



Georgia Tech  
Bioinformatics

# Genomic Ancestry Inference to Decompose Genetic and Environmental Contributions to Cancer Disparities

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**Cancer health disparities** happen when there are higher rates of new diagnoses and cancer death rates among certain races, ethnicities, or other population groups.

Cancer health disparities are a pressing social and scientific problem.

<https://www.cancer.gov/about-cancer/understanding/disparities>

# Examples of cancer disparities

Although cancer incidence and mortality overall are declining in all population groups in the United States, certain groups continue to be at increased risk of developing or dying from particular cancers.

- Black men and women have higher death rates than all other racial/ethnic groups for many, although not all, cancer types.
- Despite having similar rates of breast cancer, Black/African American women are more likely than White women to die of the disease.

<https://www.cancer.gov/about-cancer/understanding/disparities>

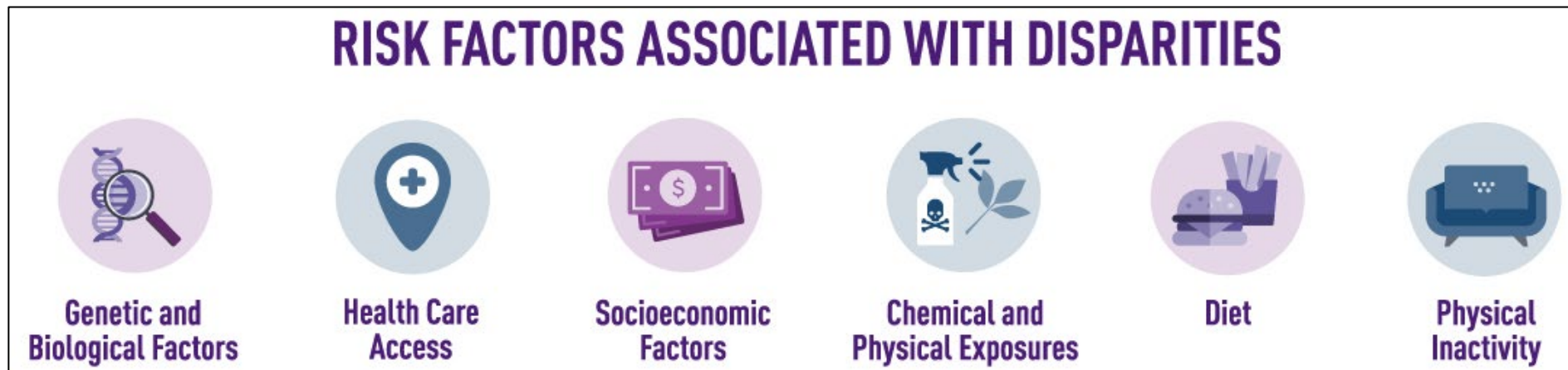
# Examples of cancer disparities

- Black men are twice as likely as White men to die of prostate cancer and continue to have the highest prostate cancer mortality among all US population groups.
- Hispanic and Black women have higher rates of cervical cancer than women of other racial/ethnic groups, with Black women having the highest rates of death from the disease.
- American Indians/Alaska Natives have higher death rates from kidney cancer than any other racial/ethnic group.
- American Indians/Alaska Natives have the highest rates of liver and intrahepatic bile duct cancer, followed by Hispanics and Asians/Pacific Islanders.

<https://www.cancer.gov/about-cancer/understanding/disparities>

# Causes of cancer disparities

- Cancer disparities are complex and multifactorial, with varying contributions from ***genetic***, ***social***, and ***environmental*** risk factors



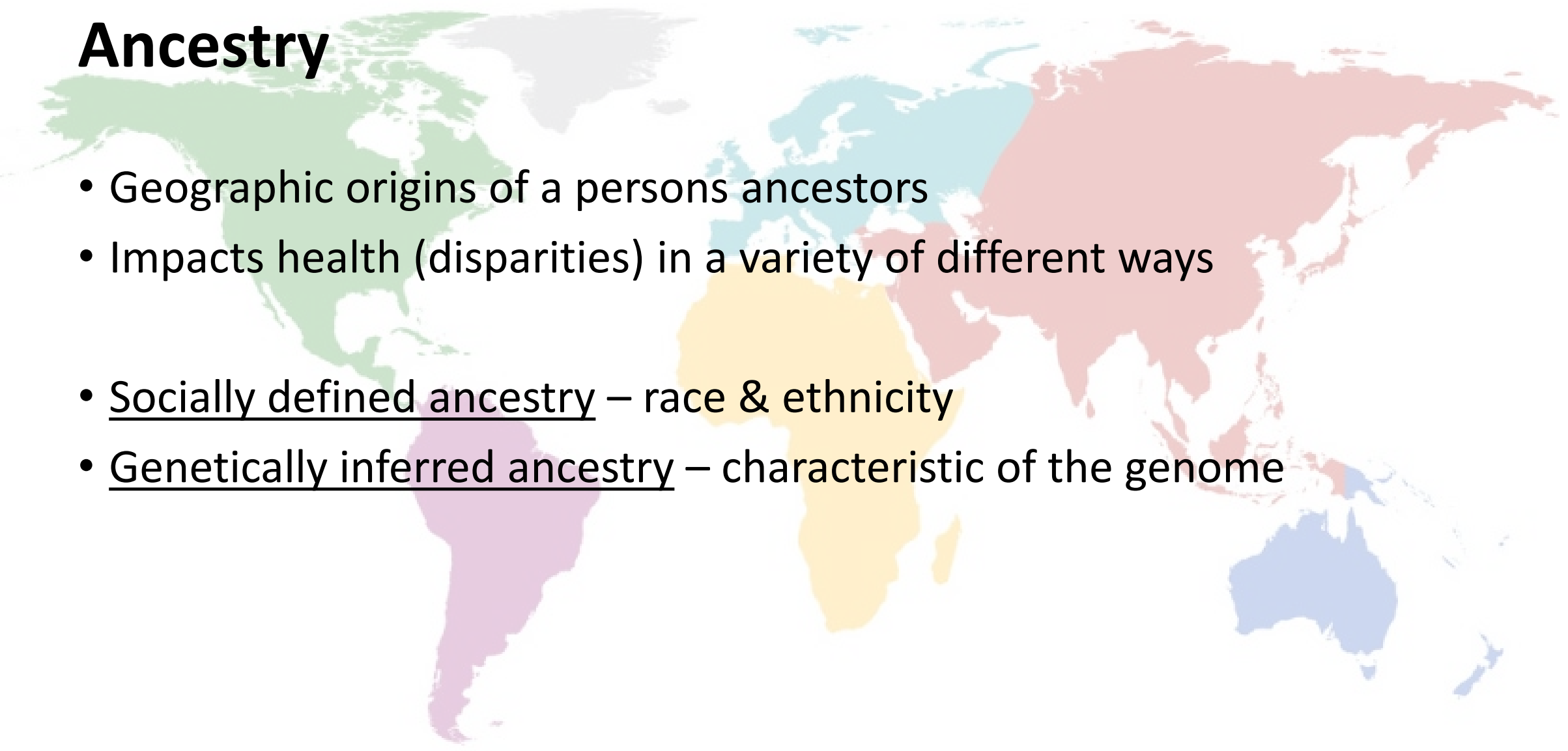
<https://www.cancer.gov/about-cancer/understanding/disparities/what-are-cancer-disparities-infographic>

We believe that **genomic ancestry inference** can be used to help decompose *genetic, social, and environmental* contributions to cancer disparities.

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# Ancestry



- Geographic origins of a persons ancestors
- Impacts health (disparities) in a variety of different ways
- Socially defined ancestry – race & ethnicity
- Genetically inferred ancestry – characteristic of the genome

# Both are important for health!

- Socially defined ancestry
  - Social environment
  - Lived experiences
- Genetically defined ancestry
  - Health-related genetic variants
- Challenge: social and genetic dimensions of health co-vary across racial and ethnic groups, difficult to tease apart their effects

# Genetically inferred ancestry

- Characteristic of the genome
- Can be inferred:
  - ***Independent of the social dimensions of race & ethnicity***
  - Objectively and with precision
  - Categorical or continuous variable
  - At different levels of relatedness
    - Continental
    - Subcontinental (fine scale)
  - At different levels of resolution
    - Genome-wide
    - Haplotype (location) specific



# Association of Genetic Ancestry and Molecular Signatures with Cancer Survival Disparities: A Pan-Cancer Analysis



Kara Keun Lee<sup>1,2,3</sup>, Lavanya Rishishwar<sup>2,3,4</sup>, Dongjo Ban<sup>1,2,3</sup>, Shashwat Deepali Nagar<sup>2,3</sup>, Leonardo Mariño-Ramírez<sup>5</sup>, John F. McDonald<sup>1,2</sup>, and I. King Jordan<sup>1,2,3,4</sup>

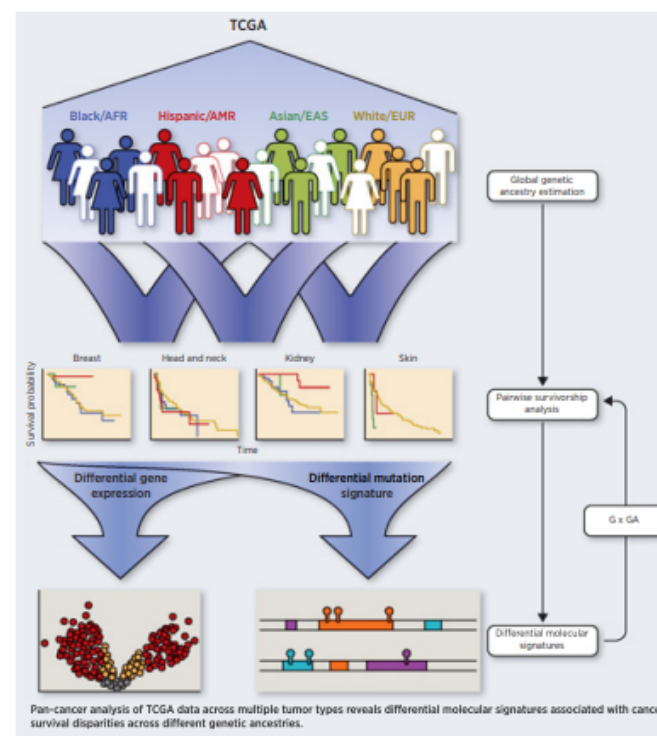
*Cancer Res* (2022) 82 (7): 1222–1233.

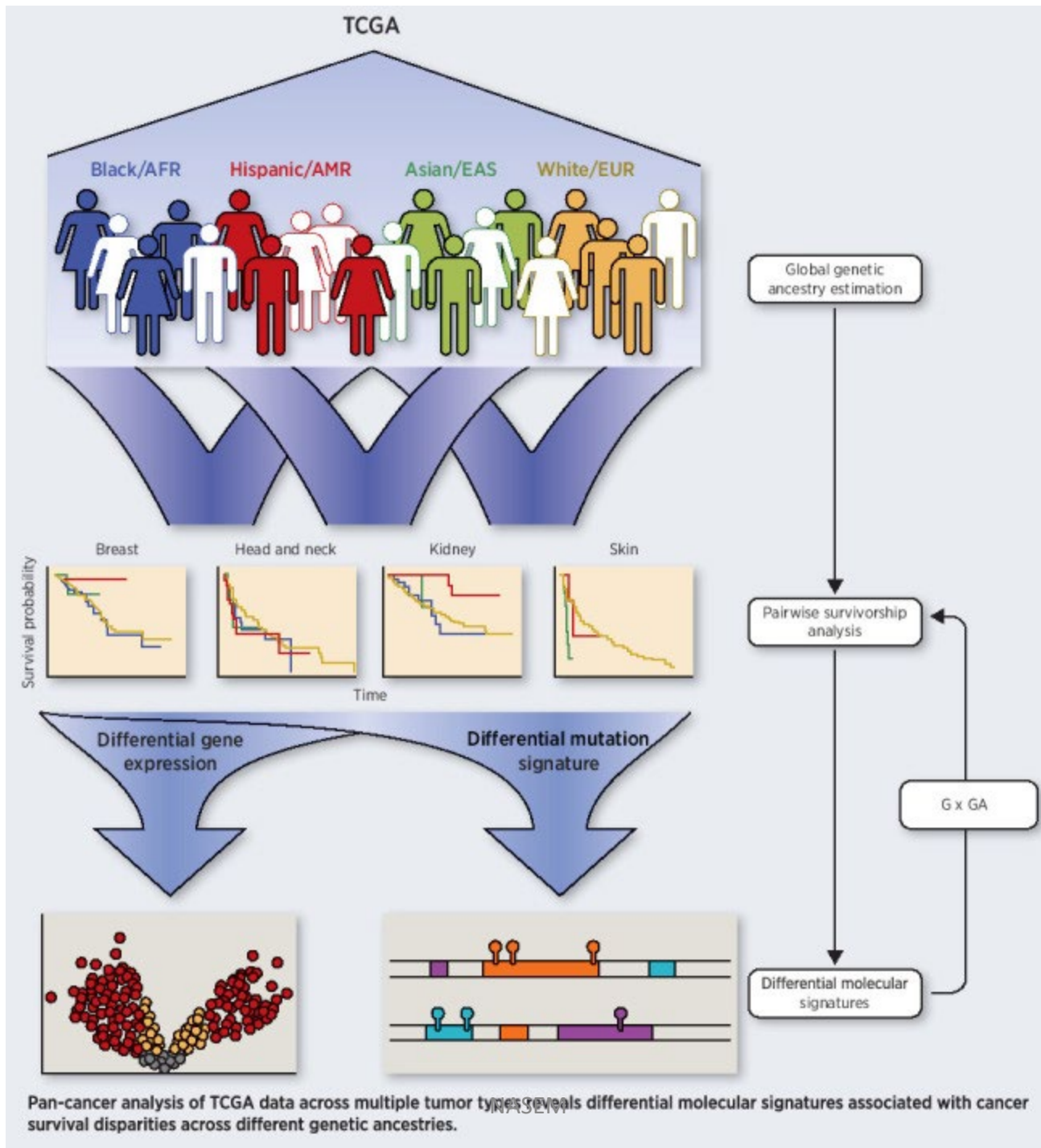
## ABSTRACT

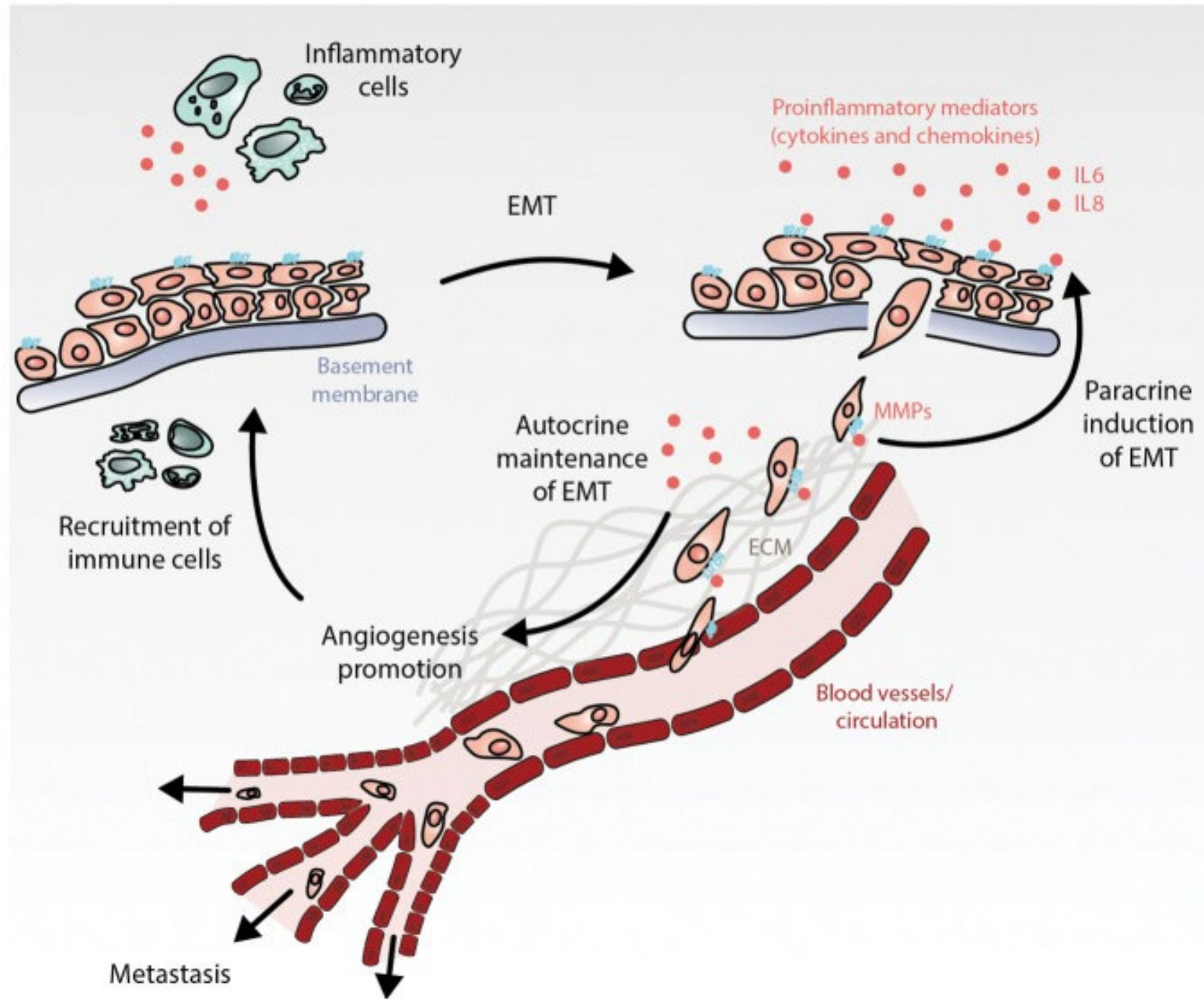
While overall cancer mortality has steadily decreased in recent decades, cancer health disparities among racial and ethnic population groups persist. Here we studied the relationship between cancer survival disparities (CSD), genetic ancestry (GA), and tumor molecular signatures across 33 cancers in a cohort of 9,818 patients. GA correlated with race and ethnicity but showed observable differences in effects on CSD, with significant associations identified in four cancer types: breast invasive carcinoma (BRCA), head and neck squamous cell carcinoma (HNSCC), kidney renal clear cell carcinoma (KIRC), and skin cutaneous carcinoma (SKCM). Differential gene expression and methylation between ancestry groups associated cancer-related genes with CSD, of which, seven protein-coding genes [progesterone and adiponectin receptor family member 6 (*PAQR6*), Lck-interacting transmembrane adaptor 1 (*LIME1*), Sin3A-associated protein 25 (*SAP25*), MAX dimerization protein 3 (*MXD3*), coiled-coil glutamate rich protein 2 (*CCER2*), refilin A (*RFLNA*), and cathepsin W (*CTSW*)] significantly interacted with GA and exacerbated observed survival disparities. These findings indicated that regulatory changes mediated by epigenetic mechanisms have a greater contribution to CSD than population-specific mutations. Overall, we uncovered various molecular mechanisms through which GA might impact CSD, revealing potential population-specific therapeutic targets for groups disproportionately burdened by cancer.

**Significance:** This large-cohort, multicancer study identifies four cancer types with cancer survival disparities and seven

cancer-related genes that interact with genetic ancestry and contribute to disparities.







## **Association of Genetic Ancestry and Molecular Signatures with Cancer Survival Disparities: A Pan-Cancer Analysis**



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- This large-cohort, multicancer study identifies four cancer types with cancer survival disparities and seven cancer-related genes that interact with genetic ancestry and contribute to disparities.
- Regulatory changes mediated by epigenetic mechanisms have a greater contribution to cancer survival disparities than population-specific mutations.
- We uncovered various molecular mechanisms through which genetic ancestry impacts cancer survival disparities, revealing potential population-specific therapeutic targets for groups disproportionately burdened by cancer.

# Challenges & opportunities

1. **More data** from diverse, underrepresented populations is needed. Population biobanks and cancer registries.
2. **Better methods** so that insights from current studies can be applied across populations (ancestries).
3. **Human capacity** must be developed so that investigators from diverse backgrounds can contribute to cancer disparities research.

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