A Role for Genomics in Addressing Health Disparities?

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Discourse on precision medicine, genomics, and health disparities

"give everyone the best chance at good health" (Collins & Varmus NEJM 2015;372:793-5)

"improve outcomes for communities with disparities in health" (Flyer for community engagement with AIAN communities)

"understand the complex interplay that creates health disparities" (Bustamante et al Nature 2011;475:163-5)

Social conditions as fundamental causes of disease

Disadvantage creates conditions that put people "at risk of risks"

Influencing

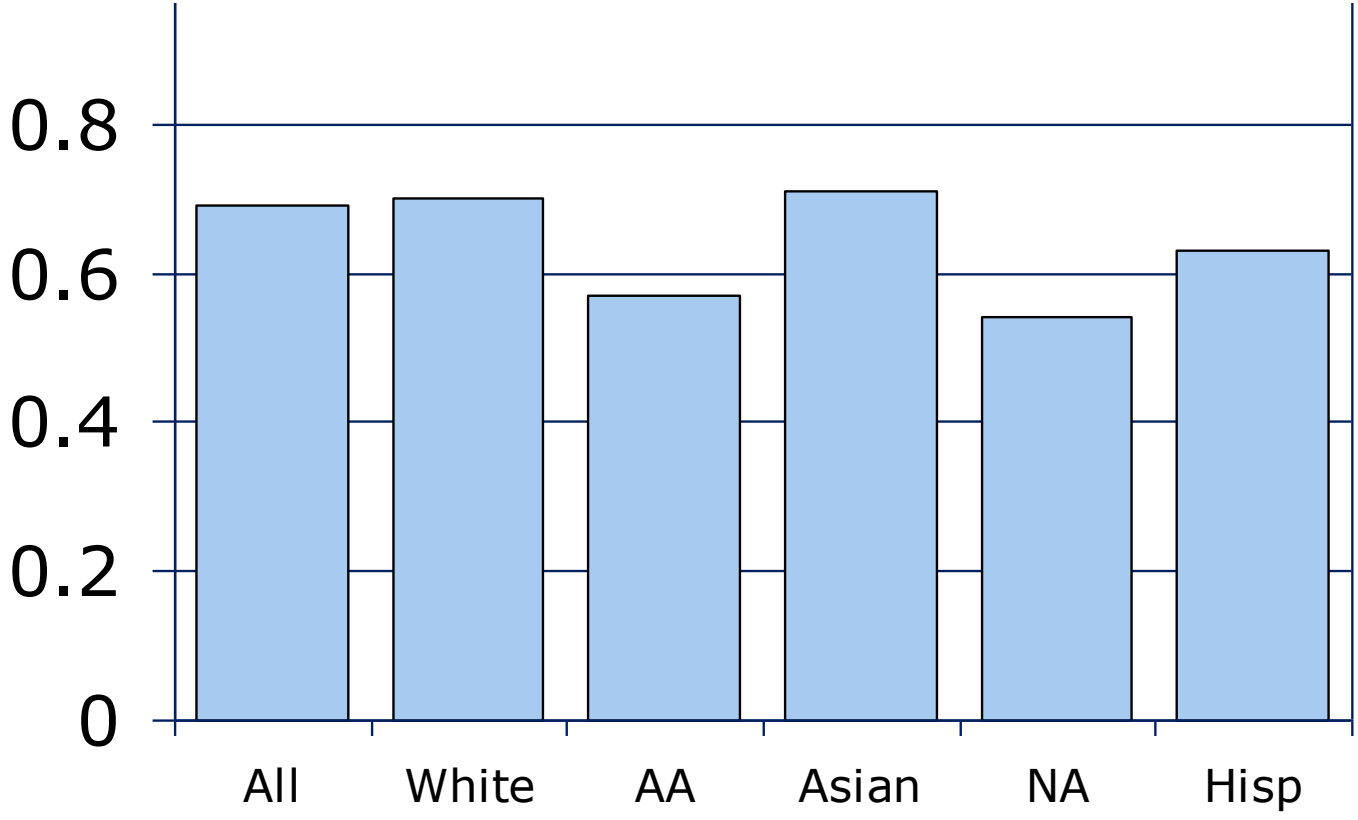
- Multiple risk factors
- Multiple diseases

…and maintaining an association with disease, even when intervening mechanisms change

Link & Phelan J Health Soc Behav 1995(Extra):80-94

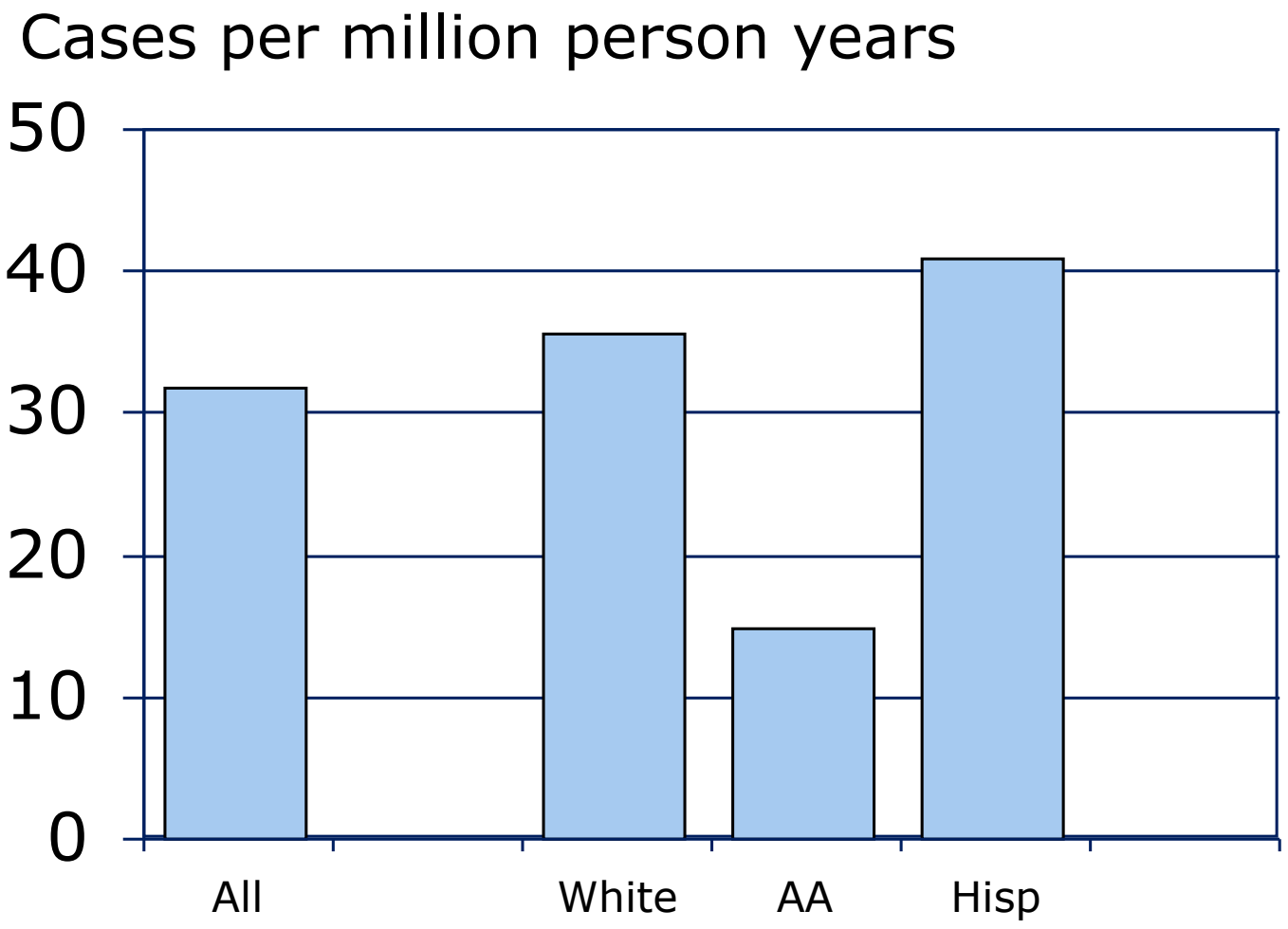
Survival by race in childhood acute lymphoblastic leukemia (ALL)

Lower 5 year survival for AA, NA and Hispanic compared to white children (p<0.001-0.002)



Kadan-Lottick et al JAMA 2003;290:2008

Incidence of childhood acute lymphoblastic leukemia (ALL)



Lim et al Cancer 2014; 120:955-62

Genetic contributors to disease risk

- **5 genes associated with ALL** risk (involved in lymphoid development, cell cycle control or tumor suppression)
- **Differential prevalence of risk variants** in 2 genes (lower in African Americans) likely contributes to racial difference in incidence

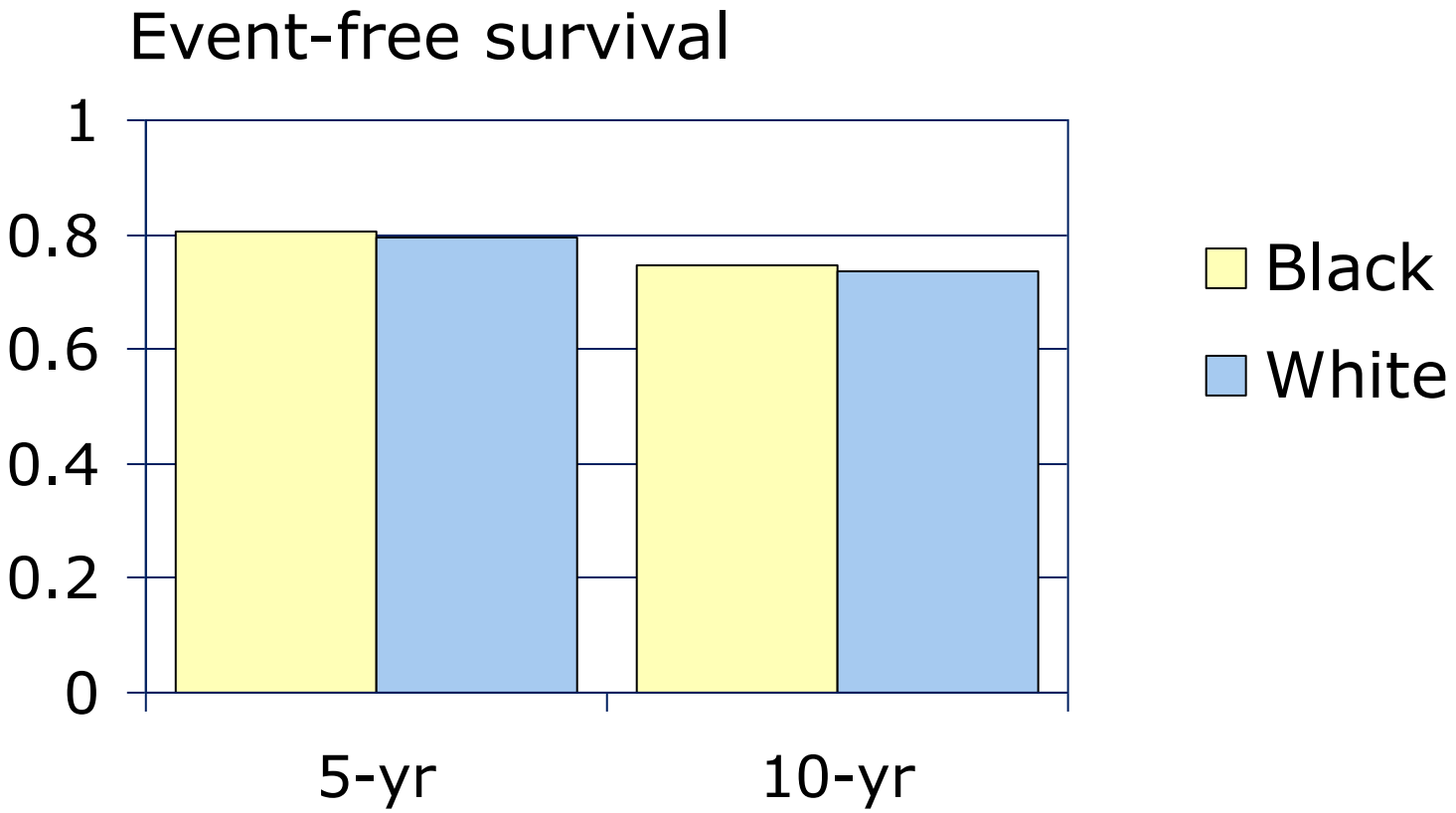
Lim et al Cancer 2014; 120:955-62
Hu et al JNCI 2013:733-741
Pui et al JAMA 2003; 290:2001

Another difference

- **Higher rate of poor prognostic indicators** seen in black children in US and Africa in some studies – eg:
  - High leukocyte count
  - Unfavorable T-cell immunophenotype
  - Chromosomal translocation t(1:19) with E2A-PBX1 fusion
  - Also, less likely to have hyperdiploid blast cells
- Could population genetic differences contribute? Or environmental exposures?

Hu et al JNCI 2013:733-741; Pui et al JAMA 2003; 290:2001; Macharia. East Afr Med J 1998; 73:638-42; Gunier et al Environ Res 2017; 156:57-62

Results of therapy for ALL in Black and White children - St. Jude



Pui et al JAMA 2003; 290:2001

Type 2 diabetes

- Accounts for 90-95% of diabetes
- >100 gene variants contribute to risk, with small additive effects
- In studies of ancestral groups:
  - Differences in variant prevalence
  - Some variants found exclusively or predominantly in specific groups

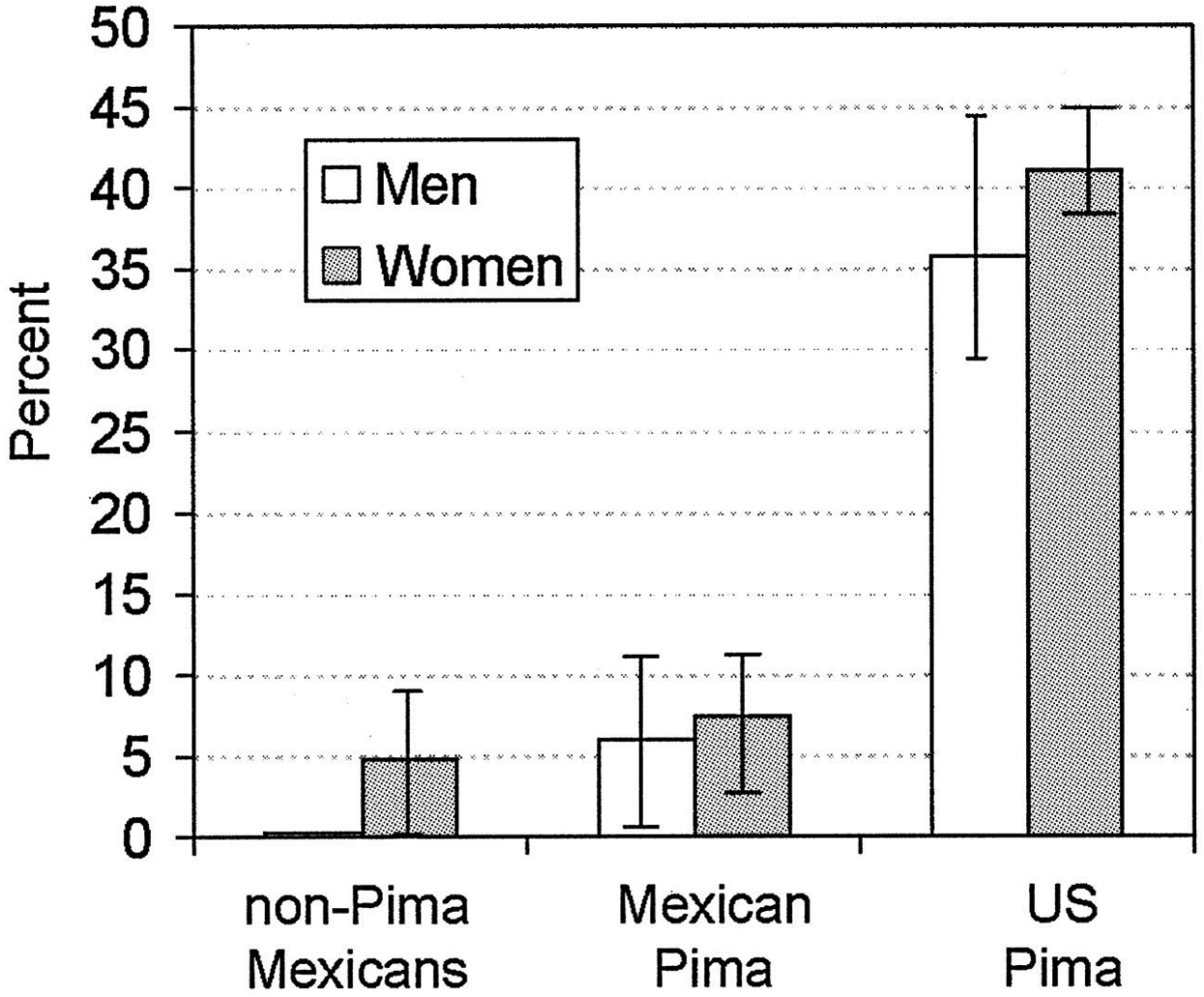
Could genetics account for the high rate of diabetes in the Arizona Pima?

Study of two Pima populations

- Located in Arizona, US and Sierra Madre mountains of Mexico
- Share common ancestry distinct from other Native American groups, with bootstrap value of 95% (947/1000)

Schulz et al.Diabetes Care 2016;29:1866-77

Age-adjusted prevalence (±95% CIs) of diabetes in non-Pima Mexicans, Mexican Pima Indians, and U.S. Pima Indians.



Leslie O. Schulz et al. Dia Care 2006;29:1866-1871

American Diabetes Association

Other differences between the two Pima Indian populations

- Physical activity
  - 2.5-fold↑ for men, 7.0-fold↑ for women among Mexican Pima
- Obesity
  - 10-fold↑ for men, 3.0-fold↑ for women among US Pima

Schulz et al.Diabetes Care 2016;29:1866-77

How did the Pima lifestyle change with western settlement?

- Pima agricultural economy disrupted by diversion of water to white settlements
  - Loss of healthy traditional foods
  - Poverty
- Surplus commodities (high in simple carbohydrates and processed food) introduced as dietary mainstays
- Communities experienced cultural loss, stigma and discrimination

California Newsreel. Unnatural Causes: Episode 4. http://www.unnaturalcauses.org/episode_descriptions.php?page=4

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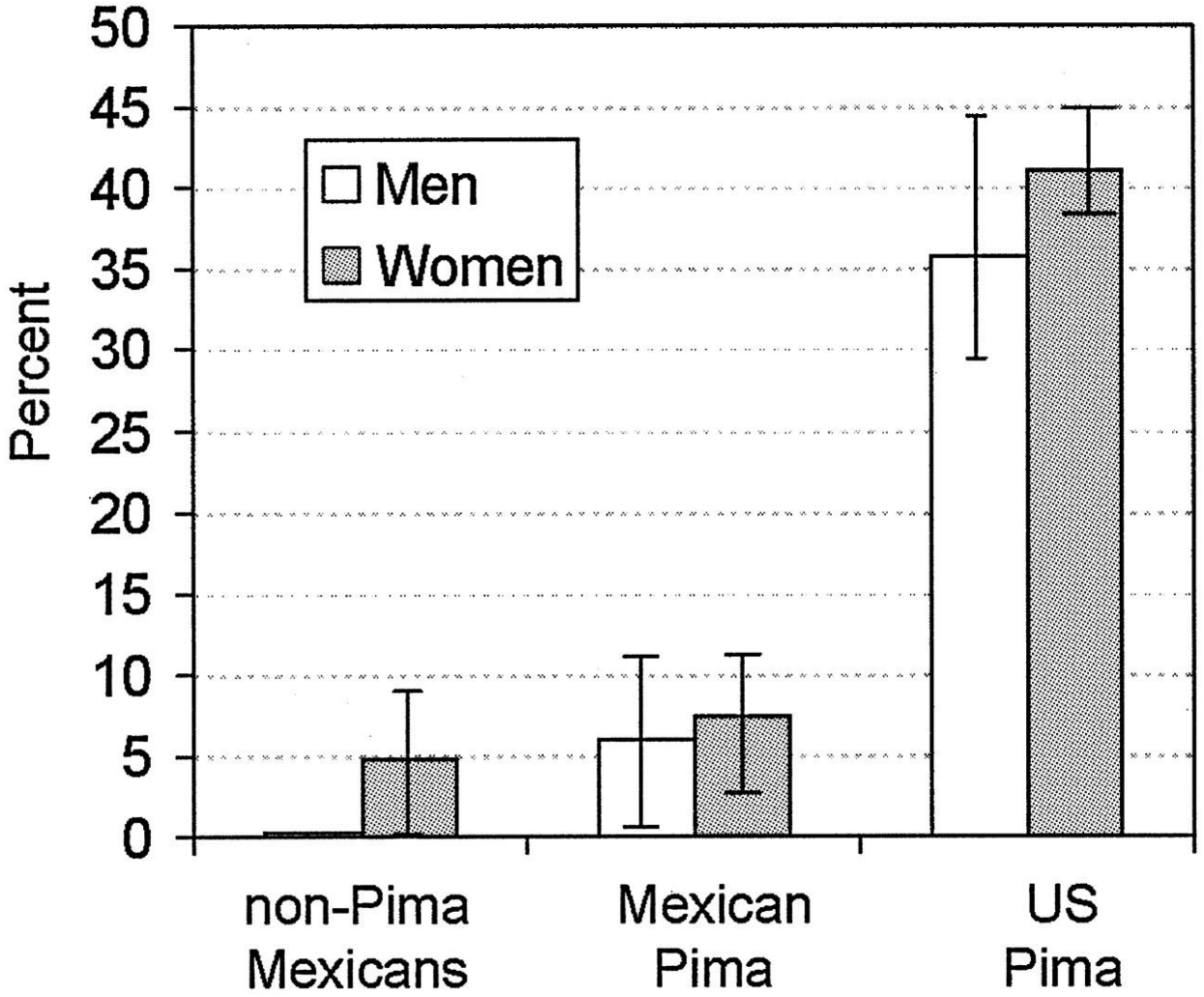

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American Diabetes Association

APOL1 & kidney disease

African Americans experience a disproportionate burden of chronic (CKD) and end-stage kidney disease (ESKD)

Risk variants in the APOL1 gene contribute to increased risk

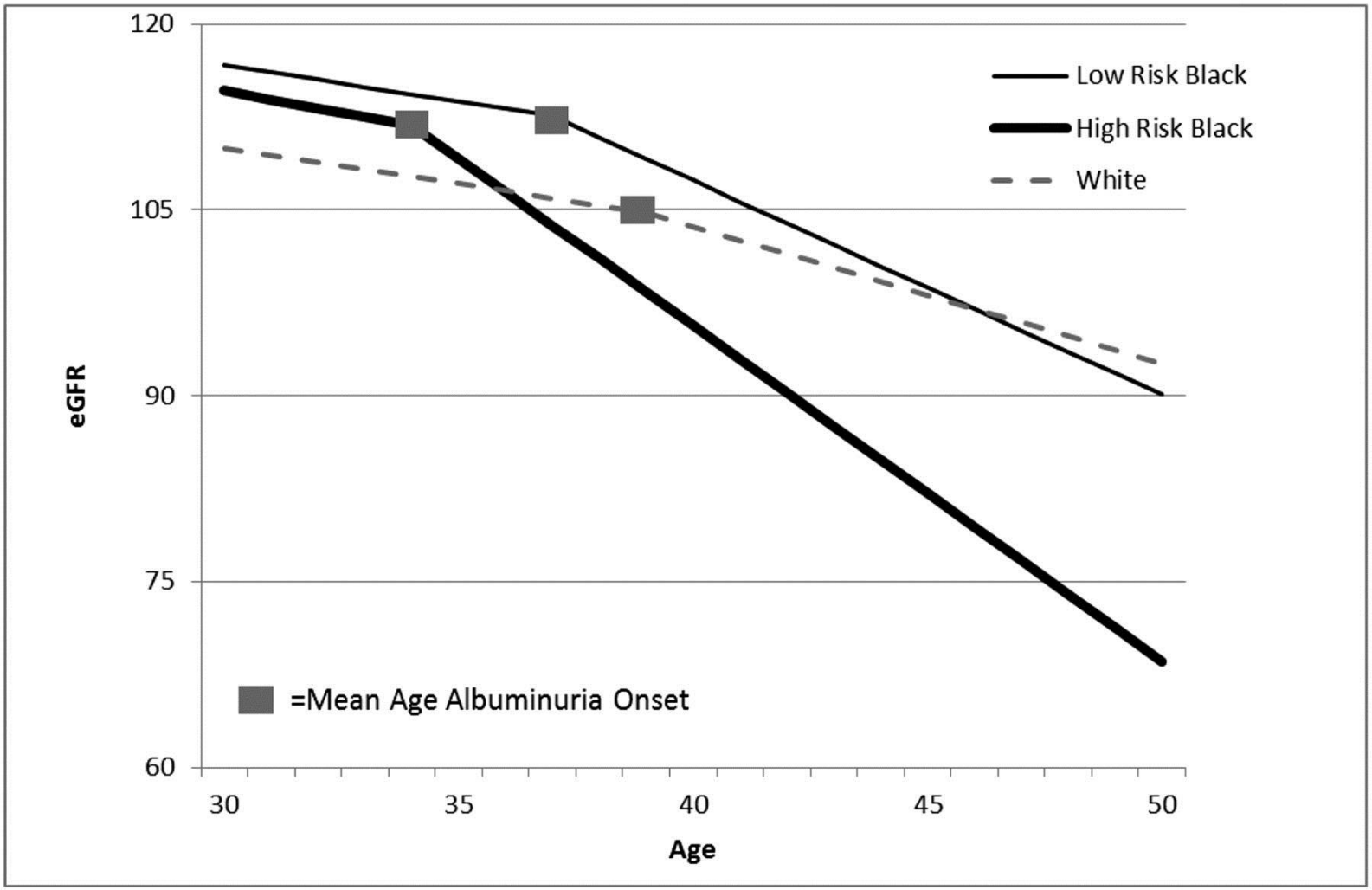
- Risk genotype (two copies of a risk variant) present in 13% of African Americans
- Penetrance estimated at 20%

Incidence of albuminuria (indicator of CKD) in the Cardia cohort

	White	Low risk Black	High risk Black
N	1651	1090	152
Albuminuria (per 1000 PY)	3.9	7.8	15.6
Relative risk	--	2.32	5.71
Corrected (smoking, BP, BMI, DM, SES)	--	1.21	3.50

Peralta et al. JASN 2016; 27:888-93

Kidney decline by race and *APOL1*



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Placing genomics in context

Genomics may:

- explain some population differences in disease incidence - sometimes aligned with outcome disparity, sometimes not

BUT

- Studied in isolation, may obscure far more important social determinants of health
- In so doing, may stigmatize disadvantaged populations and slow progress toward addressing health disparities

West et al JAMA 2017;317:1831-2
Sankar et al. JAMA. 2004;291:2985-9