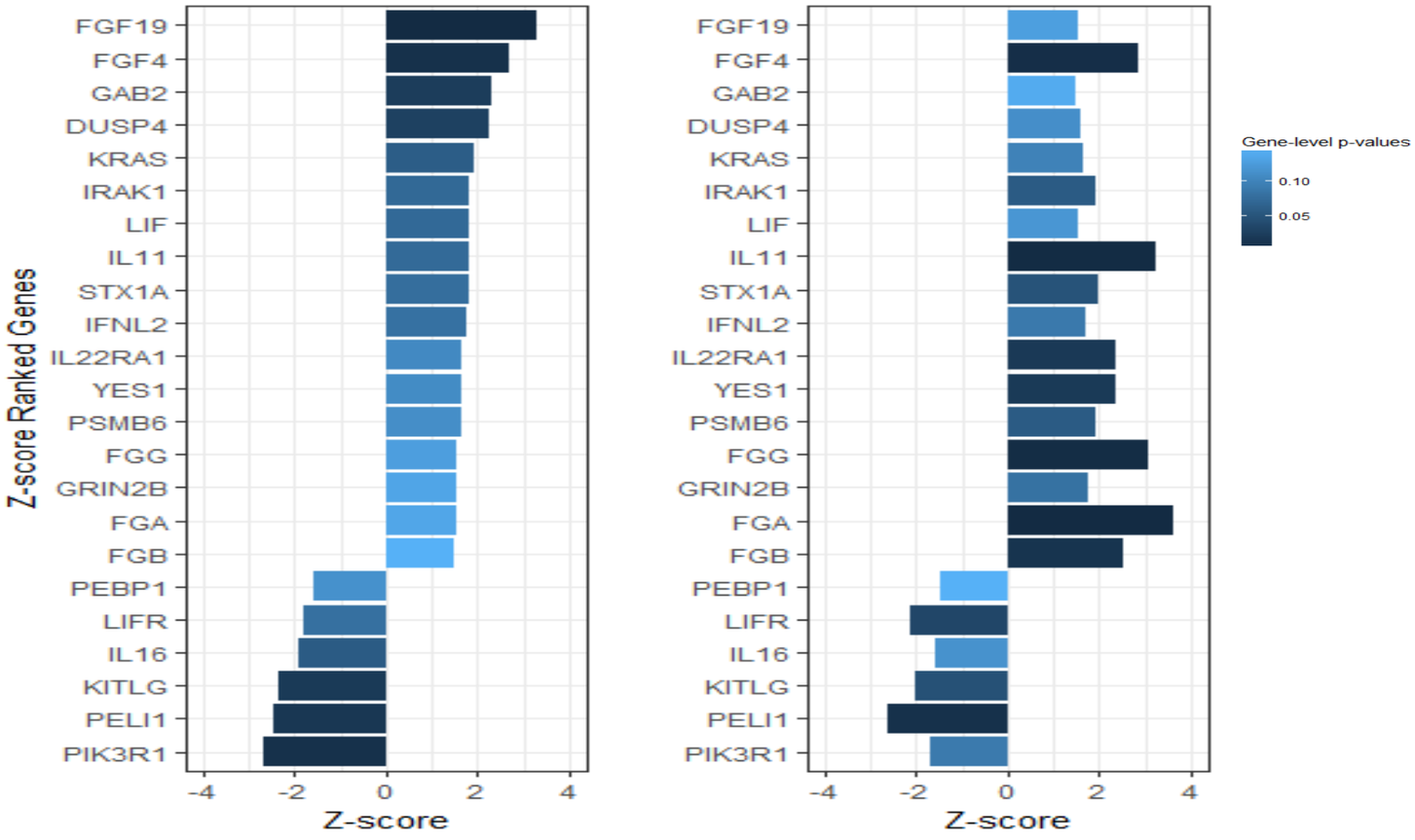
Affymetrix Whole-Transcriptome 2.1 Human Gene Array with 1.3 million probes on 280 lung cancer cases

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Fabregat et al. The Reactome Pathway Knowledgebase. 2018. Nucleic Acids Research

Gene Expression in Lung Tumors Associated with Survival

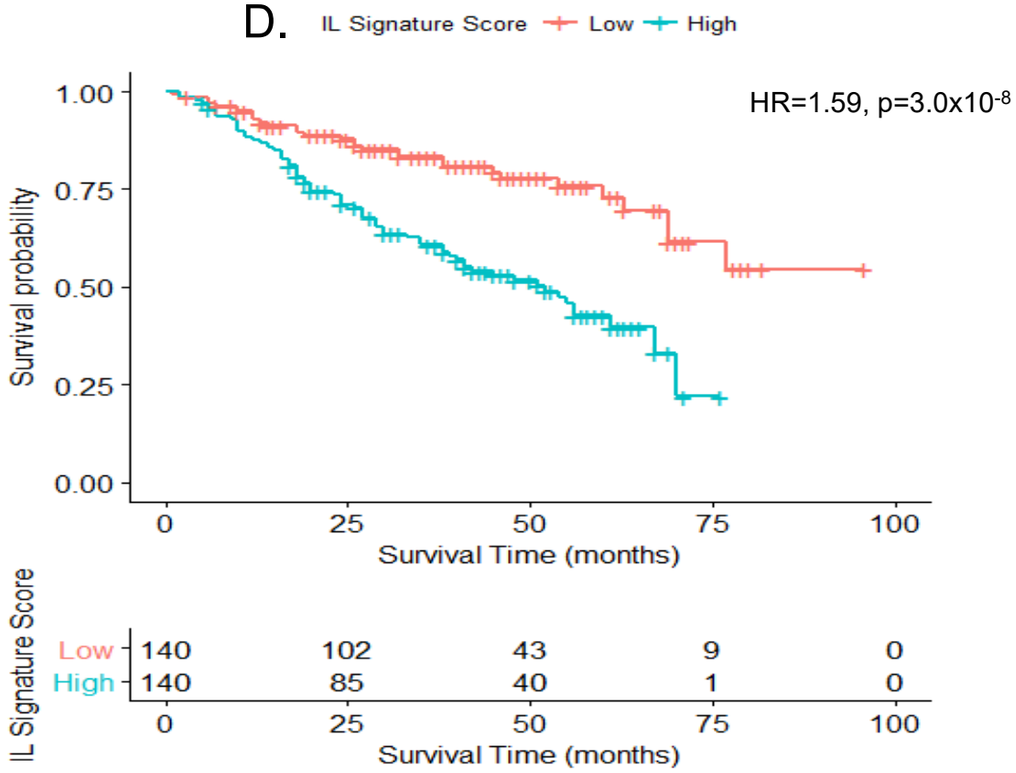
- Gene Set Enrichment Analysis (GSEA) used to measure aggregate gene effects within each immune pathway
- Cox proportional hazards model, adjusted for stage and histology
- Interleukin Signaling pathway genes were significantly associated with survival

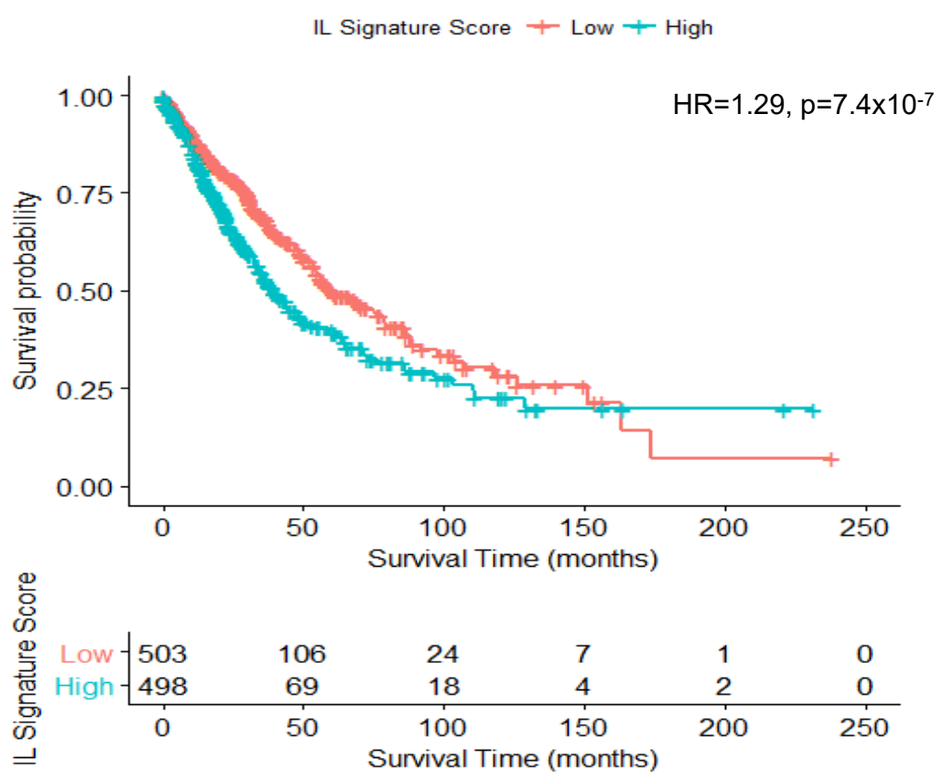


INHALE TCGA

Watza et al., Carcinogenesis, 2018

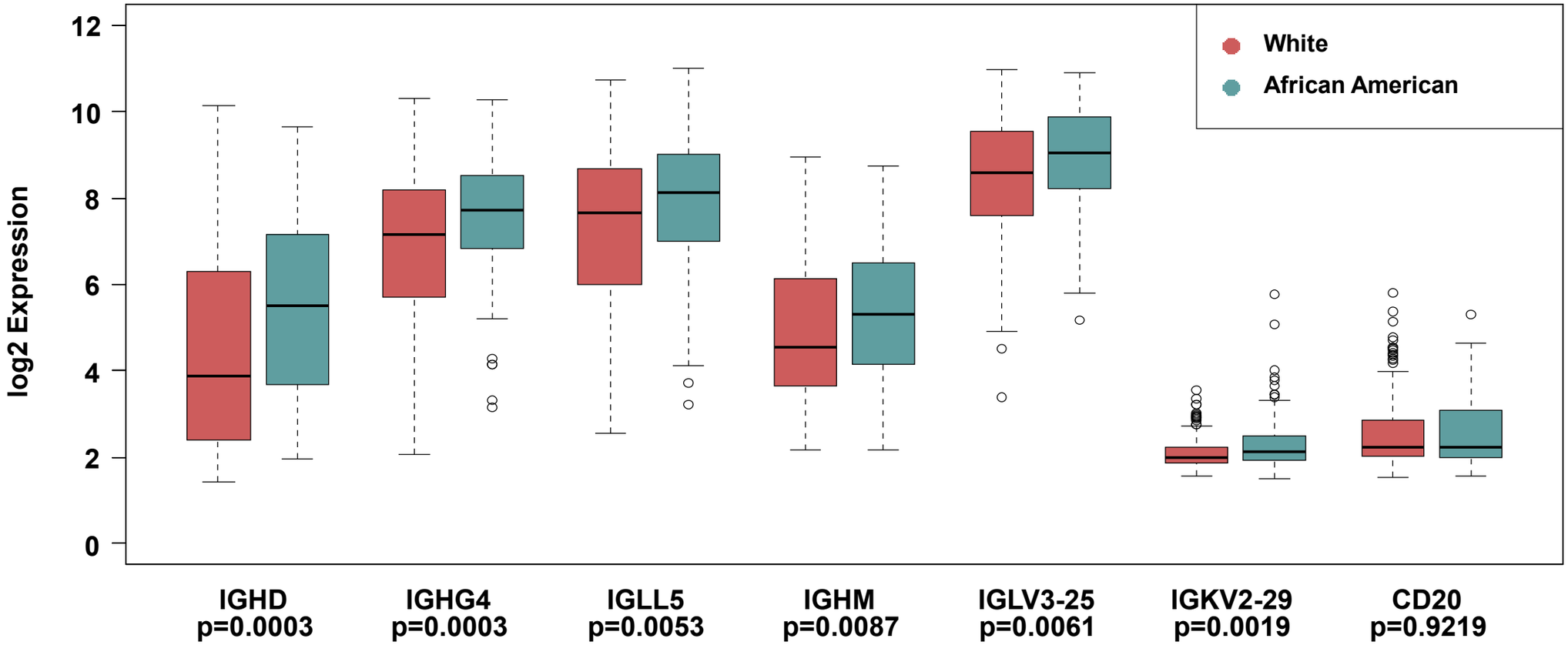
23 Gene Signature and Survival





- "Interleukin signaling" pathway shows prognostic value
- Leading edge 23-gene signature is a predictor of survival

Differential Gene Expression by Race



The most differentially-expressed (by race) immune-related genes make antibodies suggesting that B cell function might be distinct by race

Tertiary Lymphoid Structures

Are TLS related to response to immunotherapy differentially by race?

What other biomarkers are related to immunotherapy differentially by race?

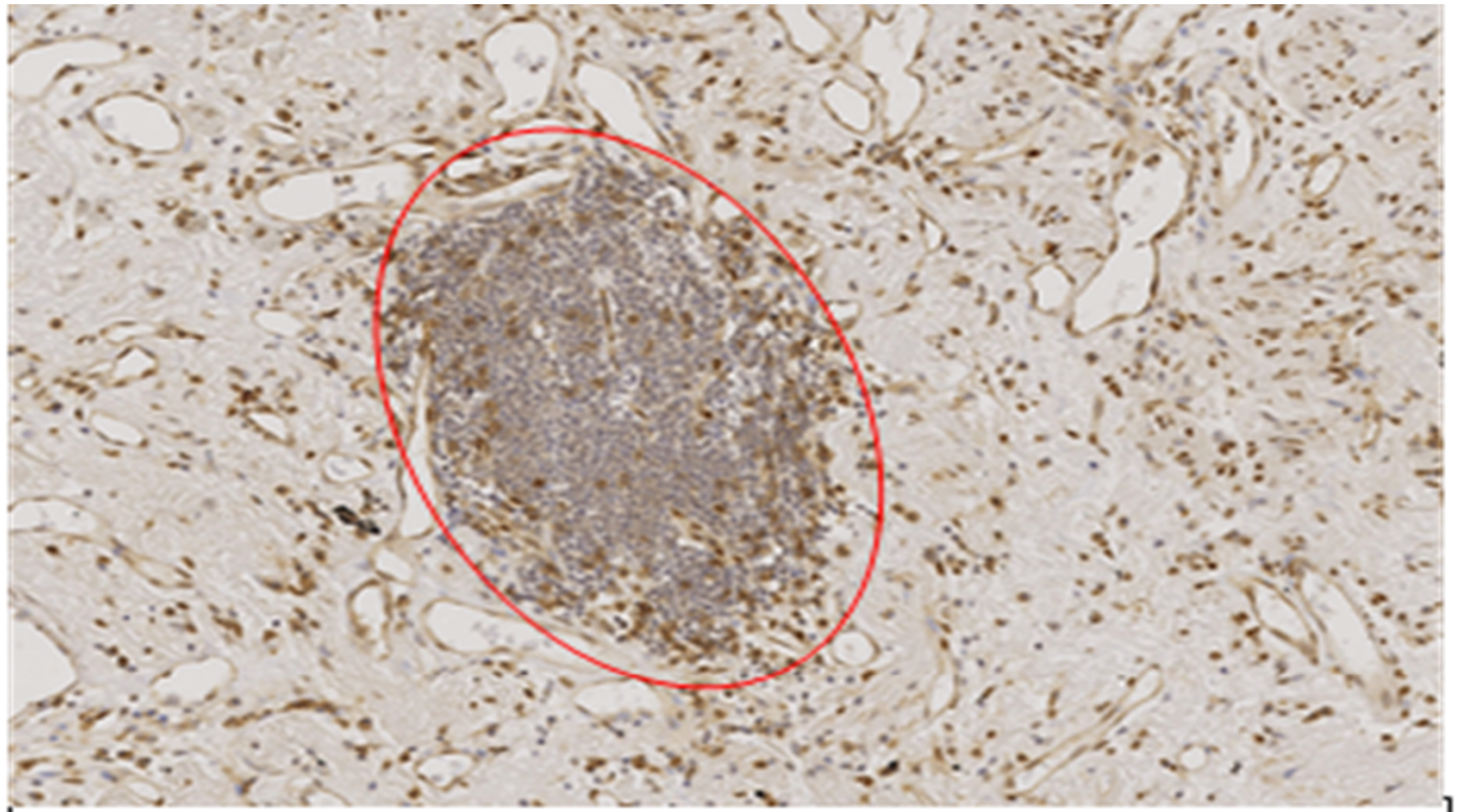


Figure 6. Putative TLS structure (red circle) identified in a CD8-stained (brown) lung cancer tissue section. Hematoxylin (blue) counterstain identifies rich aggregation of CD8+ and CD8- leukocytes.

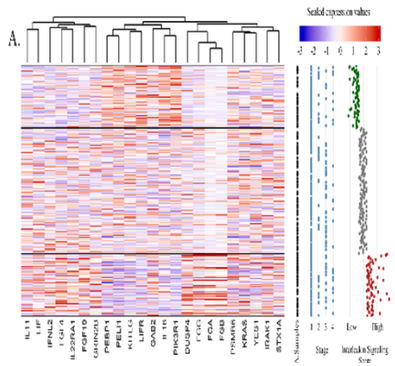
Immunotherapy for Lung Cancer

- Immunotherapy in the form of immune checkpoint inhibitors (ICIs) has been a breakthrough for the treatment of lung cancer.
- ICI's, either as single agents or in combination with platinum-based chemotherapy, are now front line therapy for metastatic non-small cell lung cancer (NSCLC).
- Treatment response varies from 25% to 60%.
- Immunotherapeutic benefit is dictated in part by *imperfect* biomarkers including PD-L1 expression and tumor mutational burden (TMB).
- Little data exist on racial disparities in biomarkers and response to ICIs; only 4% of clinical trials participants were African American

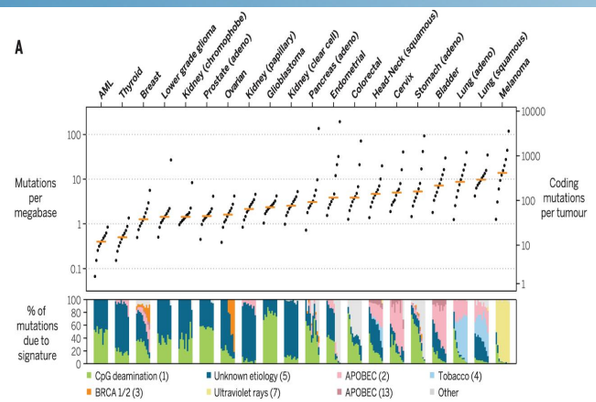
Immune Phenotypes and Outcomes

BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University

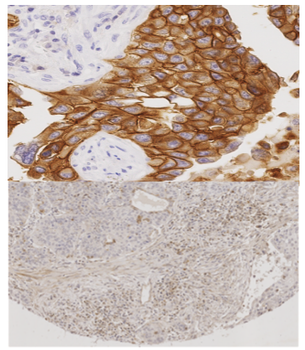
Immune phenotypes



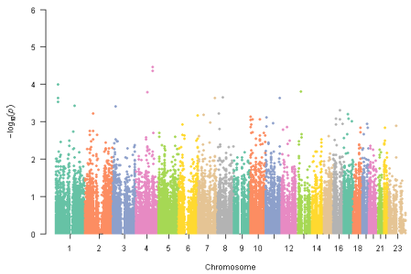
Gene expression clustering



Tumor mutation burden



PD-L1, CTLA4, TILs, TLS



Host genetics

Mediators of immune phenotypes

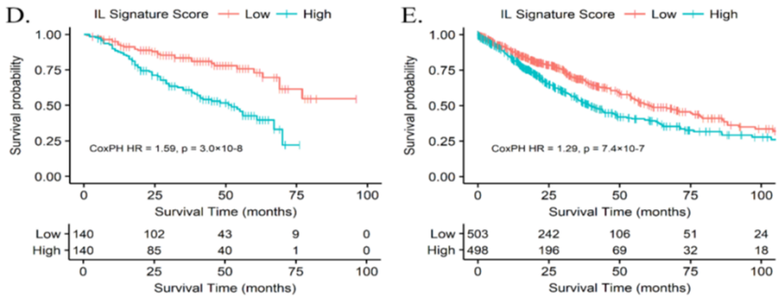
Ancestry

Age, sex, pack-years

P20 SPORE Planning Grant in Health Disparities

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Immune phenotypes as predictors of survival and response to immunotherapy



Biomarkers of ICI response

While INHALE participants were treated pre-immunotherapy, we evaluated the tumor microenvironment for biomarkers of ICI response:

- Tumor mutation burden
- PD-L1, CTLA4, immune pathway gene expression
- Immune cell infiltration
- Tertiary lymphoid structures (TLS)

Summary of immune pathway markers

- Immune signatures in lung cancer differ by race
  - IFN-related signaling
  - B cell function

- Comprehensive analyses needed to tease out race-specific biomarkers in relation to ICI response

- Immune functional analyses may shed light on pathways regulating ICI response
  - Potential biomarkers
  - Potential new drug targets

The Detroit Research on Cancer Survivors (ROCS) Study

BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University

- The largest prospective cohort of African American cancer survivors: breast, prostate, lung, colorectal, and endometrial cancer dxed age 20-79, and any cancer dxed age 20-49; metro Detroit residents at diagnosis
- 5,073 Survivors and 1074 Caregivers enrolled
- Overarching goal to understand the multiplex causes of poorer outcomes in this high-risk population

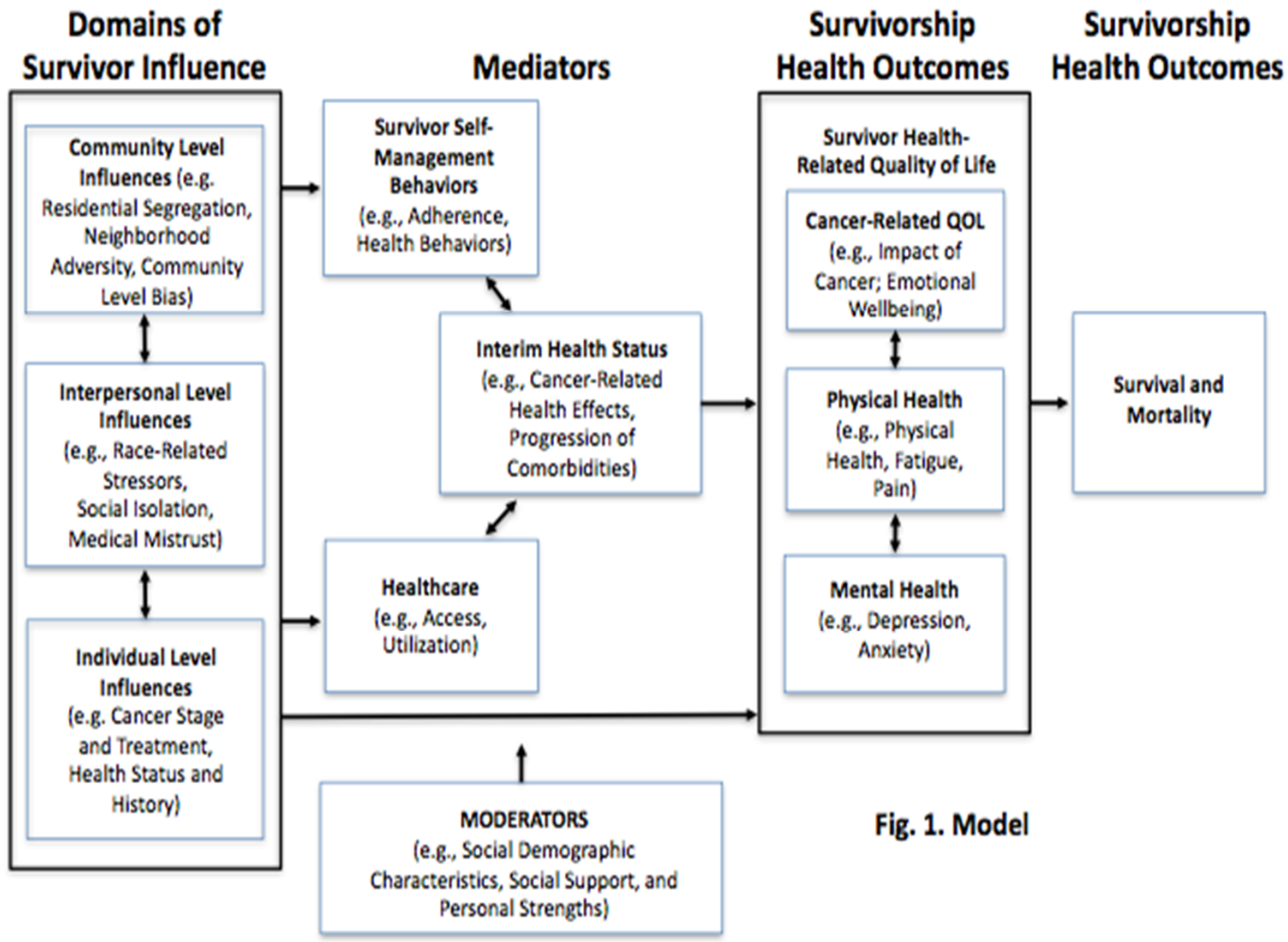
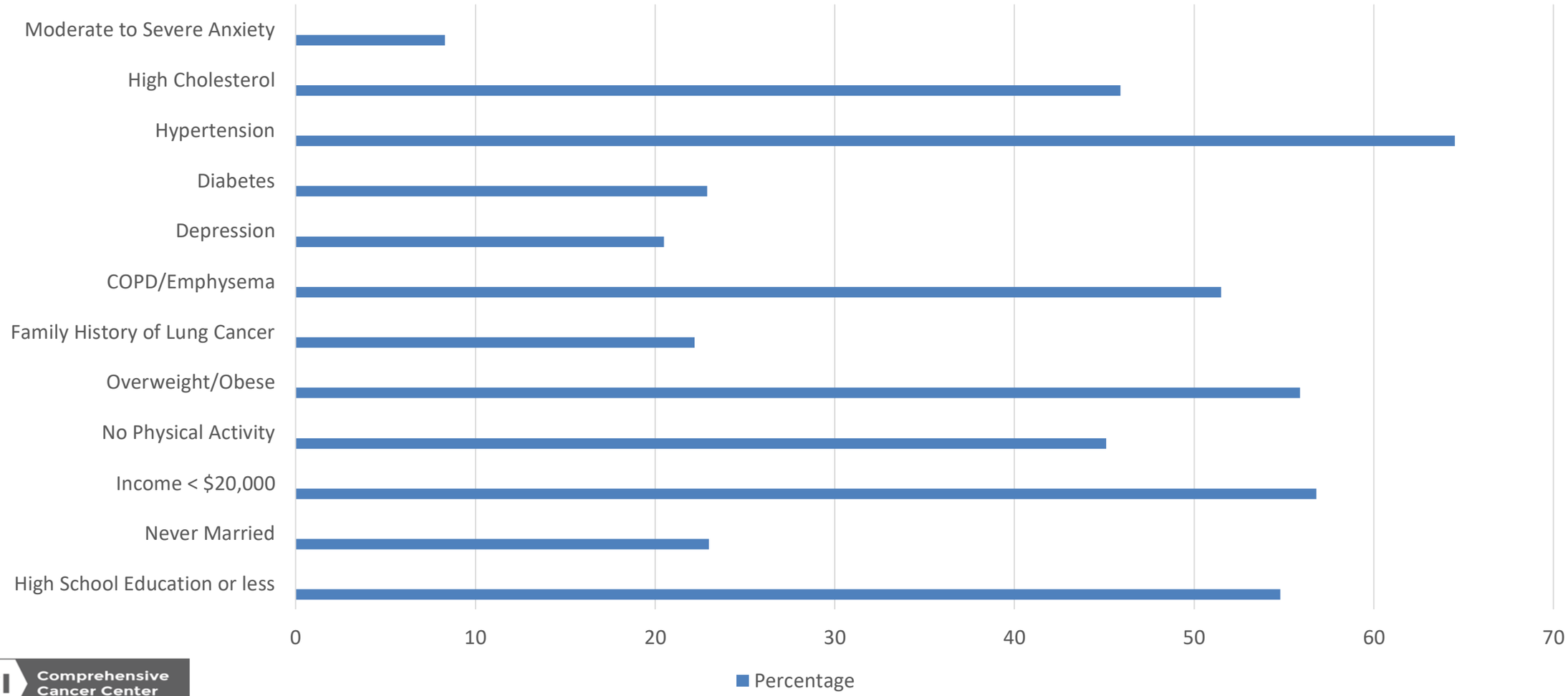


Fig. 1. Model

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

U01 CA199240

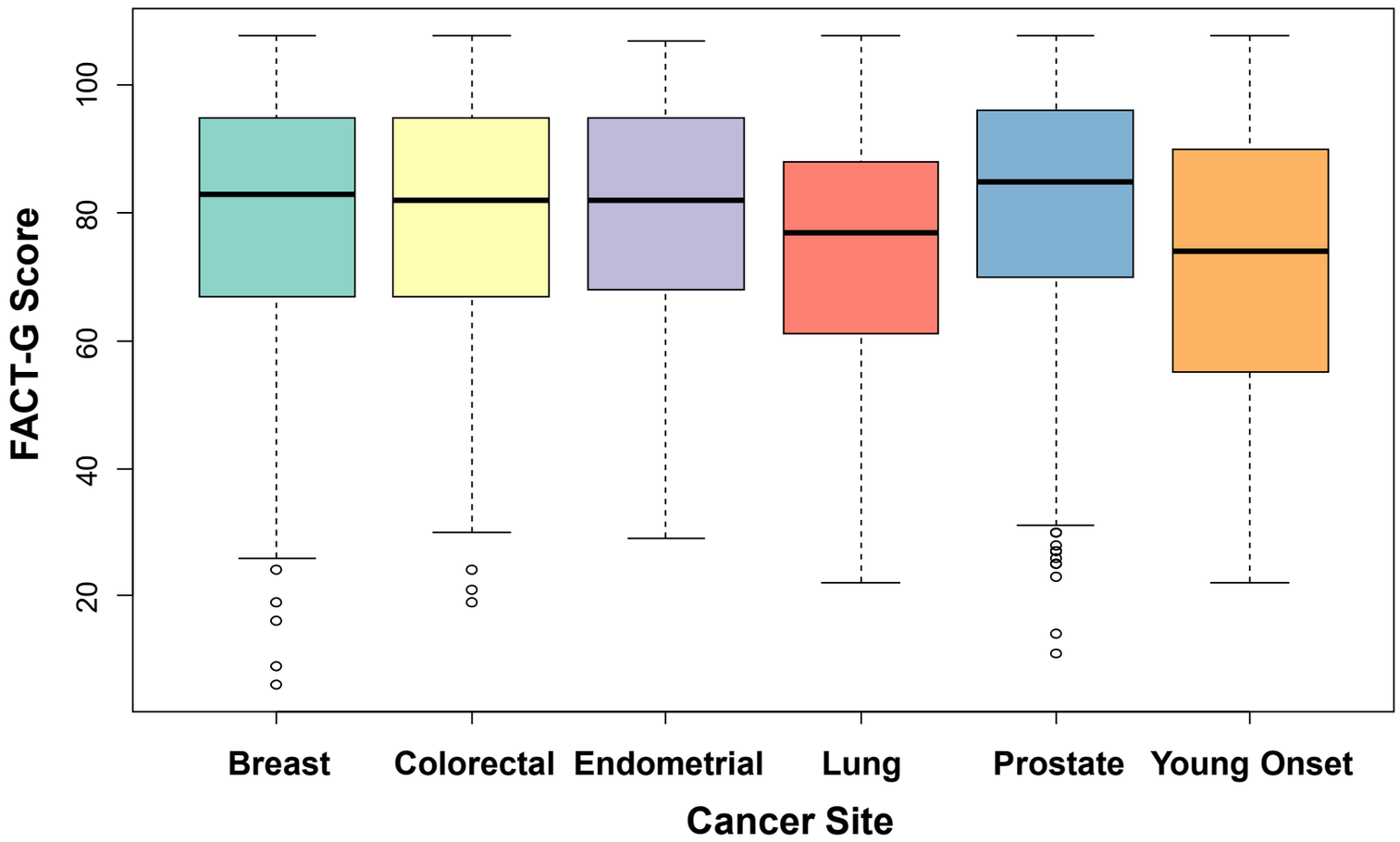
ROCS Lung Cancer Participants



Baseline Quality of Life: FACT-G Total scores

Mean FACT-G scores in cancer patients has been reported to be 82.2 in a population that is 80% white

We see lower scores at baseline, i.e., poorer overall health scores in African Americans with lung cancer.



The Detroit Research on Cancer Survivors (ROCS) Cohort

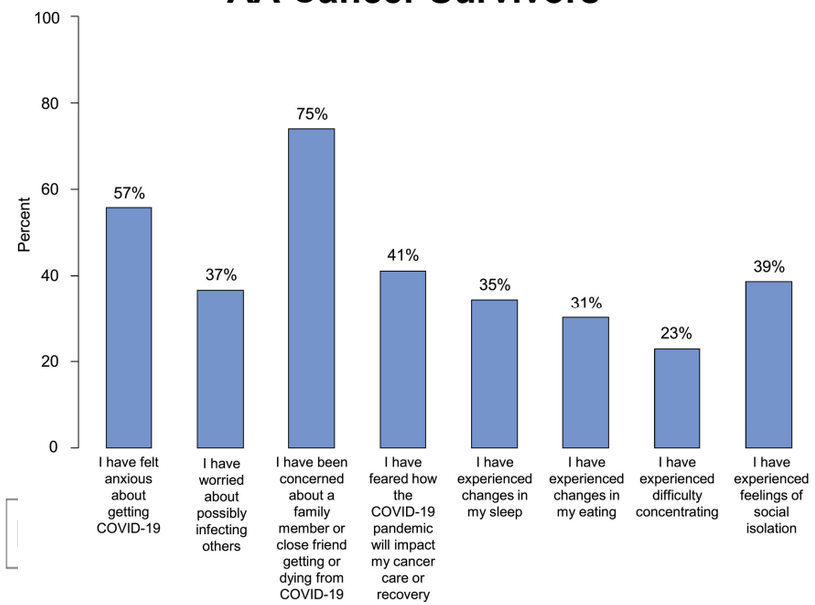
BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University

COVID-19 Supplement

U01CA199240-S3

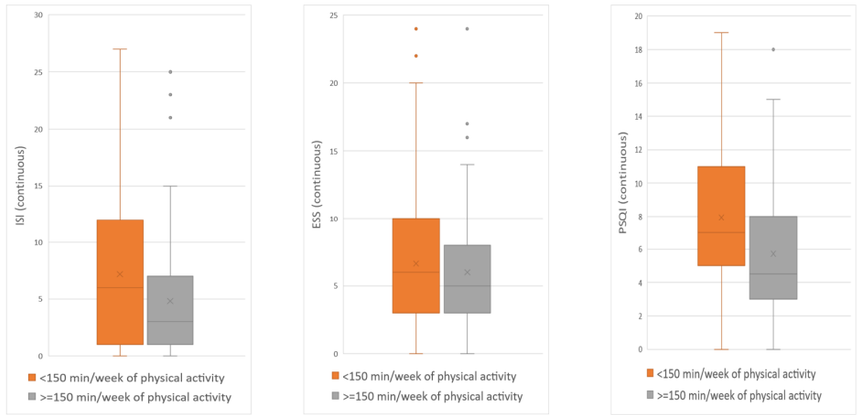
Beebe-Dimmer et al, Cancer 2022 128(4):839-848.

The IMPACT of the COVID-19 Pandemic on AA Cancer Survivors



Sleep Supplement

U01CA199240-S4



p=0.002 p=0.30 p=0.001

Sleep Health & HRQoL

	R^2
Health Behaviors	0.064
Cancer Related	0.127
Demographics	0.174
Comorbidities	0.230
Sleep Health	0.295

Health Behaviors: exercise, fruit/vegetables, alcohol, smoking

Cancer Related: age at diagnosis, months since diagnosis, cancer site, stage, treatment, treatment status

Demographics: sex, education, marital status, income, poverty, insurance

Comorbidities: arthritis, COPD/emphysema, depression, diabetes, heart condition, hepatitis, high cholesterol, hypertension, stroke, thyroid, obesity

Sleep Health: ISS, ESS, PSQI

CIDR funding

X01 HG12908

Germline Whole Exome Sequencing of ~2,400 African American Cancer Survivors

- Use bioinformatics, family structure, gene expression and somatic alterations to characterize VUS.
- Characterize germline genetic variants associated with multiple primary cancers.
- Develop an online educational intervention to increase risk-appropriate genetic testing in African Americans.

Acknowledgements

Yvonne Bush
Lynda Forbes
Chrissy Lusk, MPH
Kelly Montgomery
Dominika Mazzola
Valerie Murphy
Stephanie Pandolfi, PhD
Bridget Reno
Julie Ruterbusch, MPH
Alicia Salkowski, MS
Angie Wenzlaff, MPH
Dave Pandolfi

Donovan Watza, MD, PhD
Heather Gibson, PhD
Hirva Mamdani, MD
Shirish Gadgeel, MD
Ayman Soubani, MD
Fulvio Lonardo, MD
Greg Dyson, PhD
Felicity Harper, PhD
Hayley Thompson, PhD
Jennifer Beebe-Dimmer, PhD
Kristen Purrington, PhD
Michele Cote, PhD

NIH Grants/contracts: R01CA141769, R01CA60691, P20CA262735, R01CA87895, P30CA022453, Herrick Foundation