Integrating social and genomic landscapes to reduce cancer outcome disparities

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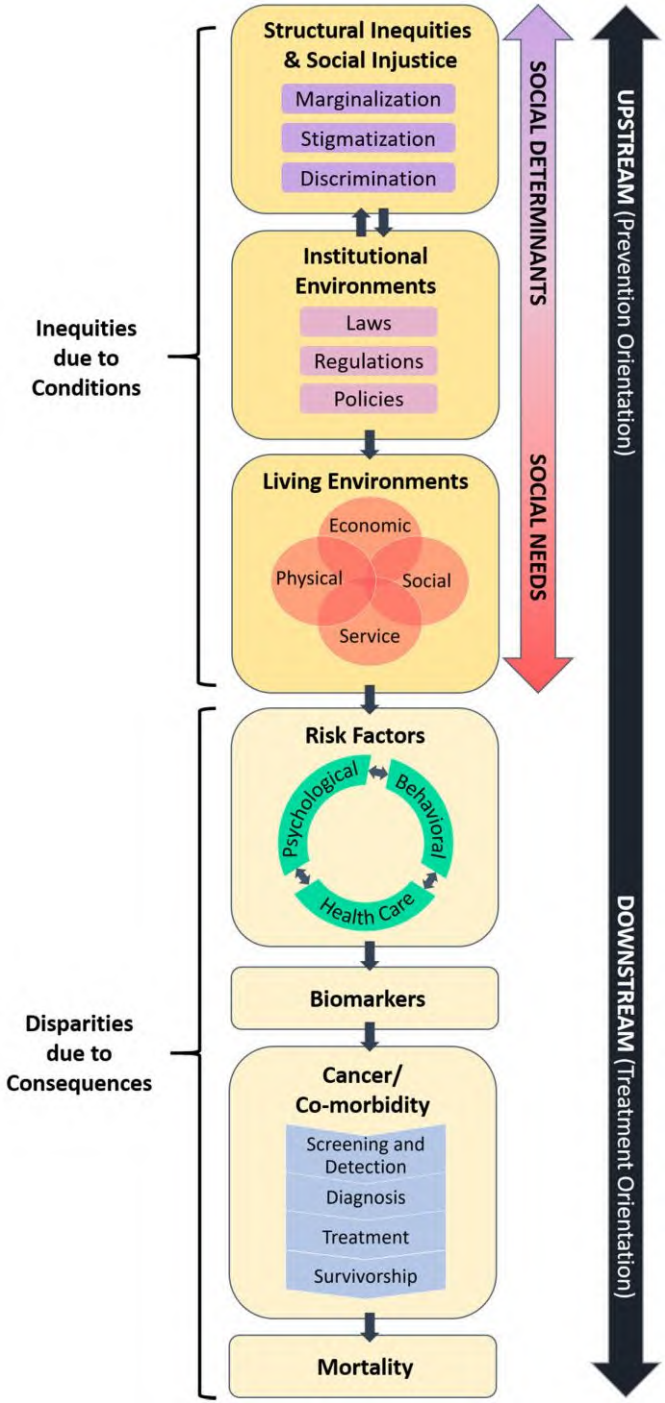
Structural racism is a critical social determinant of health.

It is a current public health issue.

It is a result of injustice.



Alcaraz K.I. et al. (2020), Understanding and addressing social determinants to advance cancer health equity in the US: A blueprint for practice, research, and policy. CA A Cancer J Clin, 70: 31-46.

Non-Small Cell Lung Cancer (NSCLC) Outcome Disparities

- Non-Hispanic Black/African American individuals develop NSCLC 5 years earlier than non-Hispanic White individuals.
- African Americans have higher NSCLC incidence and mortality rates than their non-Hispanic white counterparts.

- Black women in the US who never smoked have a higher incidence of NSCLC compared with non-smokers of European and Asian descent.
- Additionally, Black women who never smoked have higher mortality from NSCLC when compared to never smoking women of other races.

- As a result of structural racism in the US, Black communities have disproportionately higher exposure to adverse neighborhood-level factors, many of which are linked to lung cancer risk.

Yang R, Cheung MC, Byrne MM, et al. Do racial or socioeconomic disparities exist in lung cancer treatment? *Cancer.* 2010;116(10):2437-2447.
DeSantis CE, Miller KD, Goding Sauer A, Jemal A, Siegel RL. Cancer statistics for African Americans, 2019. *CA Cancer J Clin.* 2019;69(3):211-233.
Lee Y-C, Calderon-Candelario RA, Holt GE, Campos MA, Mirsaeidi M. State-Level Disparity in Lung Cancer Survival in the United States. *Frontiers in Oncology.* 2020;10(1449).
American Cancer Society. Cancer Facts & Figures for African Americans 2019-2021. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-facts-and-figures-for-african-americans/cancer-facts-and-figures-for-african-americans-2019-2021.pdf. Pub 2019. Accessed August 13, 2021.

Residential Segregation and risk of lung cancer

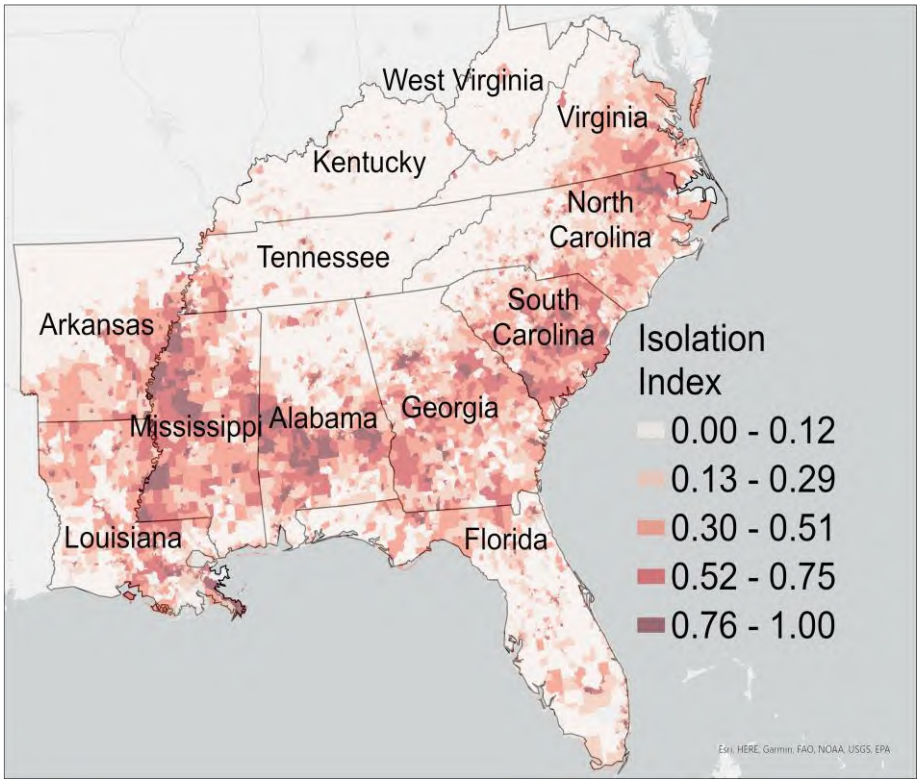
- Established in 2001, the Southern Community Cohort Study (SCCS) is a prospective cohort of more than 80,000 individuals from 12 southern states.

- Participants:
  - 71,644 individuals previously recruited to SCCS were included in the analysis

- Data collection
  - Outcome: Incident lung cancer cases (via linkage to state cancer registries & National Death Index)
  - Exposure: **Isolation Index** - (ranging from 0 to 1), with higher scores indicating a greater degree of isolation. The census block calculations were based on Census 2010 SF1 P3 data tables linked to participants' addresses that were provided at baseline.
  - Covariates: Demographics, Smoking Status, Secondhand Smoke Exposure

- Statistical Method: Parametric G computation, Mediation Analysis

The distribution of the Isolation Index within the SCCS catchment (12 states)



Demographic characteristics of the Southern Community Cohort Study

	Overall, N = 71,634[1]	NHW, N = 20,736[1]	AA, N = 50,898[1]	p-value[2]
Lung cancer cases	**1,727 (2.4%)**	**566 (2.7%)**	**1,161 (2.3%)**	**<0.001**
Isolation Index	**0.65 (0.26, 0.90)**	**0.15 (0.04, 0.39)**	**0.81 (0.55, 0.94)**	**<0.001**
$PM_{2.5}$ (ug/ml)	**10.88 (9.86, 12.02)**	**10.44 (9.35, 11.90)**	**11.02 (10.09, 12.04)**	**<0.001**
(missing)	325 (0.5%)	195 (0.9%)	130 (0.3%)	
Sex				**<0.001**
Female	42,032 (59%)	12,561 (61%)	29,471 (58%)	
Male	29,602 (41%)	8,175 (39%)	21,427 (42%)	
Smoking Status				**<0.001**
Current	30,092 (42%)	8,120 (39%)	21,972 (43%)	
Former	15,725 (22%)	5,673 (27%)	10,052 (20%)	
Never	25,817 (36%)	6,943 (33%)	18,874 (37%)	
Age	**50 (45, 57)**	**52 (46, 59)**	**50 (45, 56)**	**<0.001**
Educational Attainment				**<0.001**
Less than 9 years	5,687 (7.9%)	1,674 (8.1%)	4,013 (7.9%)	
HS or below college	43,534 (61%)	11,191 (54%)	32,343 (64%)	
College and above	22,372 (31%)	7,861 (38%)	14,511 (29%)	
Not Reported	41 (<0.1%)	10 (<0.1%)	31 (<0.1%)	
Household Income Attainment				**<0.001**
Less than $15,000	40,004 (56%)	9,831 (47%)	30,173 (59%)	
At least $15,000 but less than $25,000	15,147 (21%)	3,862 (19%)	11,285 (22%)	
At least $25,000 but less than $50,000	9,578 (13%)	3,337 (16%)	6,241 (12%)	
$50,000 and more	6,007 (8.4%)	3,418 (16%)	2,589 (5.1%)	
Not Reported	898 (1.3%)	288 (1.4%)	610 (1.2%)	
Second-hand Smoke Exposure at home				**<0.001**
No	45,145 (63%)	13,005 (63%)	32,140 (63%)	
Yes	24,026 (34%)	6,843 (33%)	17,183 (34%)	
Not Reported	2,463 (3.4%)	888 (4.3%)	1,575 (3.1%)	
Second-hand Smoke Exposure at other places				**<0.001**
No	42,411 (59%)	12,729 (61%)	29,682 (58%)	
Yes	26,453 (37%)	7,002 (34%)	19,451 (38%)	
Not Reported	2,770 (3.9%)	1,005 (4.8%)	1,765 (3.5%	

Note:
[1]n (%); Median (IQR)
[2]Pearson's Chi-squared test; Wilcoxon rank sum test

Risk ratio of estimated 17-year cumulative risk of lung cancer under different threshold compared with natural course

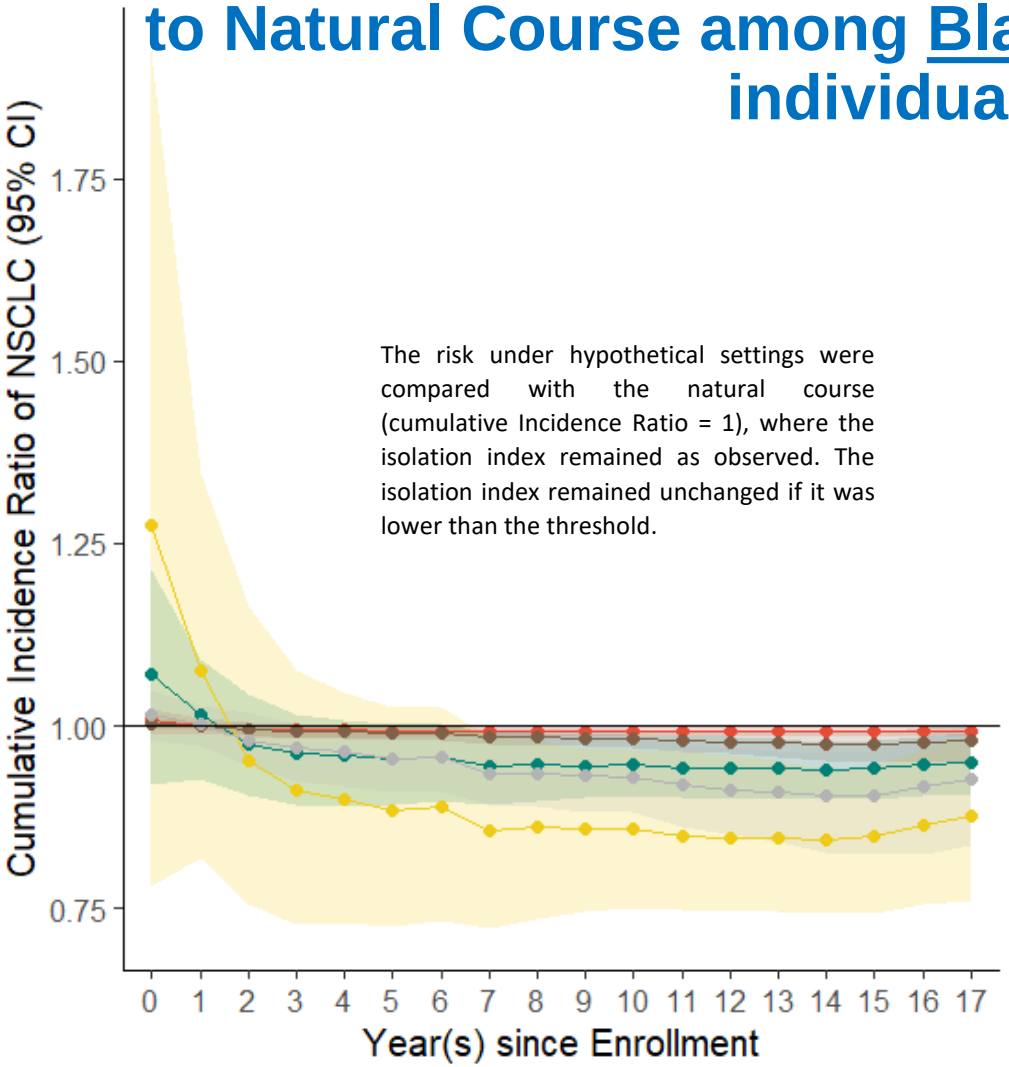
Parametric g-computation is a novel causal inference method that can be used to estimate the effect of a policy, intervention, or treatment. Unlike standard regression approaches, it can be used to adjust for time-varying confounders that are affected by prior exposures.

	African American	Non-Hispanic White
REF	REF	REF
Threshold value	Incidence ratio (95% CI)	Incidence ratio (95% CI)
0.90	**0.9928 (0.9862, 0.9983)**	0.9997 (0.9991, 1.0001)
0.65	**0.9508 (0.9059, 0.9904)**	0.9959 (0.9866, 1.0037)
0.26	**0.8765 (0.7617, 0.9882)**	0.9892 (0.9494, 1.0386)
Percentage Reduction each year (%)		
1	**0.9804 (0.9534, 0.9996)**	0.9973 (0.9831, 1.0124)
5	**0.928 (0.8364, 0.9998)**	0.9944 (0.9415, 1.0549)

Note: 1. All models were adjusted by time-varying variable **$PM_{2.5}$ exposure** and time-fixed variables **sex**, **enrollment age, education attainment**, **house income, ever smoker, second-hand smoke exposure at home** and **at other places**.

In the hypothetical treatment, we lowered the isolation index by a fixed percentage or to the threshold value for those above the threshold to estimate the risk of lung cancer in less segregated scenarios.

Cumulative Incidence Ratio of Lung Cancer and 95% CI Comparing Different Strategies to Lower Isolation Index to Natural Course among Black/African American individuals



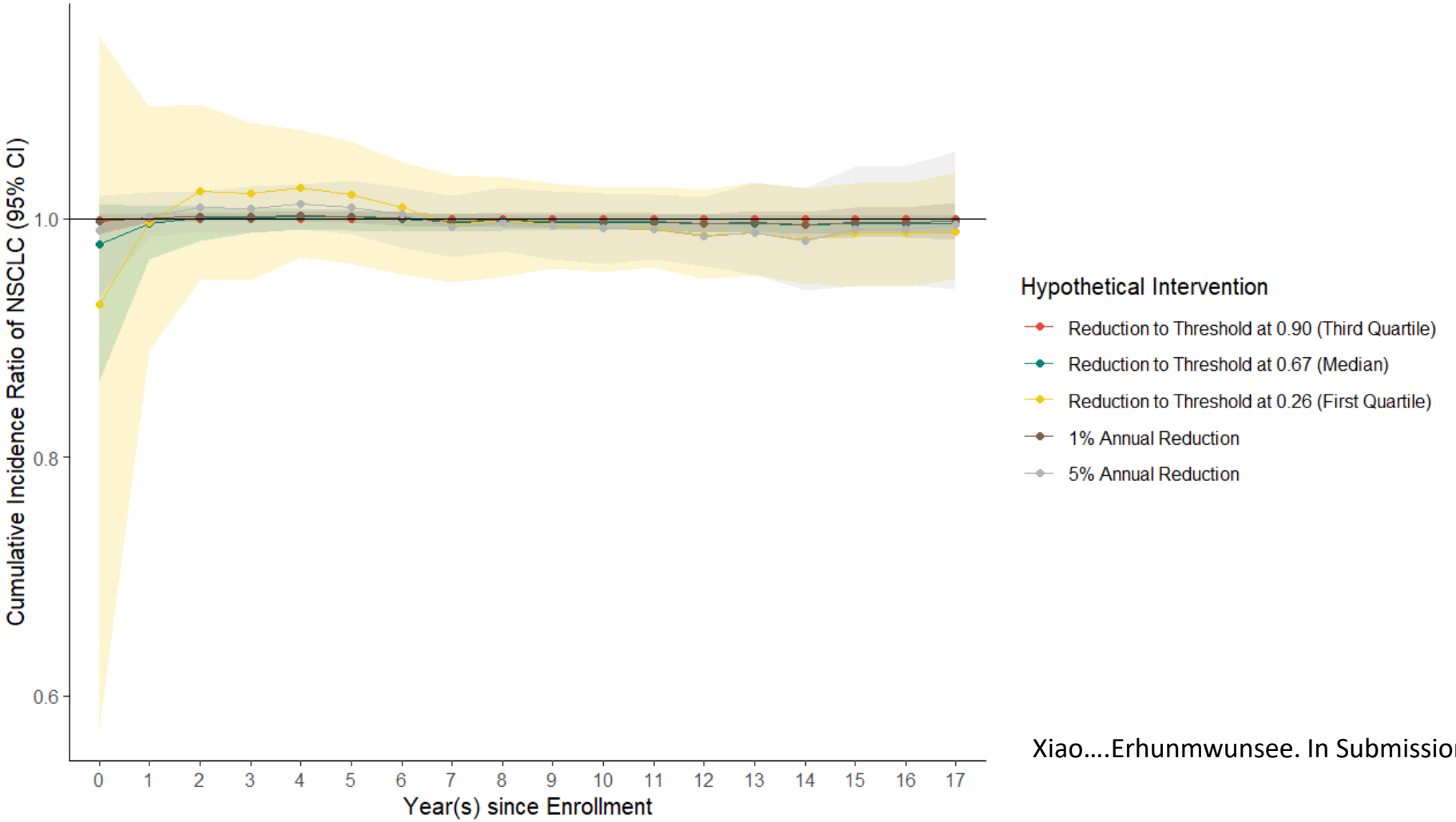
The risk under hypothetical settings were compared with the natural course (cumulative Incidence Ratio = 1), where the isolation index remained as observed. The isolation index remained unchanged if it was lower than the threshold.

Hypothetical Intervention

- Reduction to Threshold at 0.90 (Third Quartile)
- Reduction to Threshold at 0.67 (Median)
- Reduction to Threshold at 0.26 (First Quartile)
- 1% Annual Reduction
- 5% Annual Reduction

Solid line is cumulative incidence ratio estimate, with shaded areas showing 95% CIs. Cumulative incidence ratio below 1 suggests lower risk of lung cancer with the isolation index reduced to the threshold value compared to the natural course.

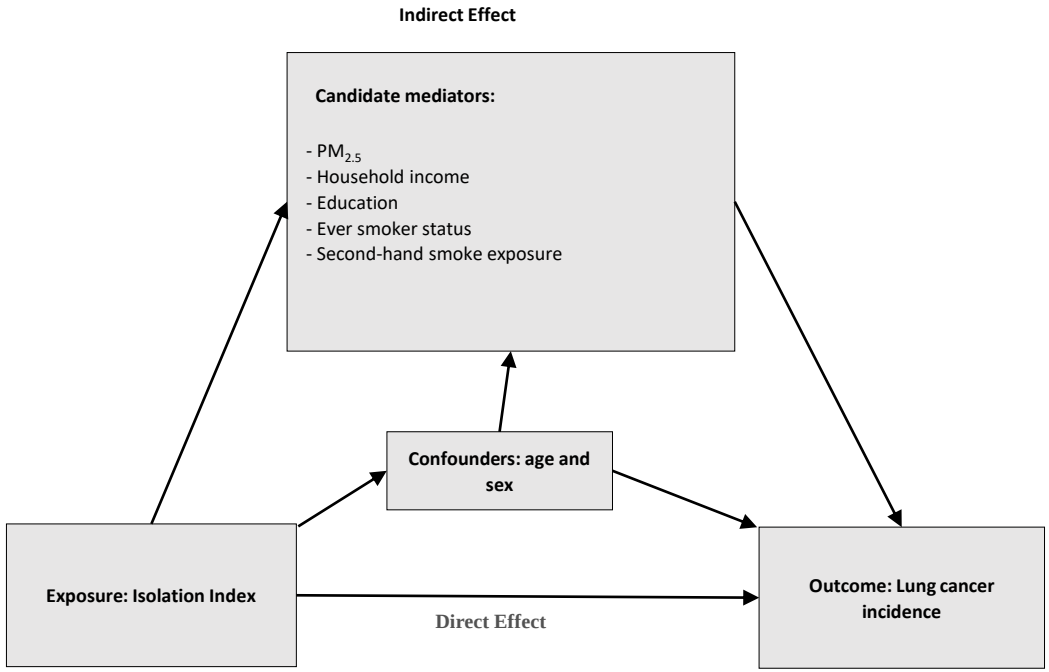
Cumulative Incidence Ratio of Lung Cancer and 95% CI Comparing Different Strategies to Lower Isolation Index to Natural Course among non Hispanic white individuals



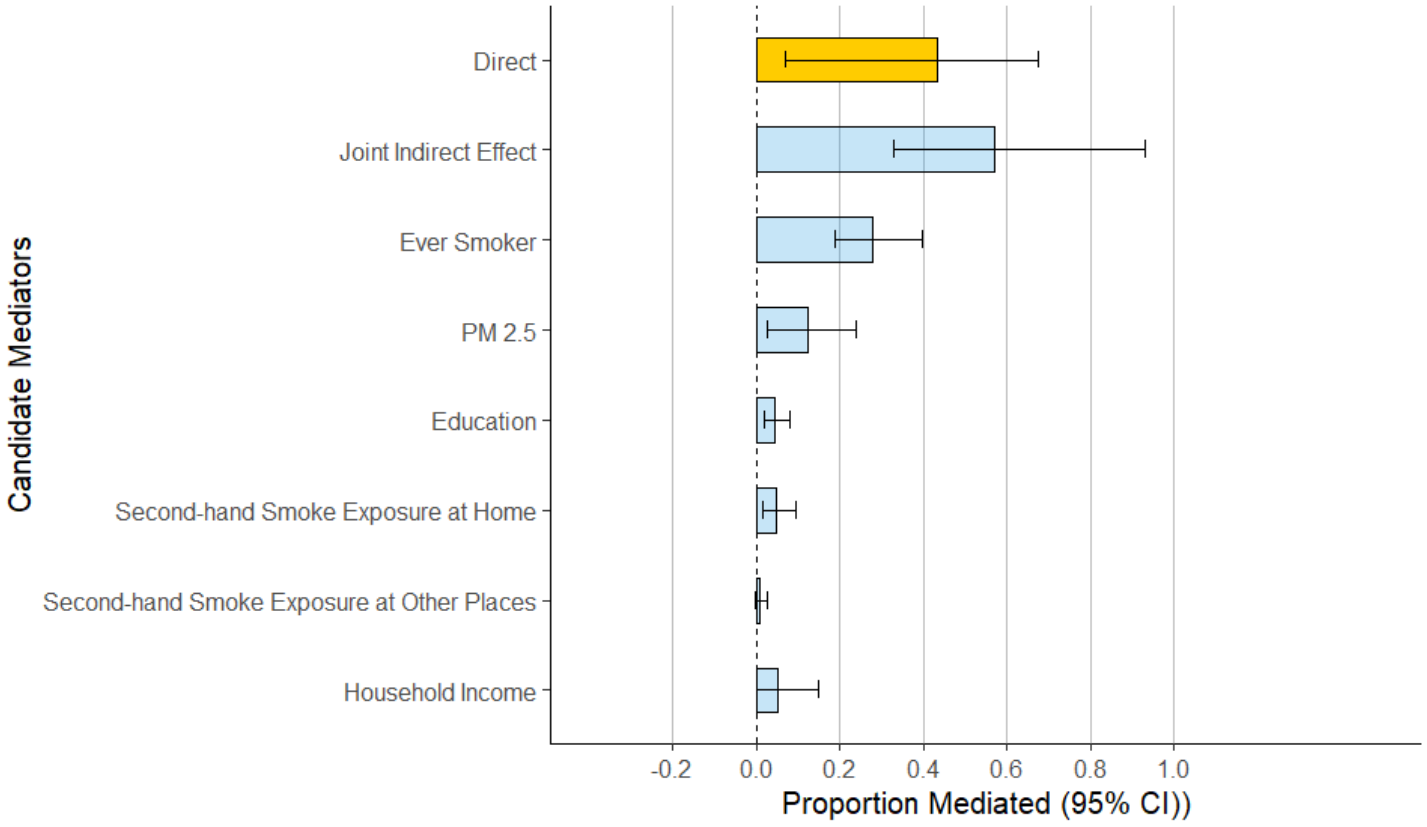
Xiao….Erhunmwunsee. In Submission.

Mediation Analysis

Directed Acyclic Graph (DAG) depicting the causal relationships between isolation index and lung cancer incidence. Age and sex were considered as baseline confounders.



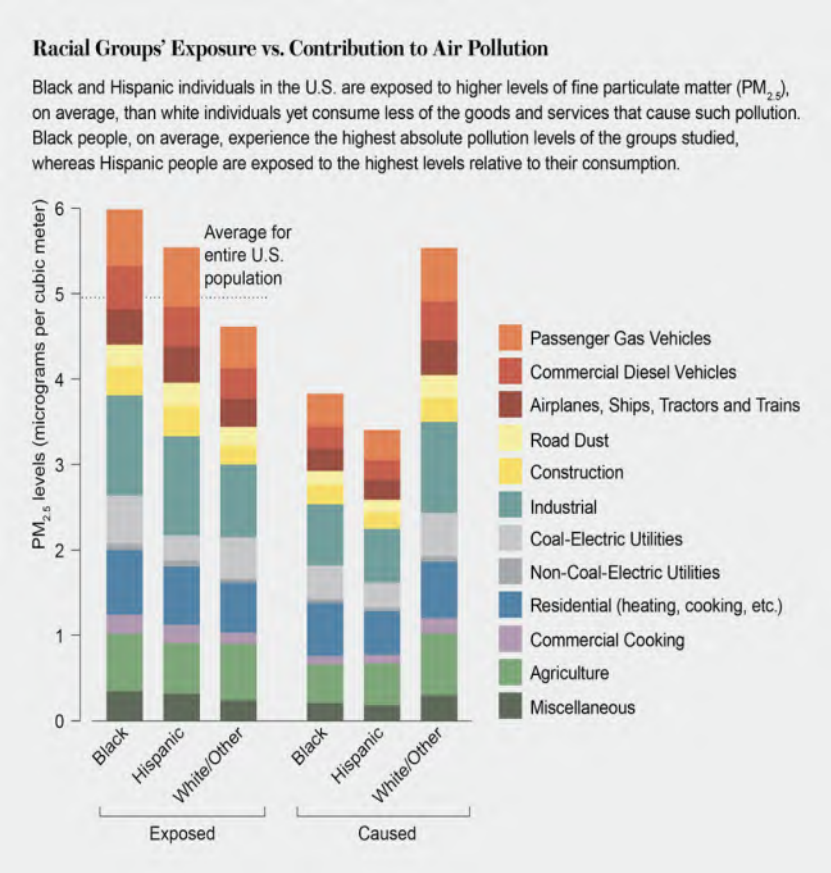
Estimated Proportion Mediated Through Candidate Mediators for the Association between Isolation Index and Lung Cancer Incidence in Black/African American individuals

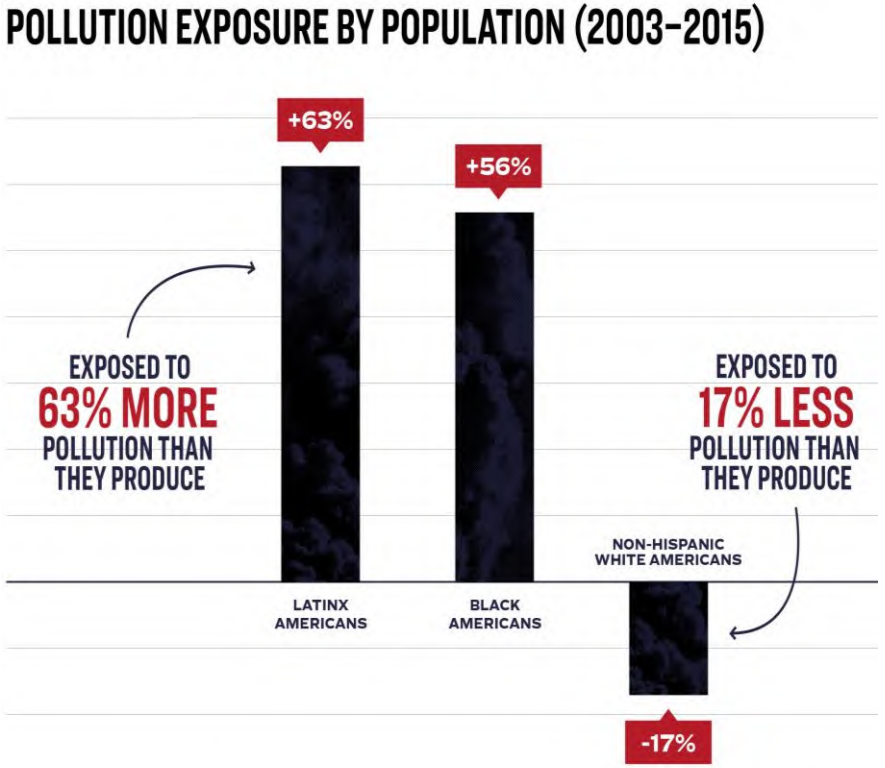


Study Conclusion

- Lower residential segregation significantly decreased lung cancer risk in Black/African American individuals but not in non-Hispanic white individuals.
- Structural racism, driving segregation, likely impacts lung cancer risk through smoking and air pollution exposure.
- These findings suggest the need for policy and research interventions addressing structural racism to reduce lung cancer risk and promote equity in population health.

Race and Ethnicity-based Disparities in Air Pollution Exposure





Source: Christopher W. Tessum et al., "Inequity in consumption of goods and services adds to racial–ethnic disparities in air pollution exposure," Proceedings of the National Academy of Sciences (March 2019).

Credit: Melissa Thomas Baum, Buckyball Design; Source: "Inequity in Consumption of Goods and Services Adds to Racial-Ethnic Disparities in Air Pollution Exposure," by Christopher W. Tessum et al., in *Proceedings of the National Academy of Sciences USA*, Vol. 116, No. 13; March 26, 2019

$PM_{2.5}$ exposure and risk of *TP53* mutation

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION | RESEARCH ARTICLE

The Association between Polluted Neighborhoods and *TP53*-Mutated Non–Small Cell Lung Cancer

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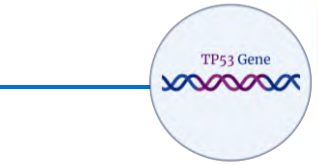
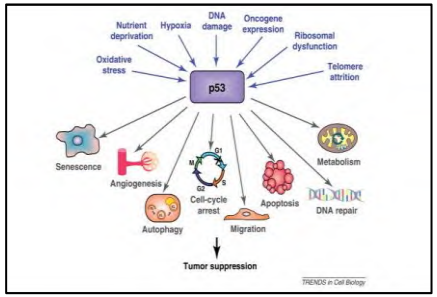
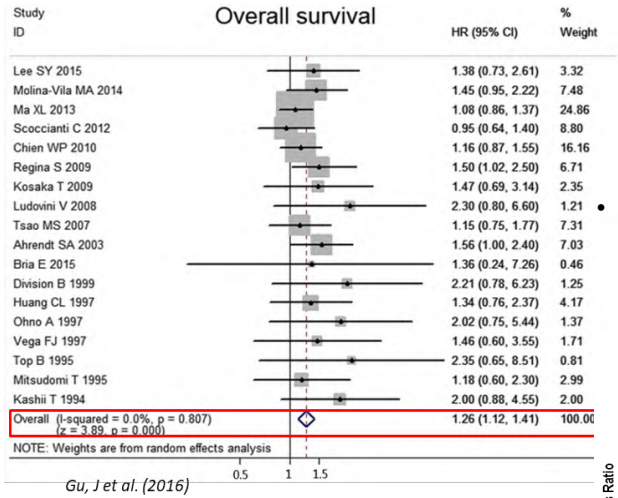


- **Participants: Retrospective cohort:** All adult COH patients with a primary NSCLC diagnosis from 2015-2018
- **Data collection:**
  - **EPA EJ Screen**
    - We used patient addresses to determine environmental exposures to $PM_{2.5}$, ozone, traffic & community demographic data from the EPA environmental justice screen.
  - **Medical Record Abstraction (MRA)**
    - We abstracted demographic, clinical and smoking data from the EMR
- **Statistical Method:** Multiple Logistic Regression

***TP53* mutations**



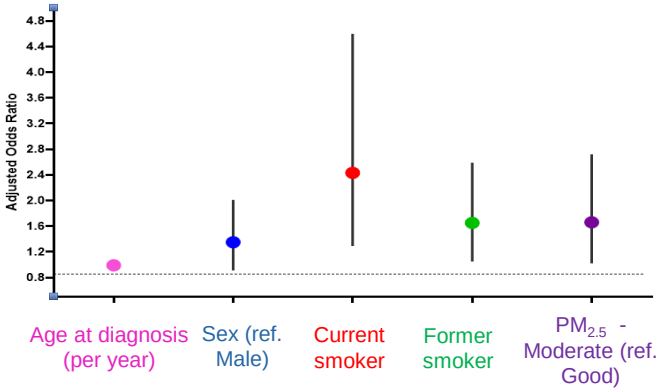
***TP53* is a tumor suppressor whose mutation not only leads to lung cancer but leads to lung cancer with poor survival.**



Gu, J et al. (2016)

In a meta-analysis of NSCLC survival studies, *TP53* mutated patients had a 1.26 hazard ratio for mortality compared to TP53 wildtype.

Adjusted odds ratios of *TP53* mutations



#: Adjusted for metrics of neighborhood-level sociodemographic (i.e. percent minority population and educational attainment less than high school education) and smoking where appropriate

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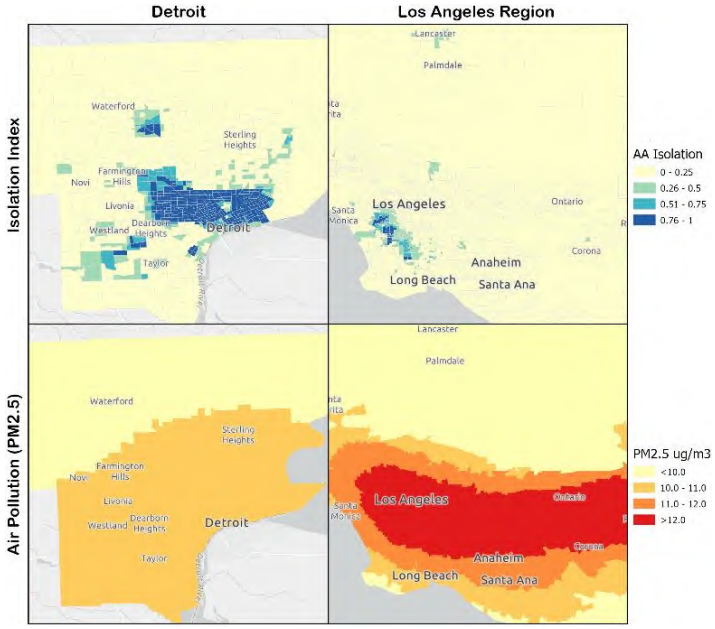
Conclusion: The frequency of *TP53* mutations in NSCLC patients was significantly higher in those who lived in areas with higher pollution levels.

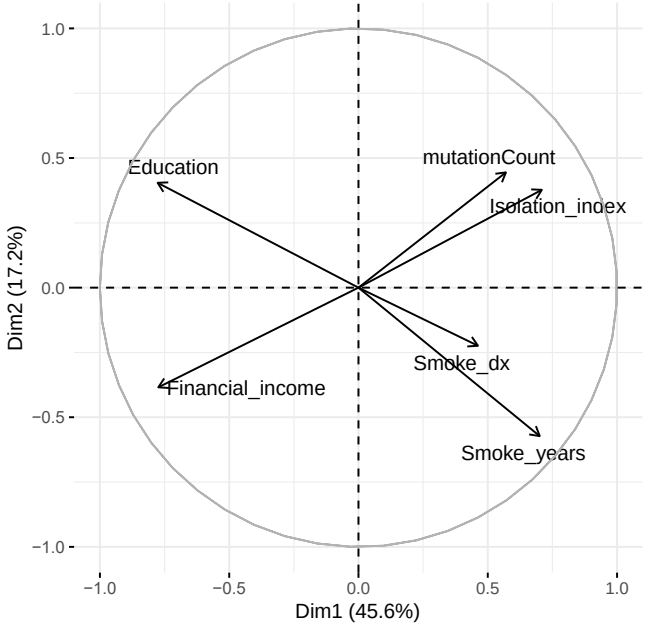
Why do African Americans develop more lethal lung cancers at earlier ages than NHW Americans?



- Tumor biopsies (Stage 1-II NSCLC) and matched blood from AA cancer survivors in Metropolitan Detroit and Los Angeles

Top: Isolation index for AA population compared to other populations computed with 2010 US Census data.
Bottom: $PM_{2.5}$ air pollution from 2015 Environmental Protection Agency EJScreen tool

Pilot WES analysis: residential segregation may be correlated with higher exonal mutational burden



Variable correlation using principal component analysis. Tumor mutation count is positively associated with isolation and negatively associated with financial income. Education is negatively associated with smoke_years. Smoke_years = smoking pack years; Smoke_dx = smoking frequency at time of diagnosis.

r = 0.32 (p = 0.05, isolation index)
r = -0.4 (p = 0.02, financial income)
r = -0.32 (p = 0.051, education)

The Impact of Racism Related Socio-Environmental Factors on African American NSCLC Mutational Signatures

Significance

Black individuals have higher exposure to air pollution, have lower access to job opportunities, well funded schools, appropriate housing, and safe spaces for recreation, and experience increased racial discrimination that could have consequences for their health and lung cancer development.

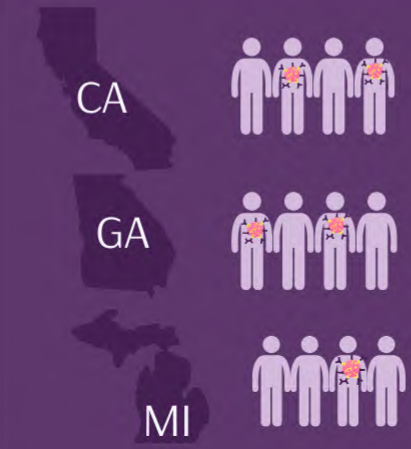
Exposures

Air Pollution

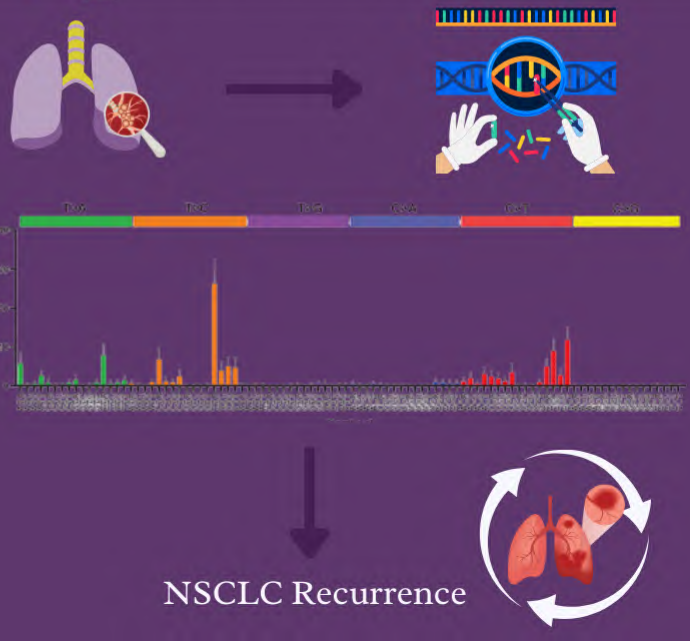
Residential Inequities

Participant recruitment

- Underwent resection of stage I-II NSCLC
- Received neoadjuvant therapy



Whole genome sequencing



NSCLC Recurrence

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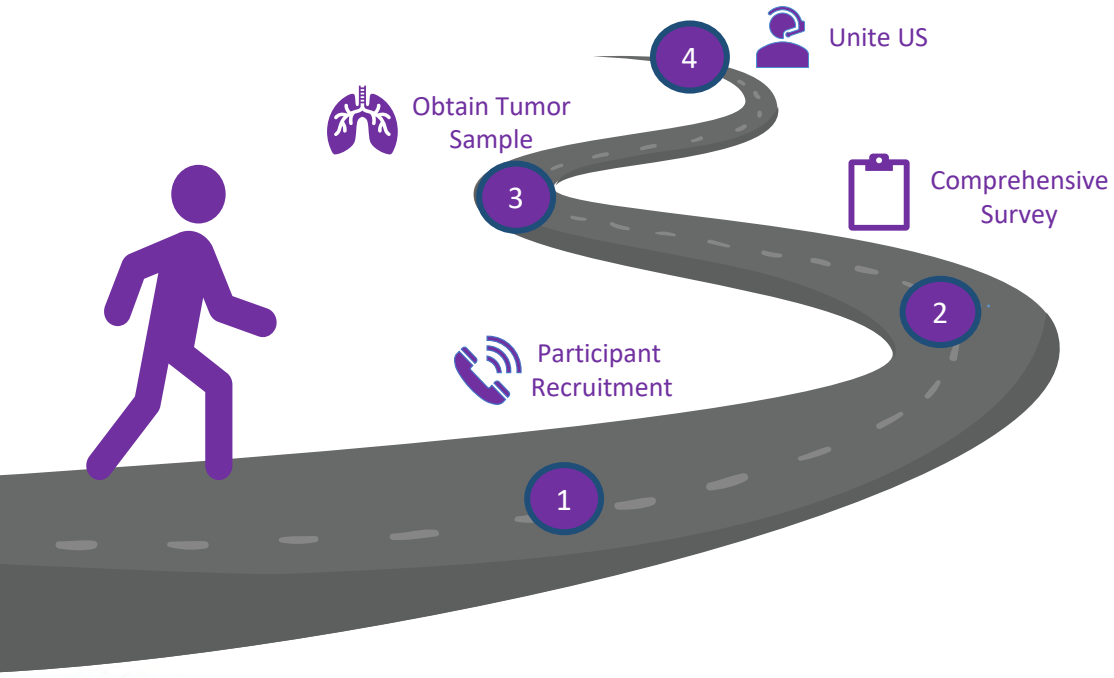
Participant Journey

Recruitment To-Date:
38 patients have completed the survey
22 patients have completed the survey, MRF, and ICF



1 African American/Black and Non-Hispanic White patients will be contacted and asked to participate in the study (verbal consent).

2 Those who consent will complete a 30-minute survey that includes questions regarding social determinants of health, residential history, and discrimination.

3 Participants who complete study activities from part 1 will be asked to complete an informed consent form and HIPAA authorization (medical release form) to obtain lung cancer surgery tumor samples.

4 If participants suggest urgent social needs, they may be referred, upon consent, to community organization Unite Us

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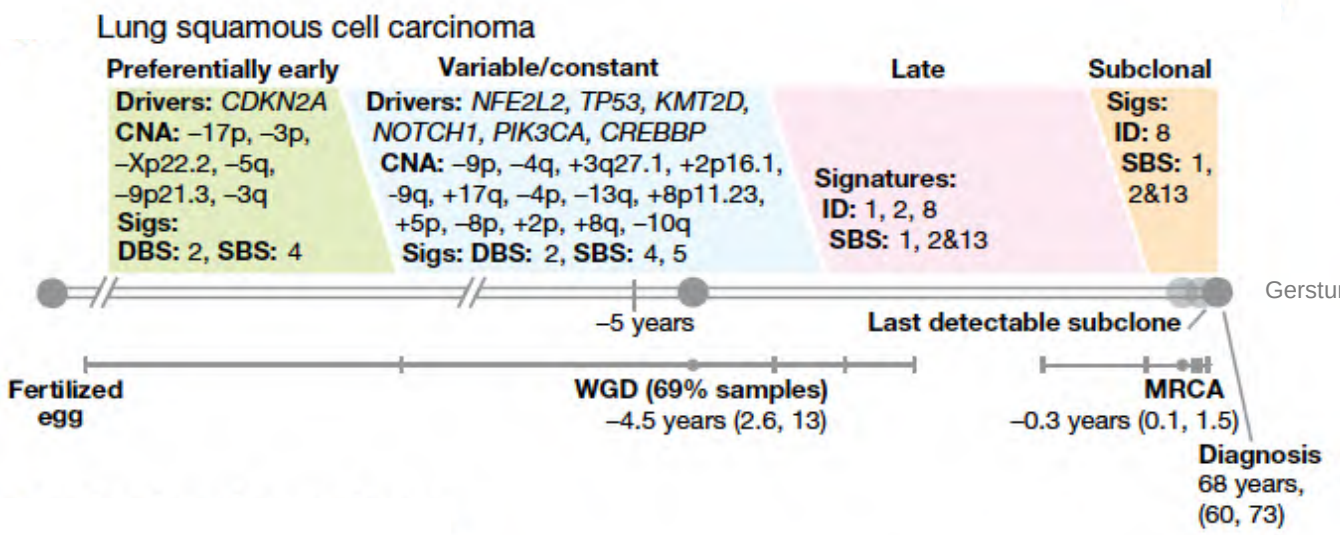
How does understanding tumor evolution advance our ability to detect and treat cancer?



Gerstung et al. (2020)

Goal – to use the genomes to model timing in clonal cancer evolution

- Help establish trajectories of molecular events that define tumor developmental cycle
- Identify and target more aggressive clonal lineages
- Characterize shared and unique molecular characteristics of each patient's tumor

Overview of Geometric Deep Learning (GDL) Analysis Workflow

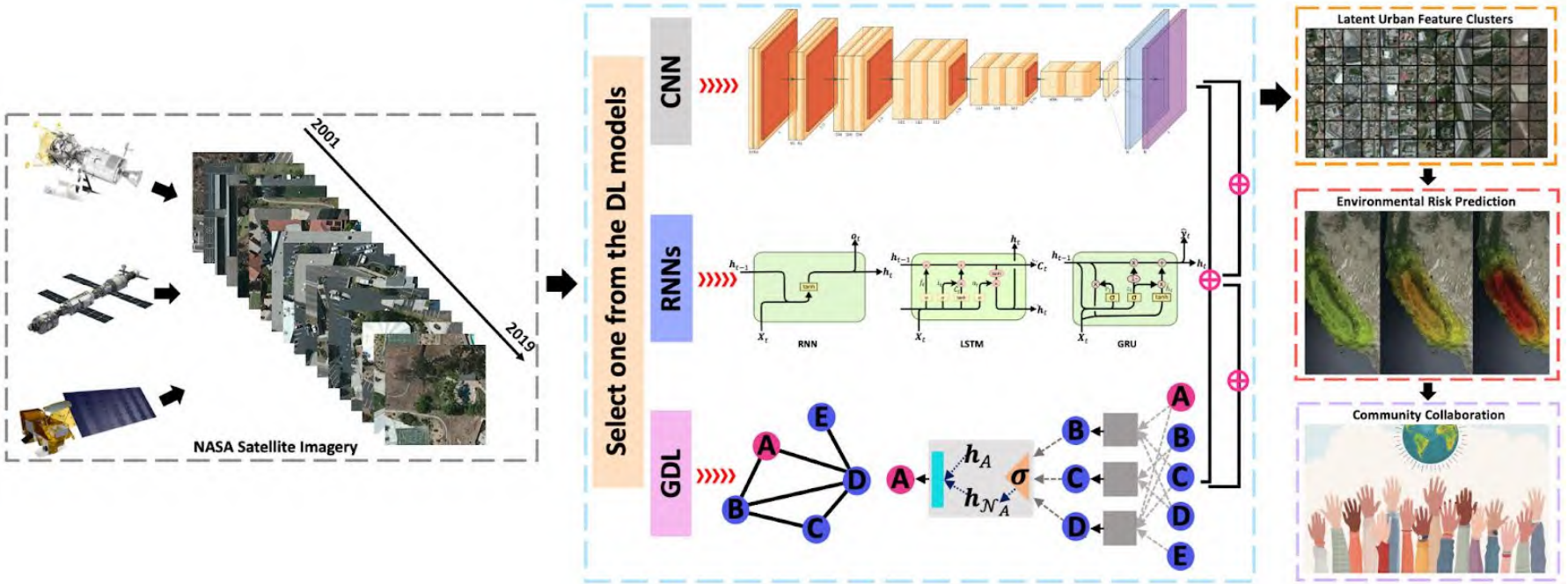


Figure 1. Urban form, environmental risk, and structural racism project workflow.

Interpreting GDL Model Outputs with NSCLC Tumor Grades and SDOH

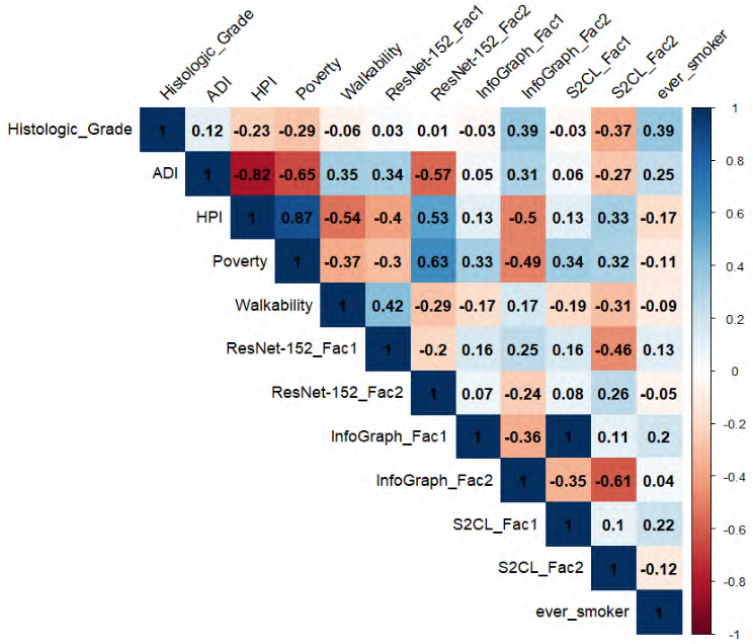


Figure 3. Correlation coefficients among SDOH variables, Model embedding, control variable, and health outcome (in dividual histologic grade).

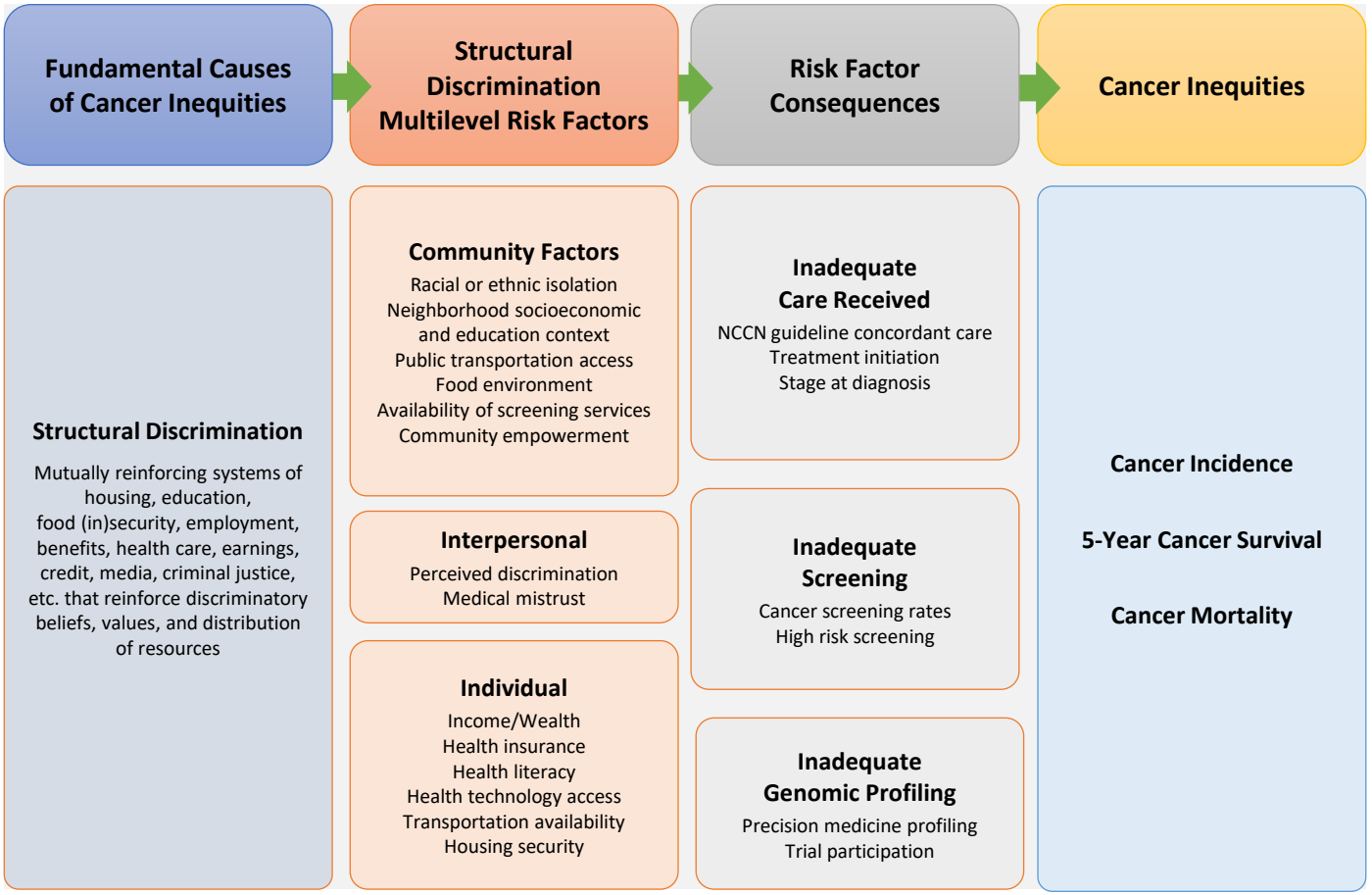
Table 1. *p-values* for Pearson and Spearman correlations methods among SDOH variables, model embedding, control variable, and health outcome (histologic grade).

	Histologic Grade	
	Pearson	*Spearman*
ADI	0.574	0.667
HPI	0.263	0.261
Poverty	0.160	0.182
Walkability	0.763	0.847
ResNet-152_Fac1	0.891	0.773
ResNet-152_Fac2	0.965	0.961
InfoGraph_Fac1	0.879	0.937
InfoGraph_Fac2	0.054*	0.101
S^2CL_Fac1	0.902	1.000
S^2CL_Fac2	0.072*	0.050**
Ever Smoker	0.055*	0.048**

A total of 27 pathological stage I-III NSCLC patients who underwent surgical resection without neoadjuvant therapy at COH between 2013 and 2021, were linked to nearby SDOH metrics (by residential census tract) and the nearest satellite tile. The control variable for NSCLC (*ever_smoker*) was also compared.

GDL models may be better at either representing several elements of the environment as one measure (complexity), or at measuring latent features that are not found in SDOH factors.

Conceptual Model of Structural Discrimination and Cancer Health



Conceptual model of structural discrimination as a fundamental cause, operating through risk factors and consequences, of cancer inequities

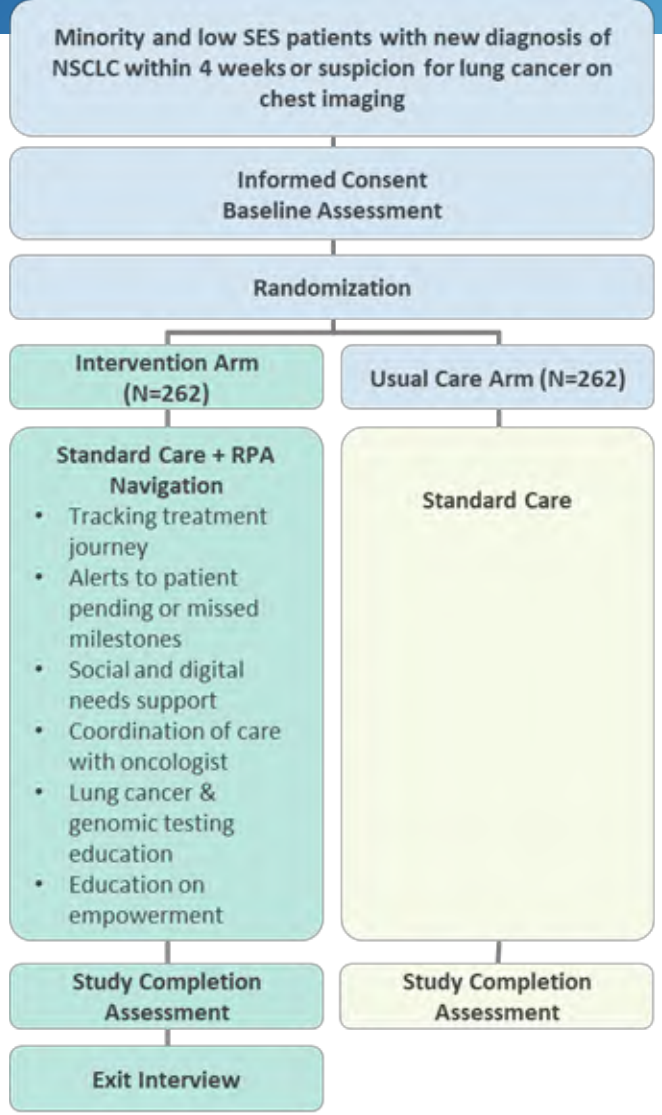


Figure 1. Study schema.

- Our proposed intervention assesses the multilevel impact of **structural discrimination** (I.e., at individual, interpersonal, and community levels) on receipt of guideline concordant care and uses a culturally tailored application to reduce burden of these barriers.
- Our pragmatic RCT will enroll recently diagnosed NSCLC patients and test a technology that
  - assesses multilevel SDOH
  - addresses social needs
  - tracks participants along their treatment journey
  - alerts providers and navigators when milestones are not met
  - and educates on empowerment and health equity advocacy
- We will determine if use of a digital, bot enabled, multilevel NSCLC navigation intervention influences receipt of the first course of stage-specific treatment as recommended by NCCN guidelines.
- Our primary endpoint is whether patients receive the first course of stage-specific treatment as recommended by NCCN guidelines.
- Our secondary endpoints are time to first therapy, time to genomic testing, receipt of molecular profiling prior to treatment for stage II-IV disease, enrollment in biomarker driven trials, self-activation and self-reported satisfaction.

Conclusion & Steps Forward

Summary: Social context and genomic outcomes must be integrated so that there is understanding of the biological impact of SDOH. This understanding can support risk assessment, precision medicine and treatment efforts.

- 1. Normalize comprehensive individual and neighborhood level social driver/determinant screening for each patient in conjunction with tumor and other clinical and outcome metrics
- 2. Recognize what high social risk for our respective and **collective** catchment means – what areas are "hotspots" for aggressive biology and poor outcomes?
  - **Collectively** conduct a comprehensive assessment of the burden of cancer across neighborhoods
- 3. **Collectively** work with legislatures to pass equity focused policy that improves the health of neighborhoods –i.e., social determinant focused
- 4. Support individuals from these high-risk areas with automatic social work referral and evaluation, navigation, transportation vouchers, telehealth opportunities and financial aid – i.e., social needs focused
- 5. Promote community-based education and awareness in high-risk areas regarding cancer risk, prevention, early detection, and treatment

Thanks and Acknowledgements

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City of Hope

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Funders

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LUNG CANCER RESEARCH FOUNDATION

COH Health Equity Pilot Award

AATS Foundation

COH Research Initiative CCPS Program Award

COH Research ACS-IRG Award

AstraZeneca

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