Race, Ancestry, and Genetic Risk
(Identity, Geography, and Science)

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Race

Categorization of humans on the basis of shared physical or social qualities into groups viewed as distinct within a society

Social construct, usually established by a dominant group, to establish a hierarchy within society

Membership in a racial grouping usually assigned by others (often by a dominant group)

Ethnicity

Grouping of people who identify with each other on the basis of shared attributes that distinguish them with a society (usually language, culture but may be ancestral geographic origin).

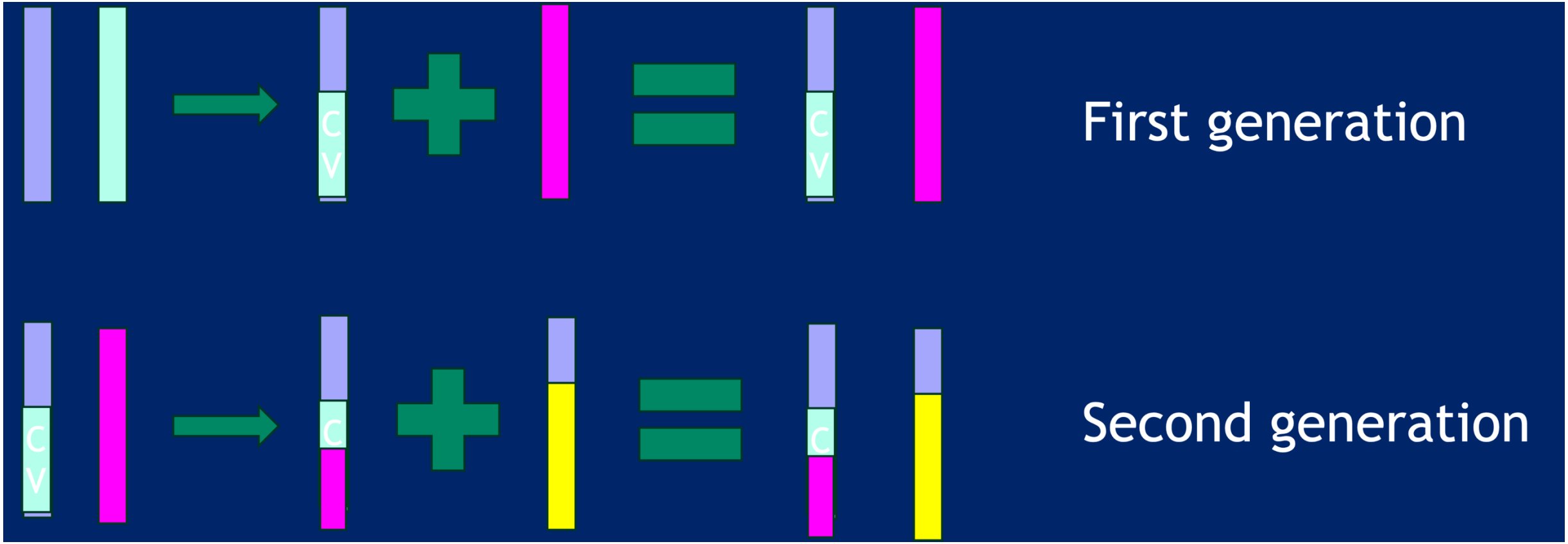
Generally, but not always, self-organized

Ancestry

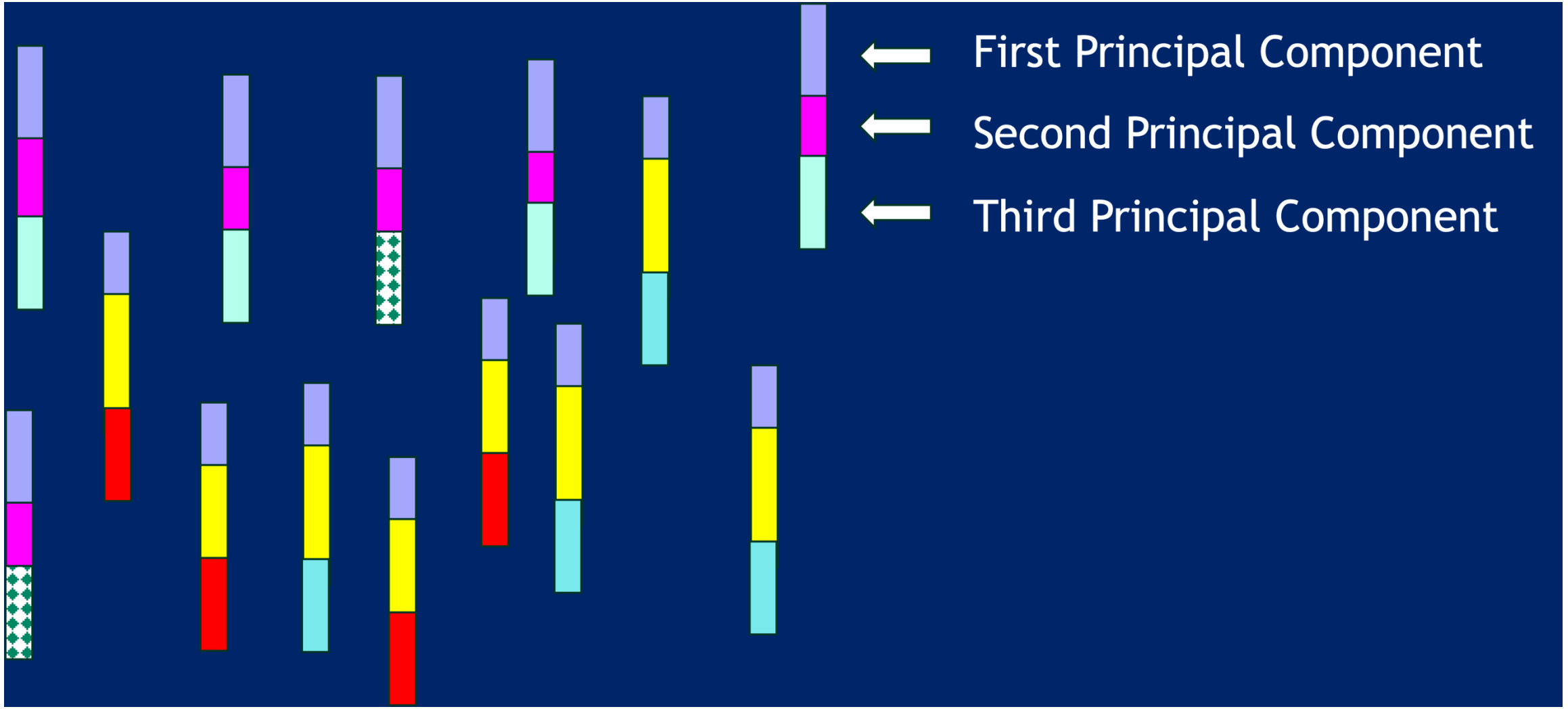
Ancestor is a parent or parent of an antecedent

Geographic correlation that changes with temporal distance

Determining ancestry by genomics

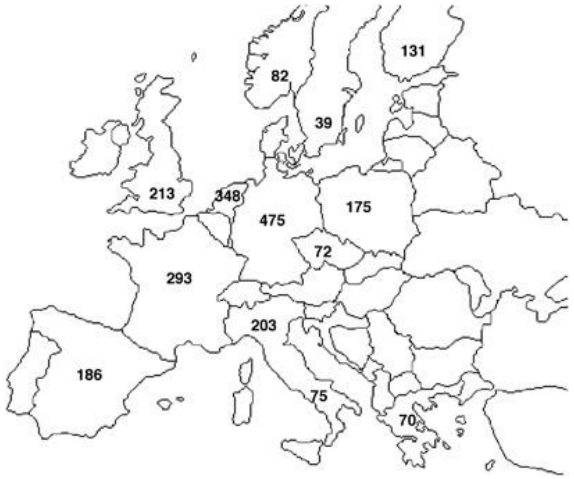


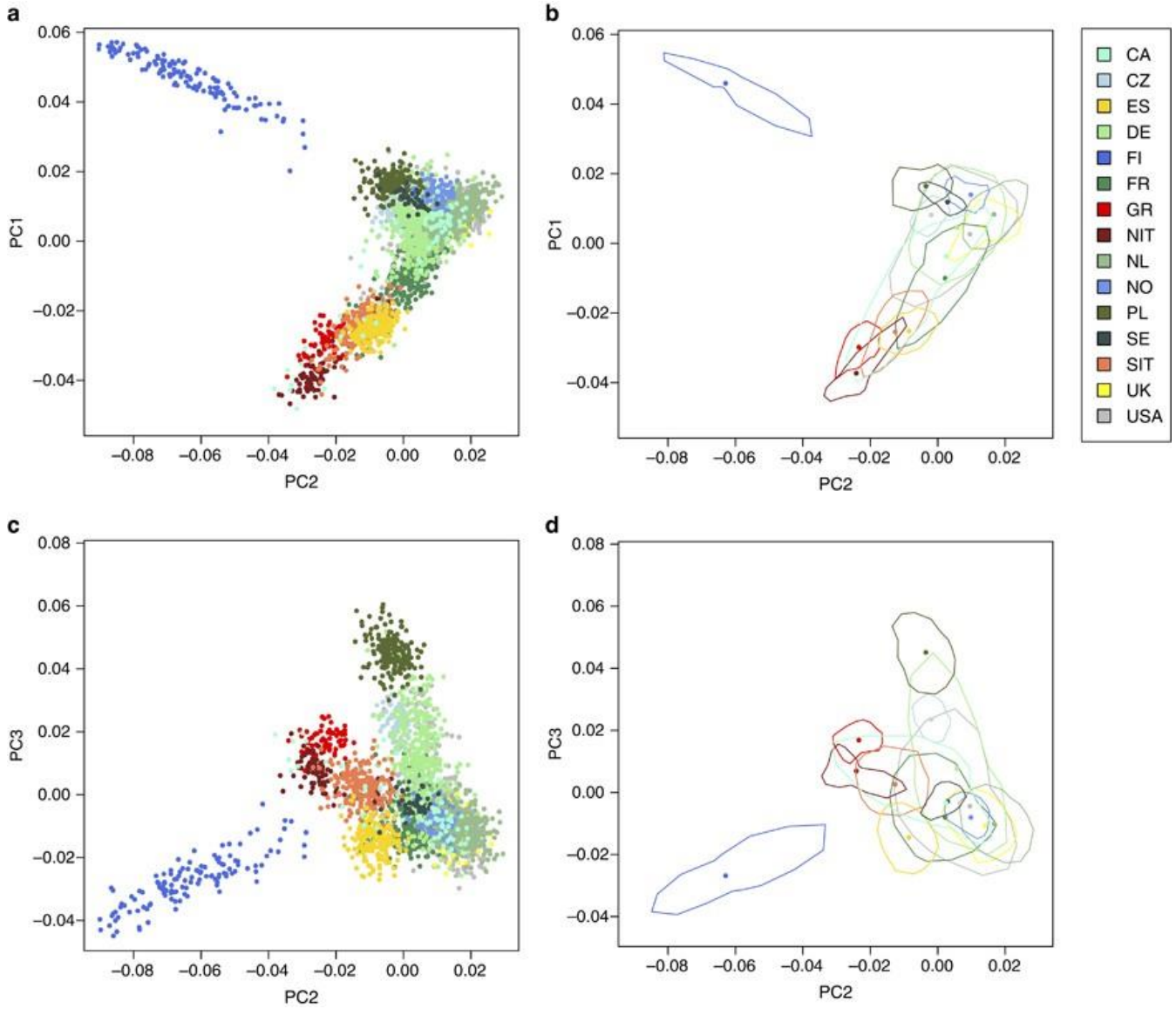
Determining ancestry by genomics



Ancestry-informative markers (AIMs)

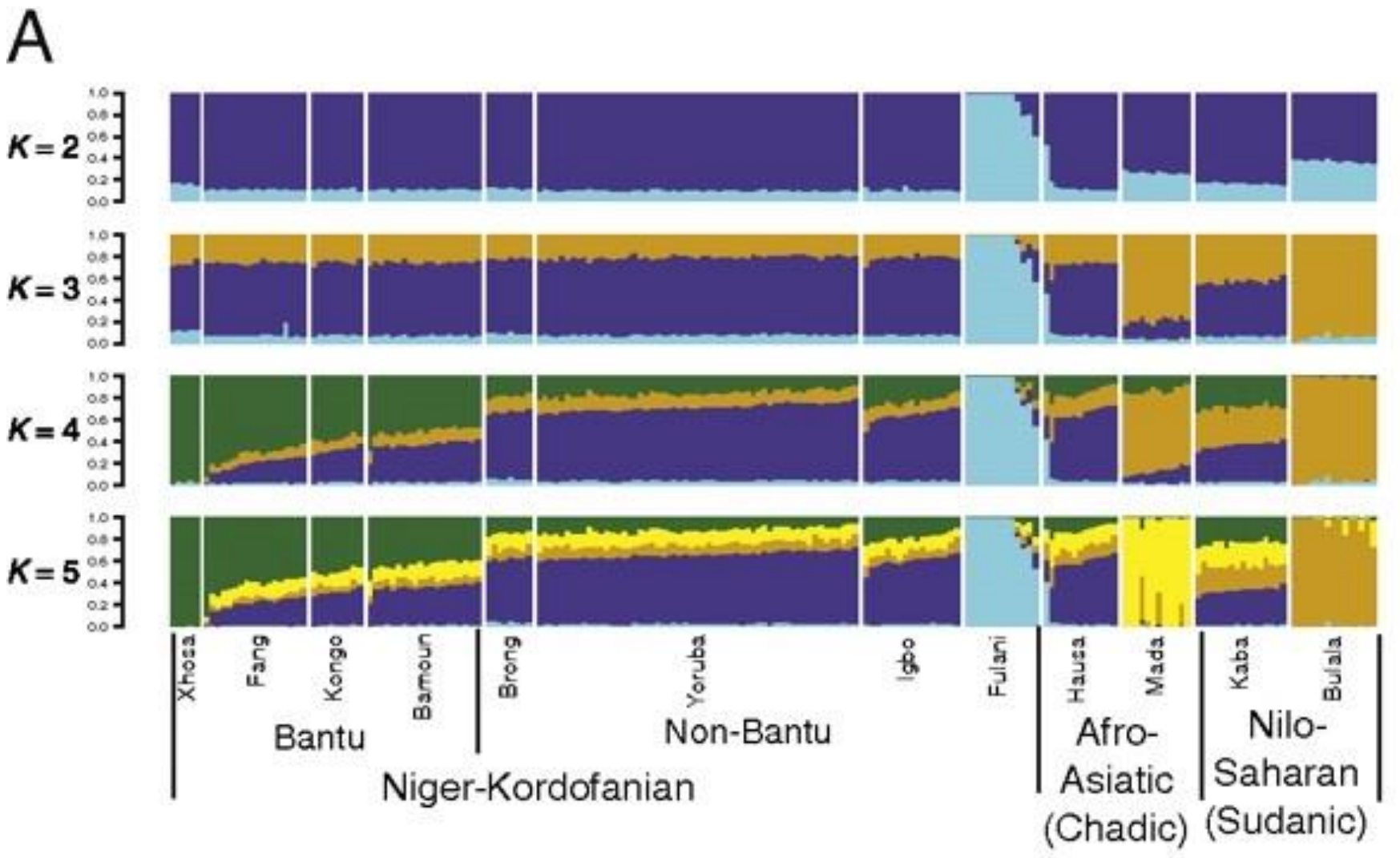
Polymorphisms (SNPs) with significantly different frequencies between ancestral populations





SIRE categories are ancestrally diverse (geography)

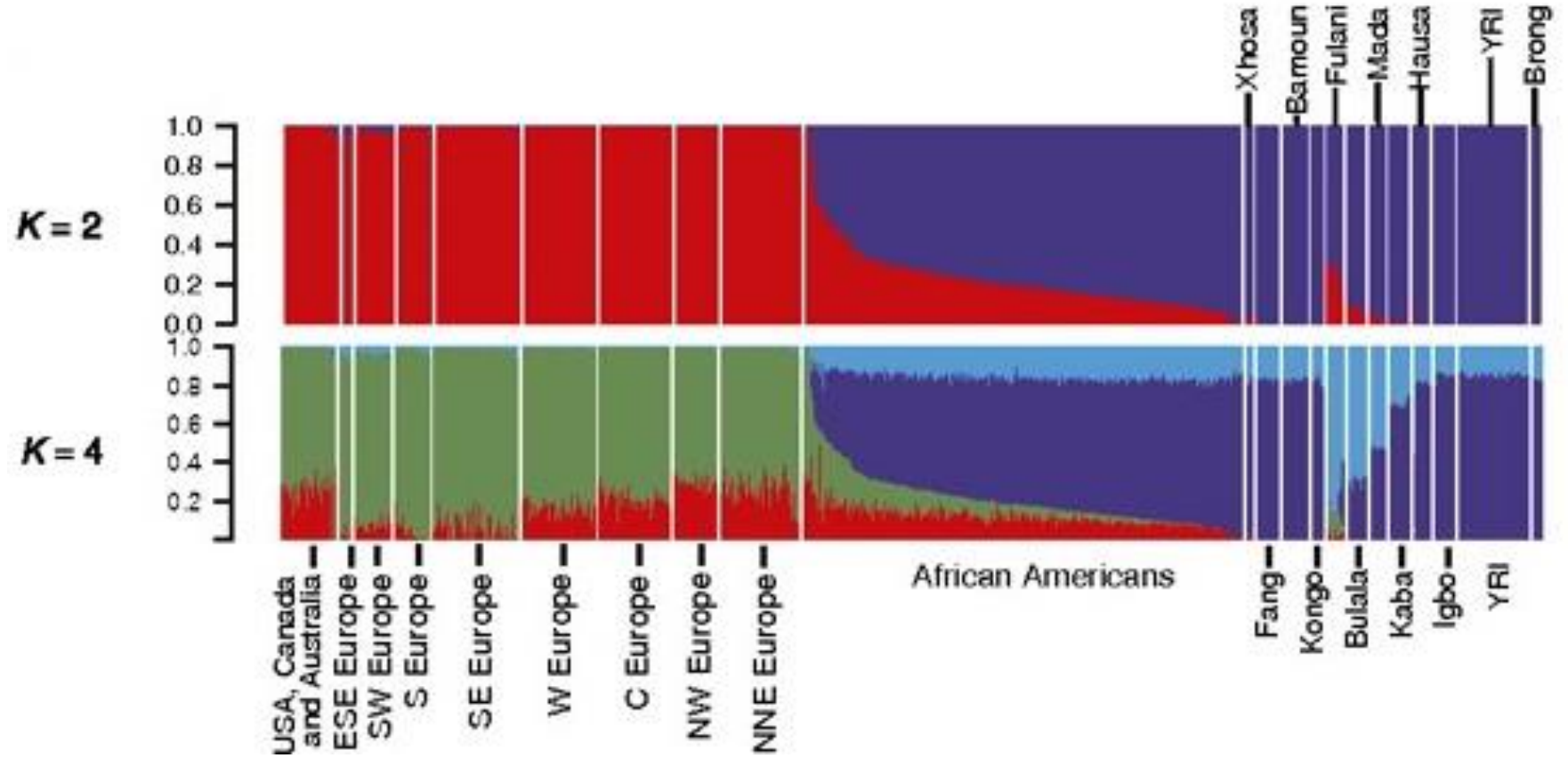
Population substructure in Sub-Saharan Africa



Bryc et al, PNAS 2010

SIRE categories may be genomically diverse (admixture)

Admixture in US self-reported African ancestry (SRAA)



Bryc et al, PNAS 2010

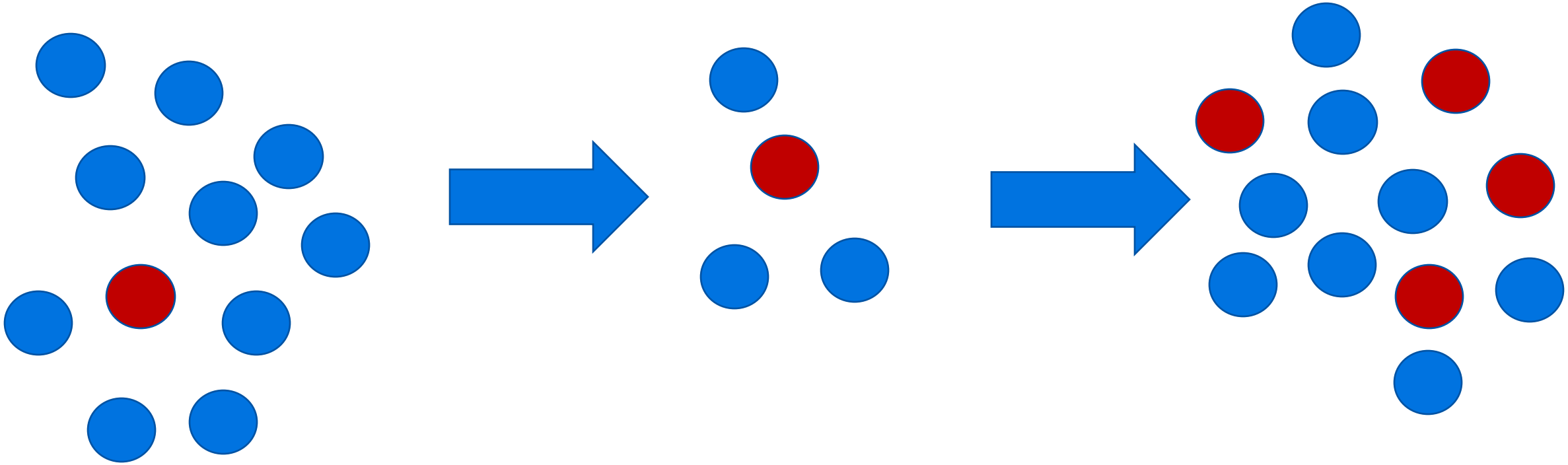
Self-identified race/ethnicity (SIRE) and genetics

Are pathogenic variants more common in specific SIRE groups?

Do variants have different implications in different groups?

How would pathogenic variants become enriched in a SIRE group?

Founder effect (historical and geographic)



How would pathogenic variants become enriched in a SIRE group?

- Founder effect
- Improved fitness
- Increased de novo mutation rate
- Ascertainment bias (apparent increase due to differential referral/acceptance of testing)

Tentative conclusions

Pathogenic variants occur at similar prevalence in NHW and Blacks

Suggestion of increased BRCA1 prevalence in SRAA

- Hypothesis: increased proportion of young TNBC in SRAA undergoing testing?
- Numerically insufficient to explain elevated TNBC risk in SRAA

Pathogenic variant prevalence in panels is similar

Highly variable prevalence in Hispanics may reflect population variation or referral bias

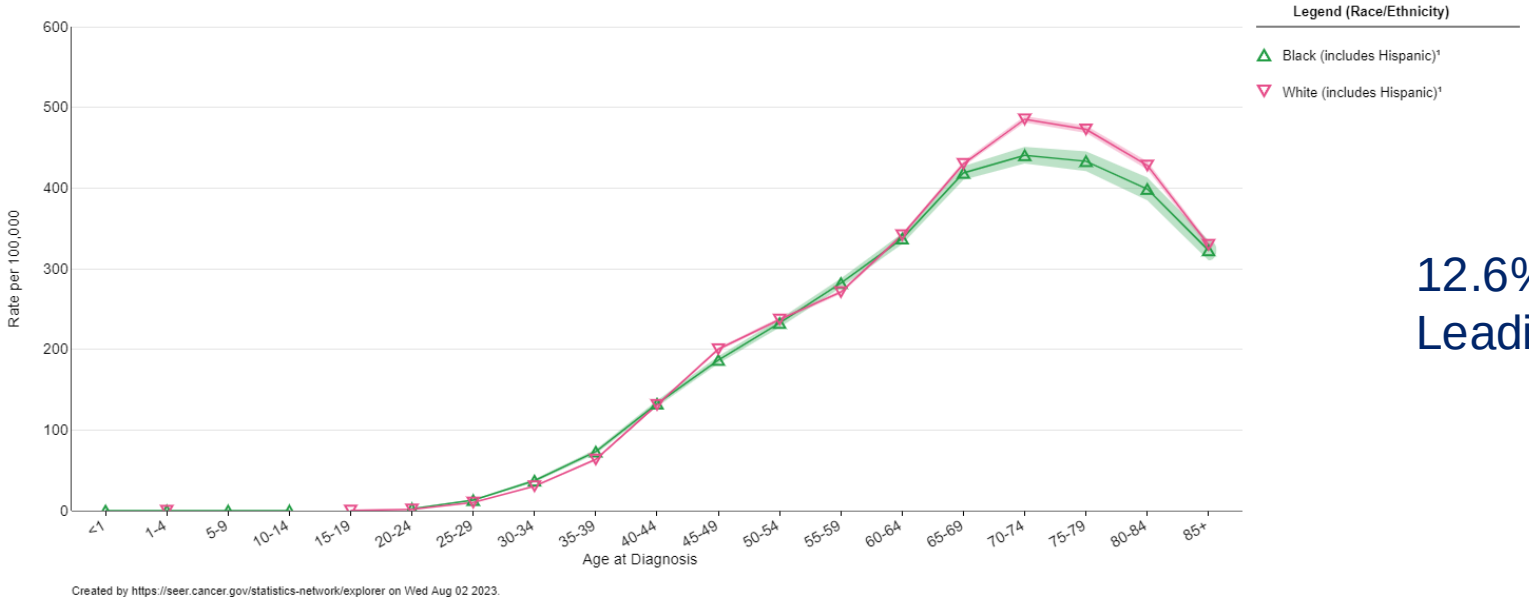
VUS more common outside NHW group

Important question

Are BRCA1 mutations more highly penetrant in SRAA?

		All BC (OR, 95% CI)	TNBC (OR. 95% CI)
Overall Population	BRCA1	7.62 (5.3-11.3)	42.88 (26.6-71.3)
	BRCA2	5.23 (4.09-6.77)	9.70 (6.0-15.5)
SRAA	BRCA1	42.79 (9.24 to >100)	129.7 (28.0 to >100)
	BRCA2	7.31 (4.08-14.29)	9.38 (4.8-19.6)

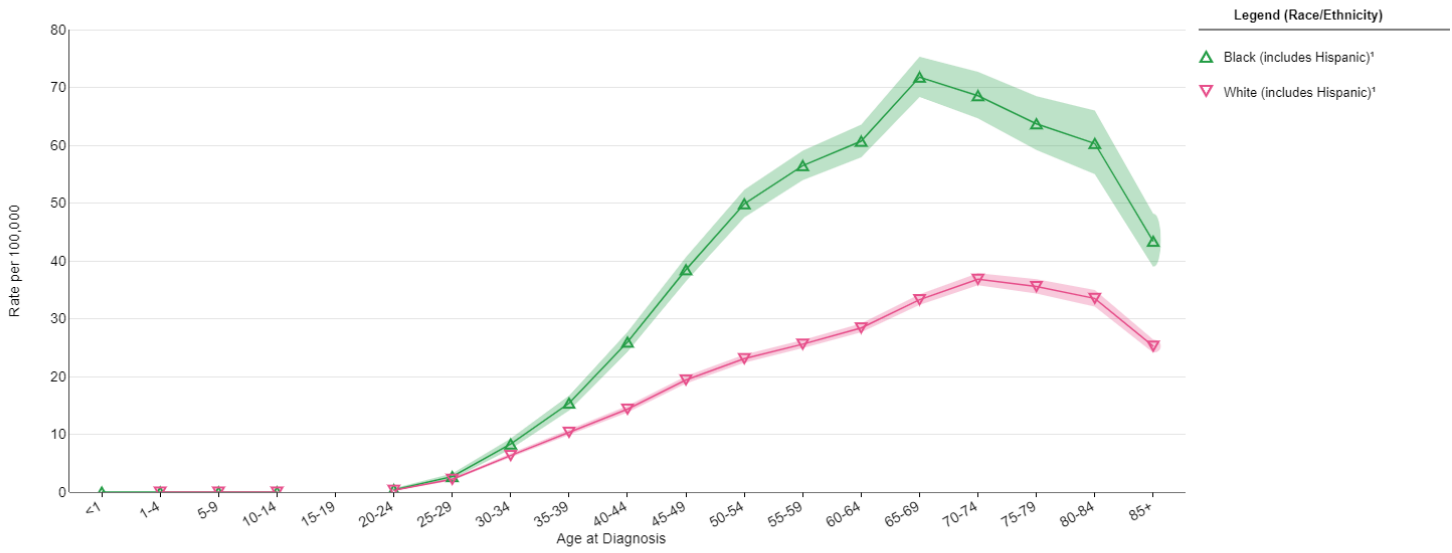
Breast
SEER Incidence Rates by Age at Diagnosis, 2016-2020
By Race/Ethnicity, Delay-adjusted SEER Incidence Rate, Female



Created by https://seer.cancer.gov/statistics-network/explorer on Wed Aug 02 2023.

12.6% of all US breast cancer in SRAA
Leading cause of cancer death in SRAA women

HR-/HER2- Breast Cancer (Female only)
SEER Incidence Rates by Age at Diagnosis, 2016-2020
Observed SEER Incidence Rate, Female By Race/Ethnicity



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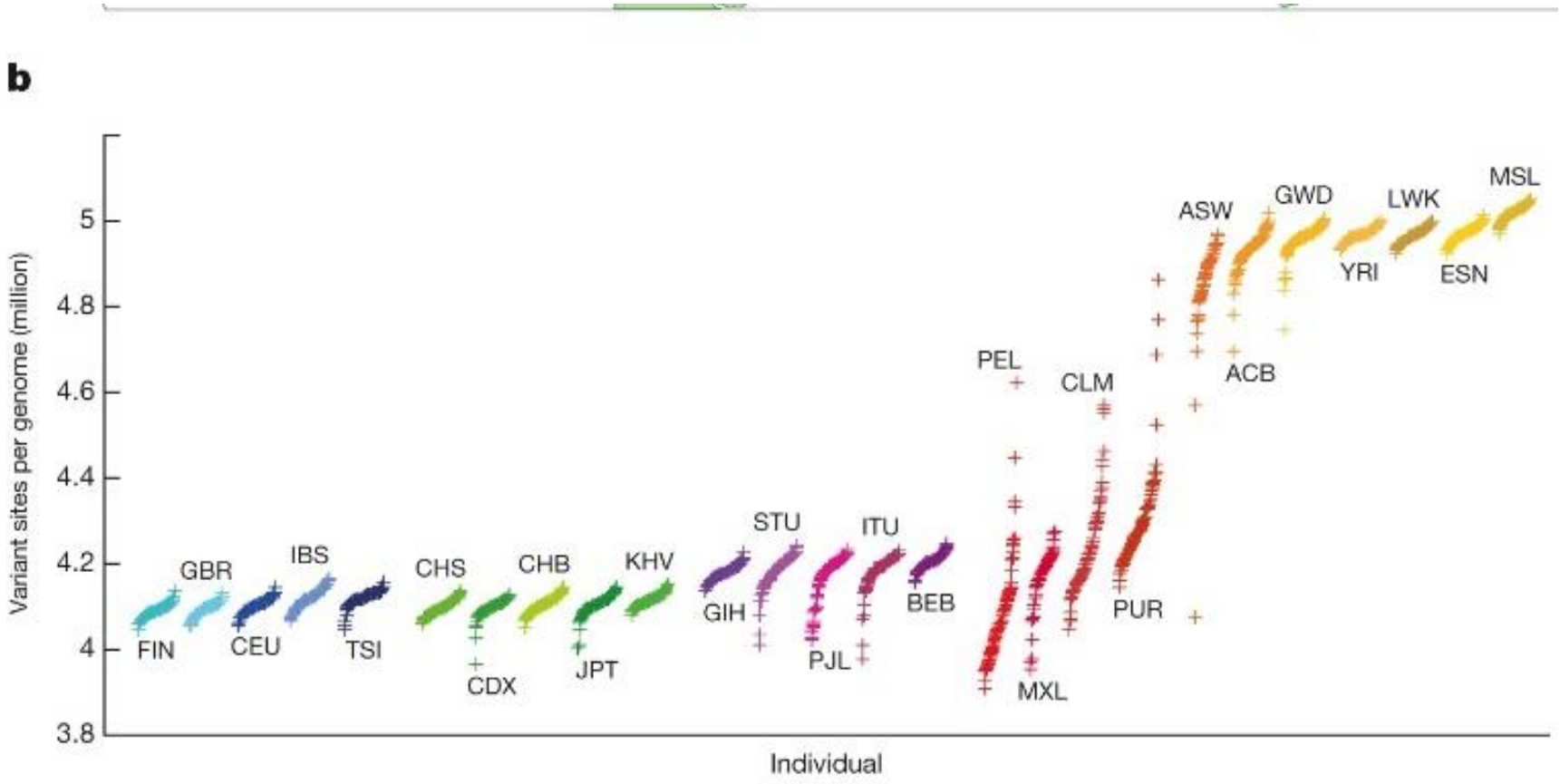
Enormous genomic diversity in African populations (potential unexplored genomic risk modifiers)



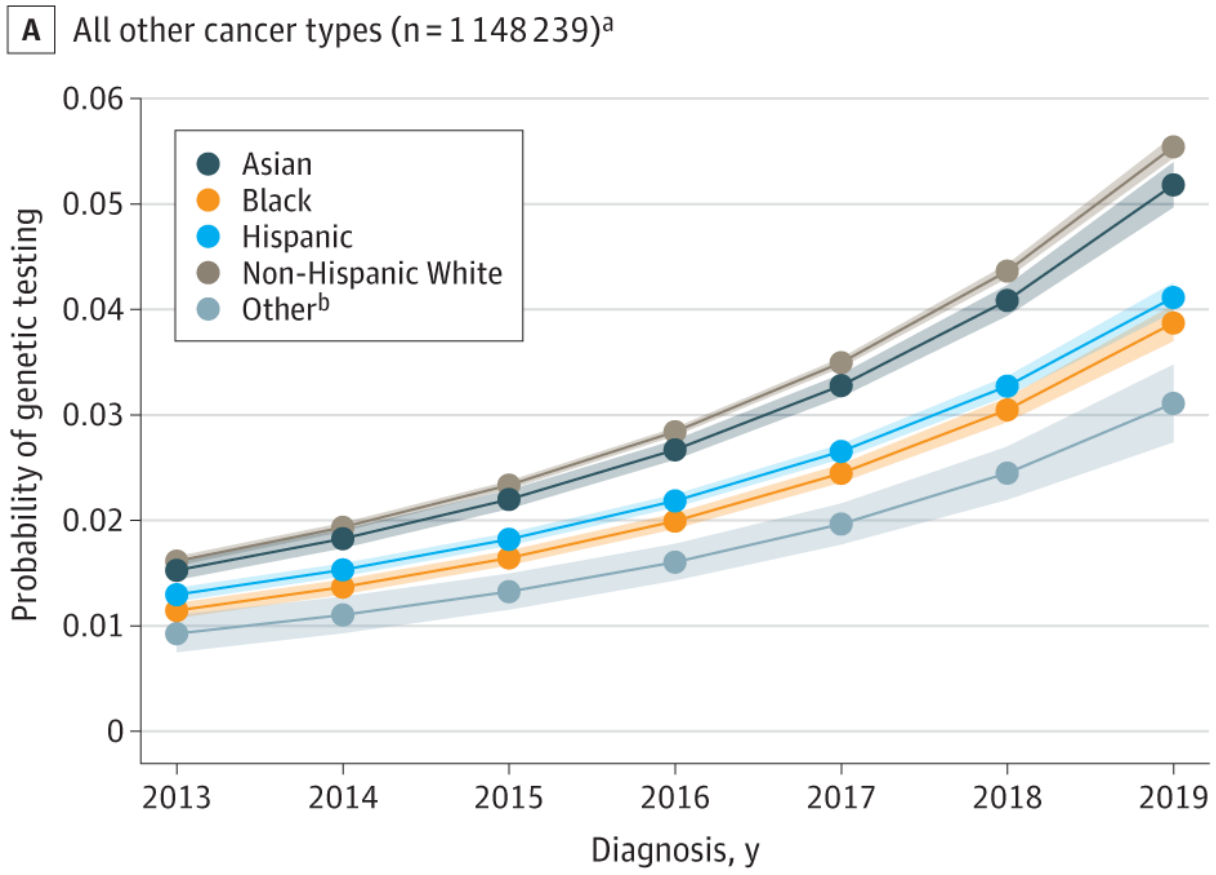
Nature **volume 526**, pages 68–74 (01 October 2015)

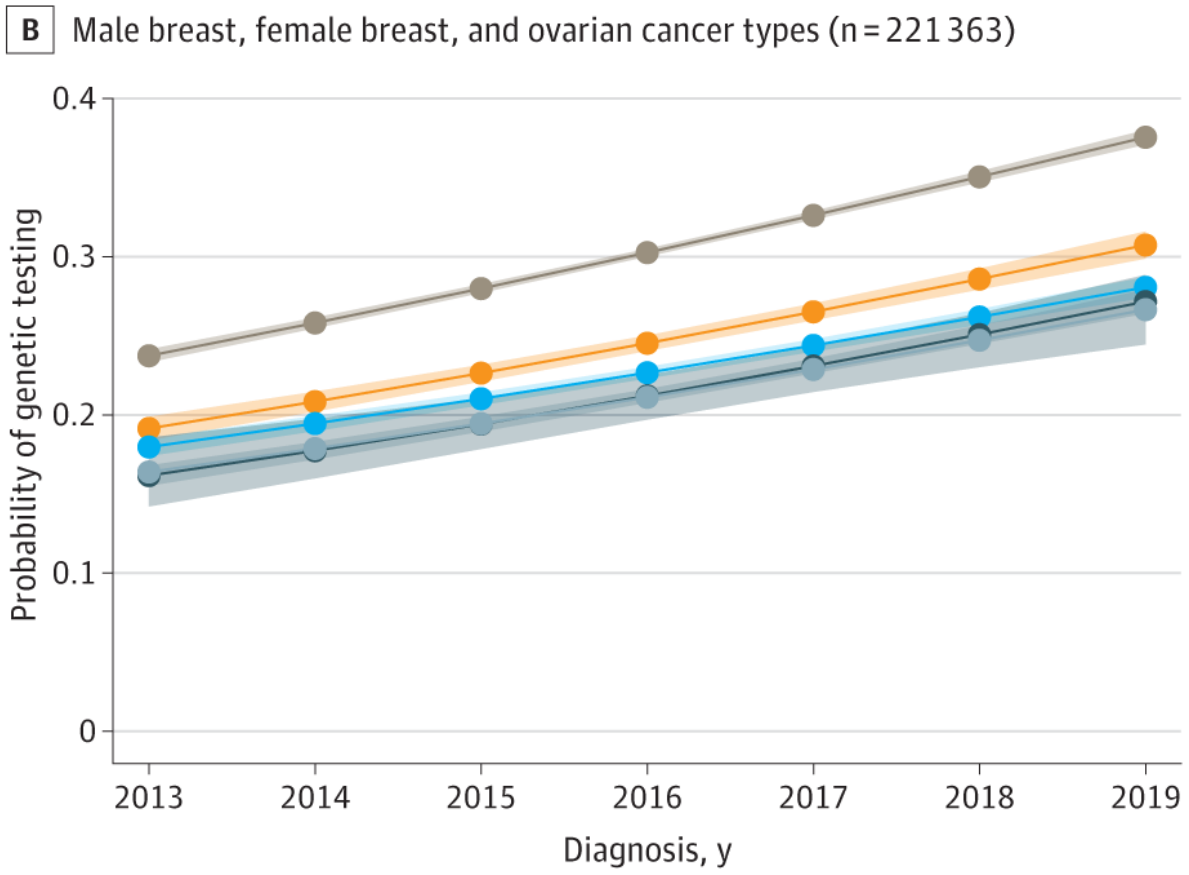
So, is race irrelevant to genetic susceptibility?

Impact on discussion of testing

Variable		Discussed Genetic Testing		Underwent Testing	
		OR (95% CI)	P	OR (95% CI)	P
Race	Black v NHW	0.06 (0.04-0.10)	<0.0001	0.18 (0.11-0.29)	<0.00001
	English L H v NHW	1.08 (0.60-1.94)	0.8	1.52 (0.96-2.39)	0.07
	Spanish L H v NHW	0.54 (0.30-0.96)	0.04	1.07 (0.62-1.83)	0.82

Impact on testing





Impact on Cascade Testing

Characteristic	All probands	Probands with at least 1 ARR tested	OR (95% CI)	p
Race	Black (n=791) White (n=9997)	94 (11.9%) 2170 (21.7%)	0.49 (0.39,0.61)	<0.0001

Conclusions

Race (self-identified or assigned) has little effect on prevalence of rare PV predisposing to breast cancer

Penetrance of *BRCA1* PV may be higher in SRAA women (?same reason as general increased risk of TNBC?)

Race appears to be a social determinant of access to genetic testing and to cascade testing after PV identified

Conclusions 2

Very little information about other racial groupings but PV seem to be similar prevalence in ancestry groups (aside from founder effects)

Impact of ethnicity unclear – studies of self-identified Hispanic women limited and complicated by enormous heterogeneity of ancestry in “Hispanics”

Increased prevalence of PV in AJ is an accident of history rather than biology or culture

Our genes do not define who we are.
Nor do they determine what we will be.
But they do reflect where we (our families) have been.