

Leveraging the Genetics of
***Racially Mixed* Children to Advance**
Precision Medicine

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**American Indian
and Alaska Native**

Multiracial

**Native Hawaiian
and Other Pacific
Islander**

Asian

Latino

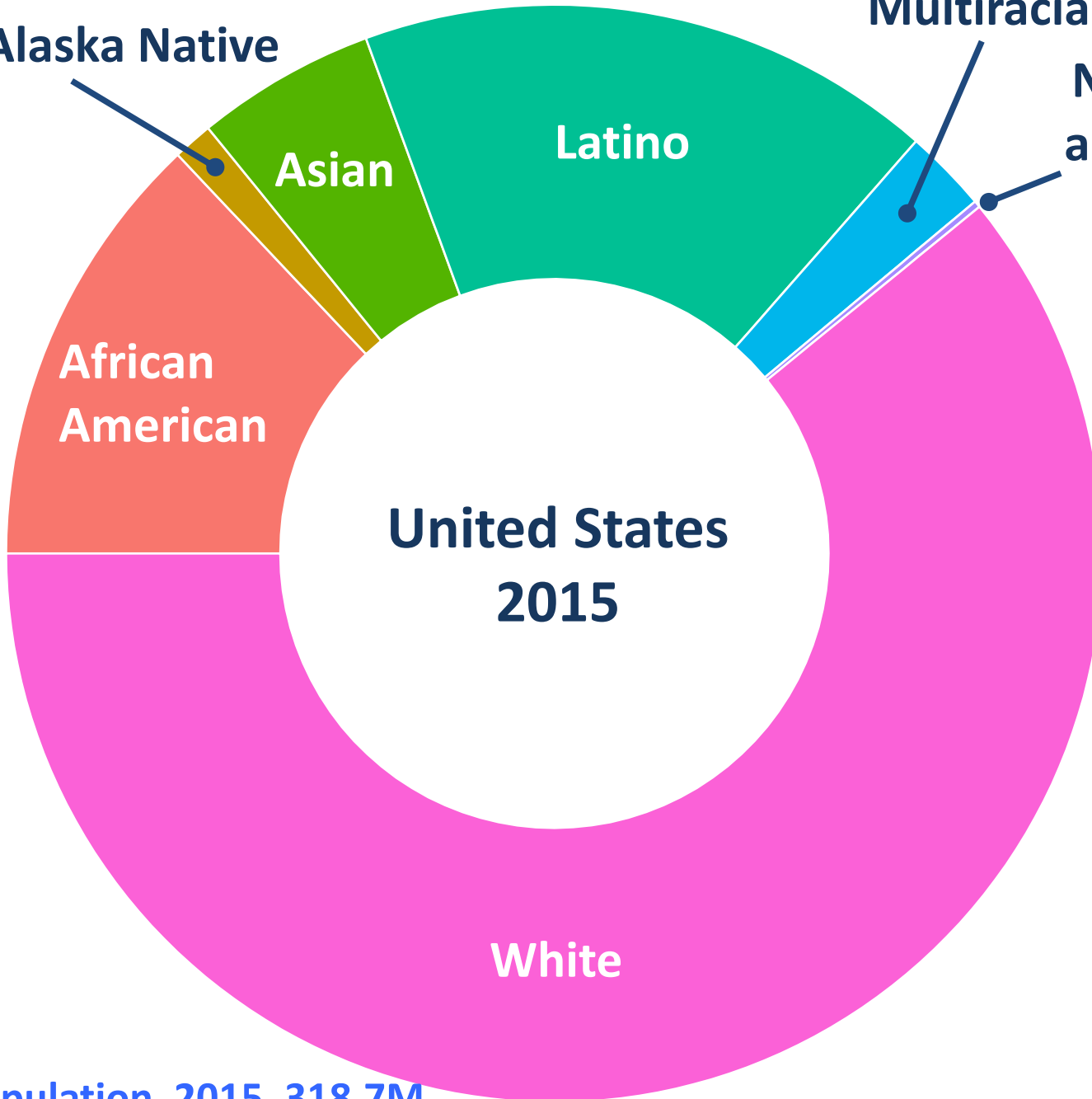
**African
American**

**United States
2015**

White

UCSF

U.S. Population, 2015. 318.7M



NIH-Funded Research

1980 - Women's Health Initiative

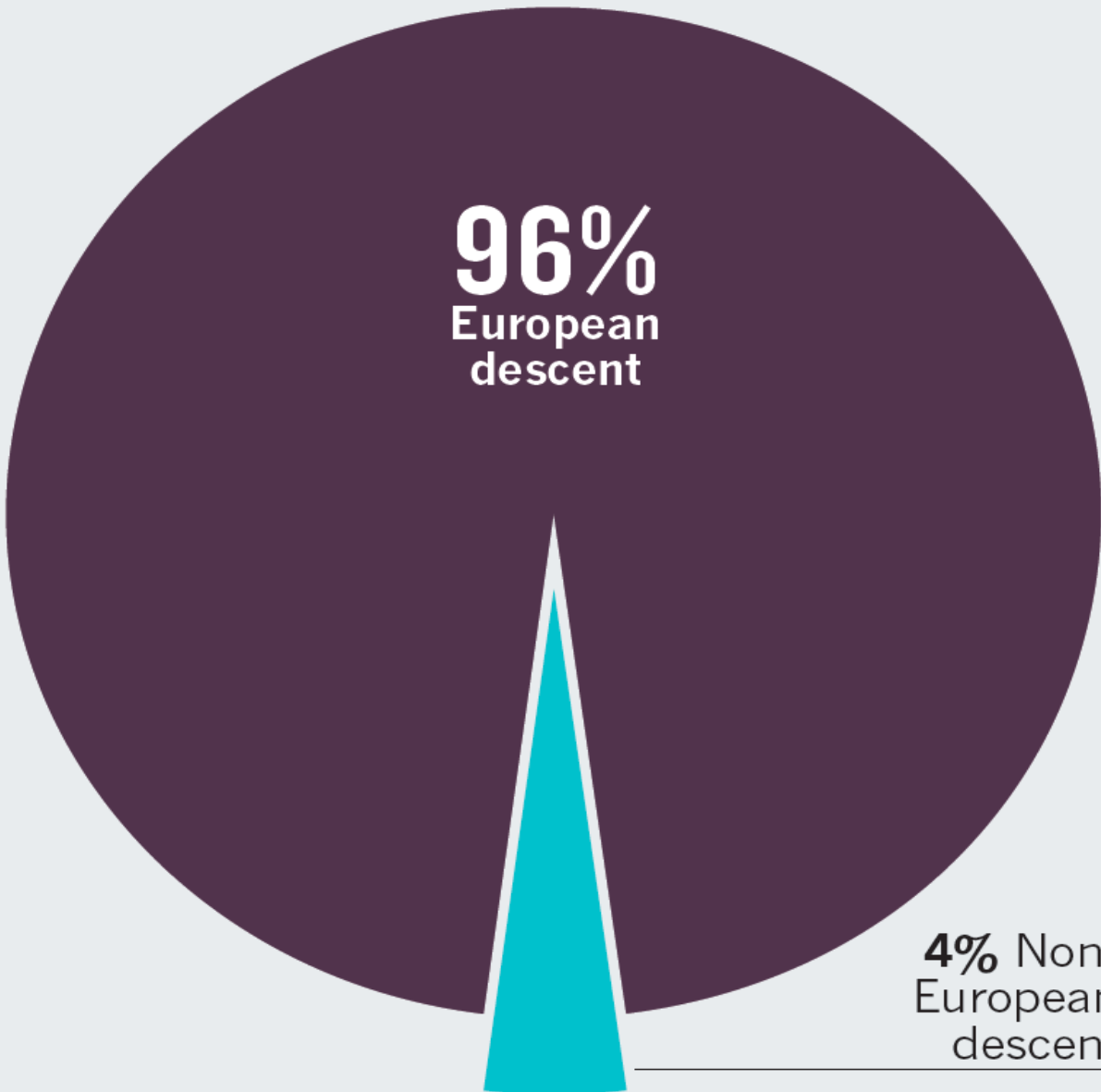
1993 – Congress *NIH Revitalization Act*

Mandated that all NIH-funded research should have the appropriate inclusion of minorities



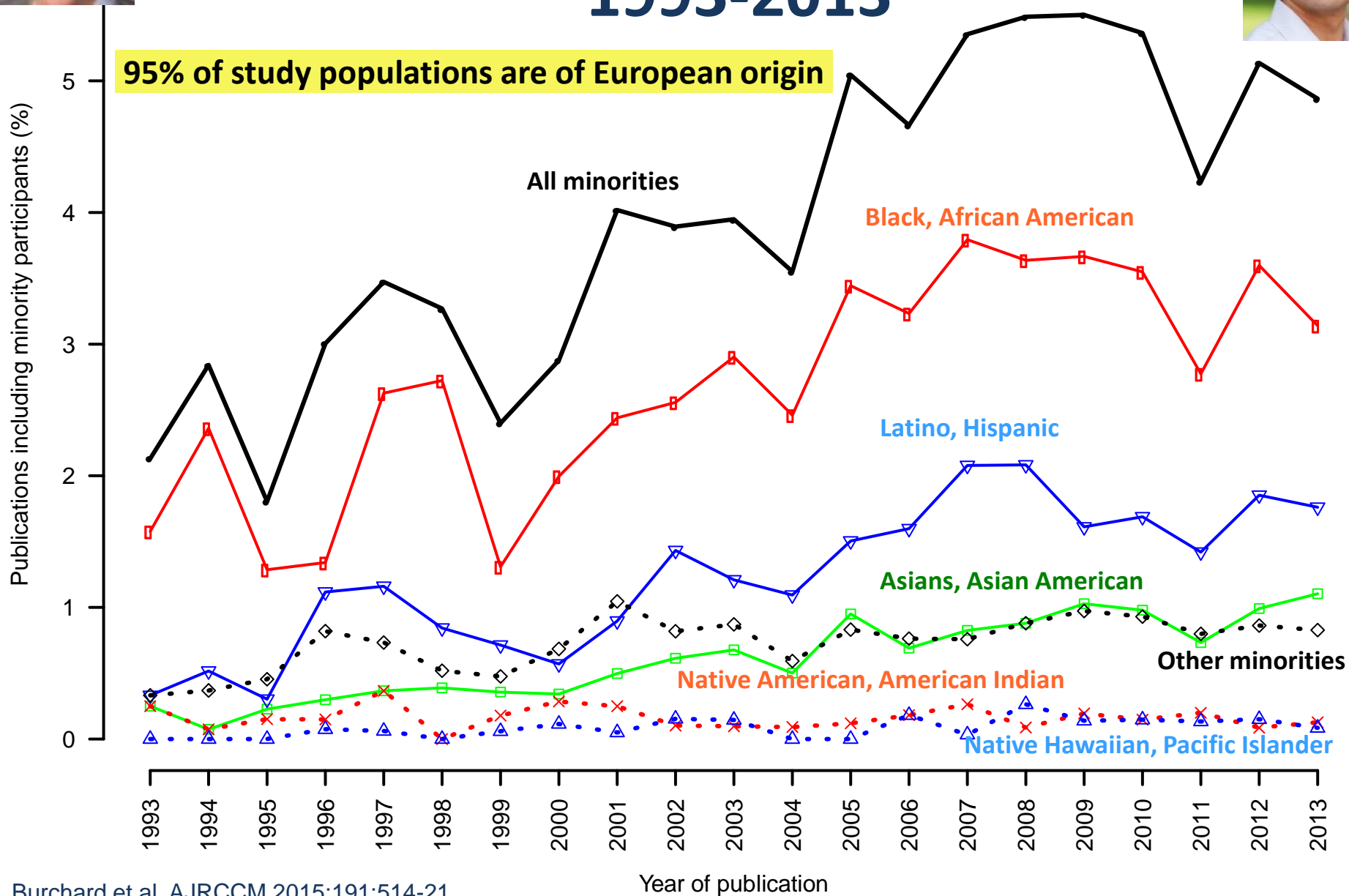
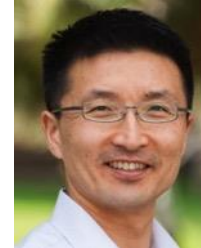
SAMPLING BIAS

Most genome-wide association studies have been of people of European descent.





NIH-Funded Pulmonary Publications 1993-2013





Making Precision Medicine

Socially Precise

What is asthma?

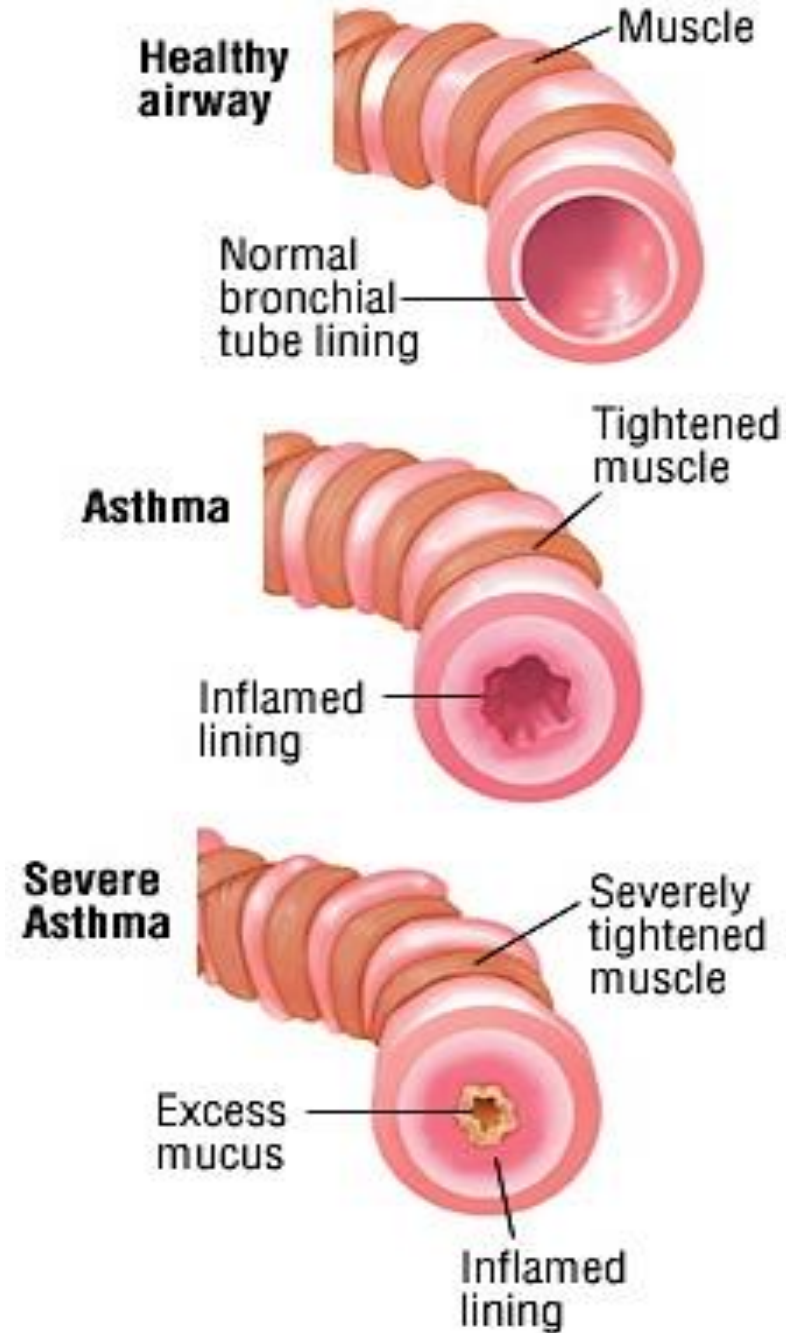
Tightening of Airways

Airway Remodeling

Thick Mucous Production

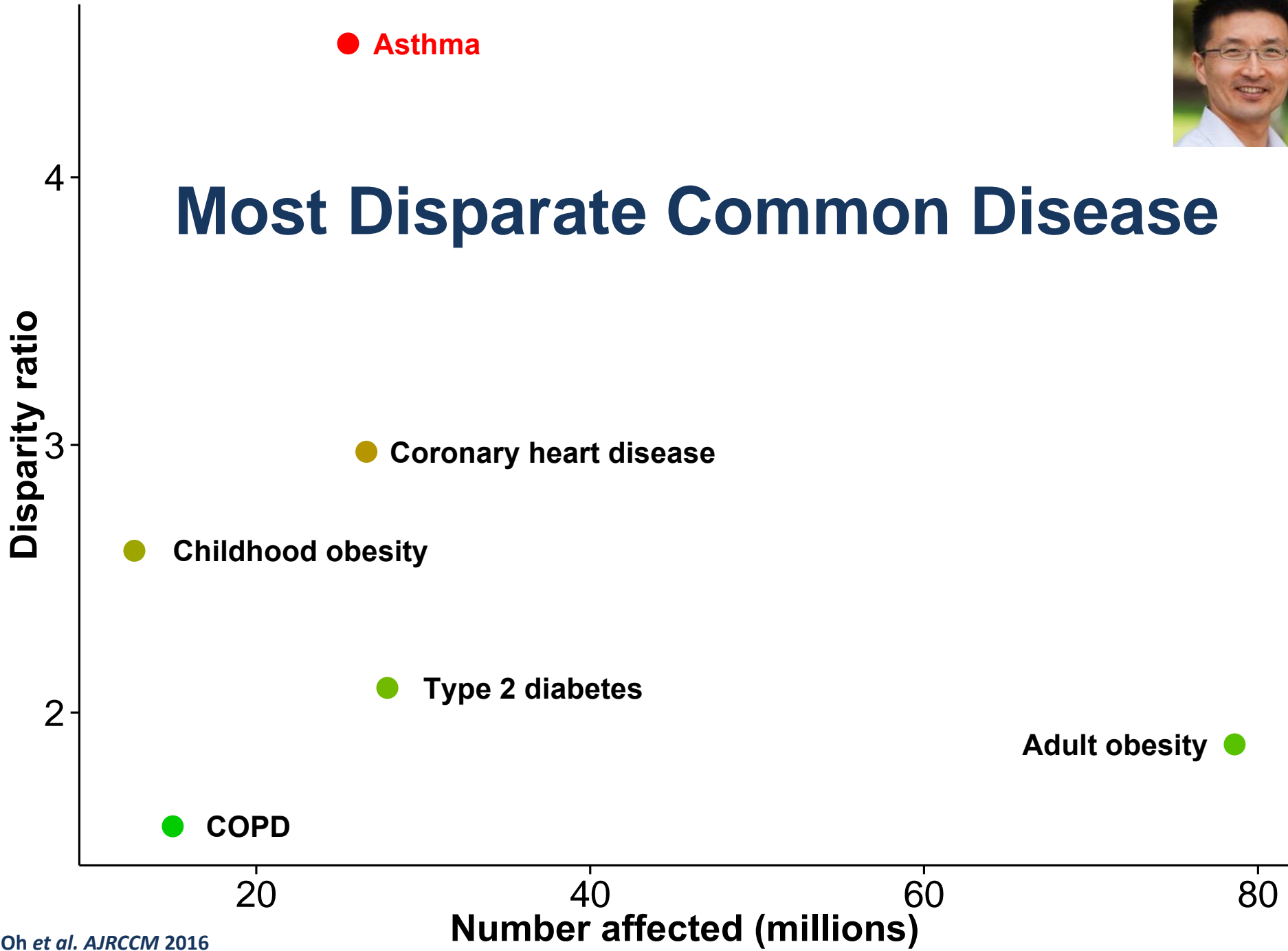
Acute and Chronic

- Wheezing
- Coughing
- Shortness of Breath



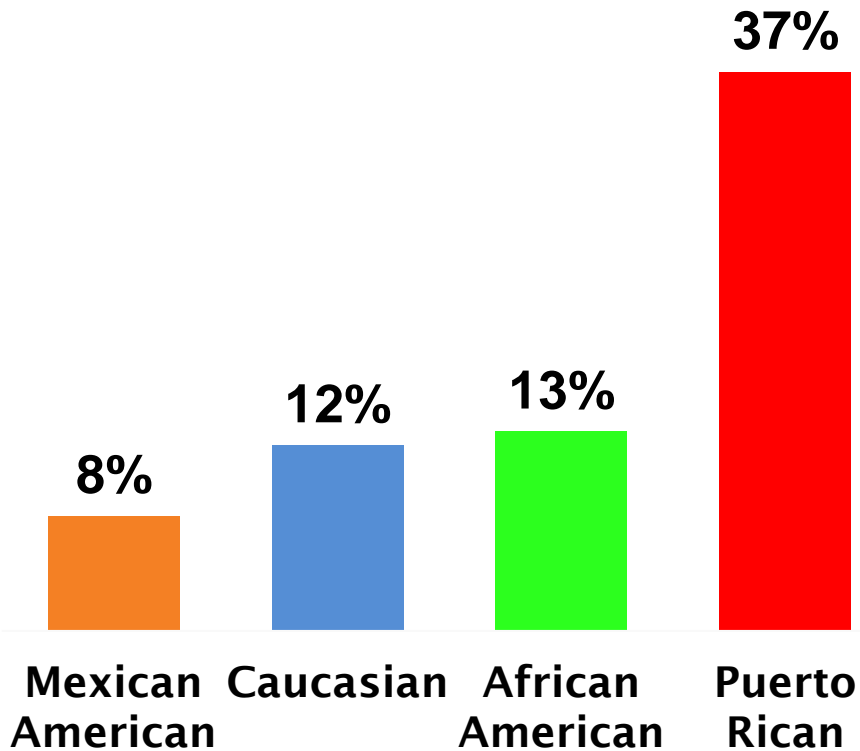


Most Disparate Common Disease

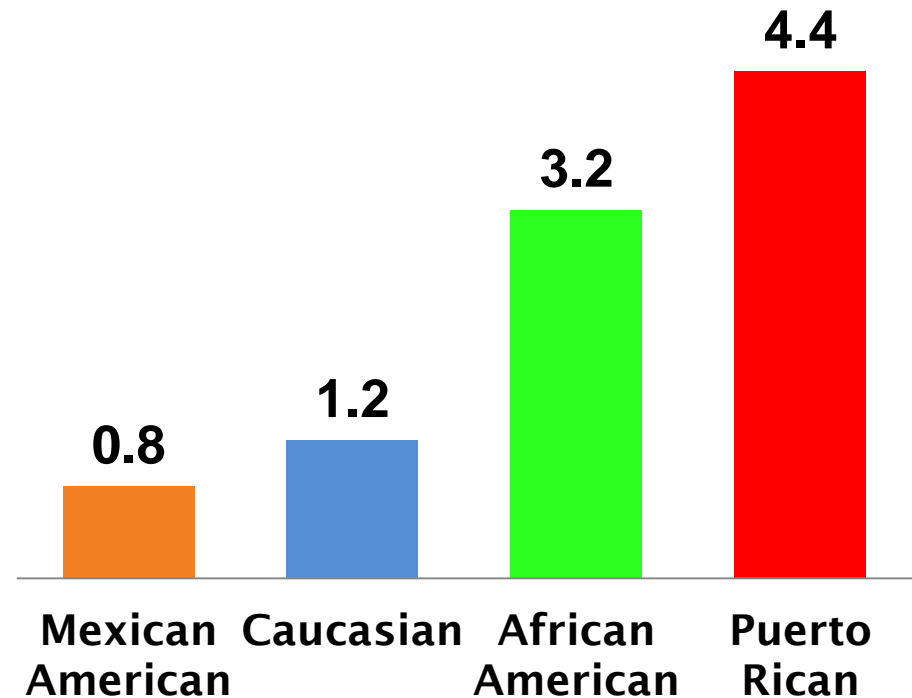


Asthma Affects ~334M Globally

Prevalence



Mortality



NHLBI Study of Latinos (SOL)

Barr et. al., *AJRCCM* 2016

Akinbami L. CDC/NCHS

UCSF

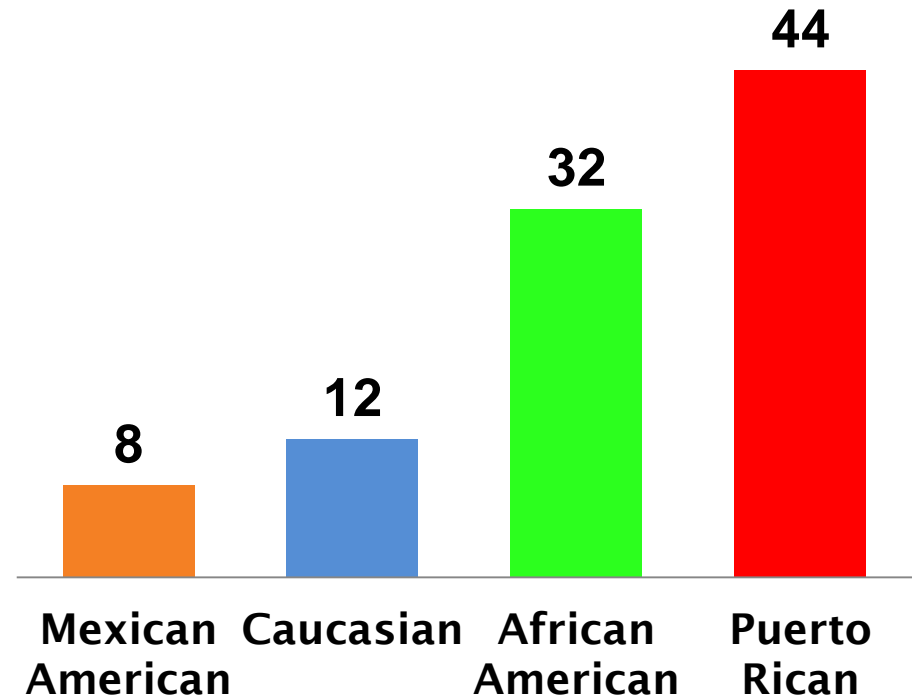
Asthma Affects ~334M Globally

Genetics

Mortality

VS.

Environment?



UCSF Asthma *Collaboratory*

We focus on the *Majority Minority*
understudied in clinical & biomedical
research

GALA & SAGE STUDIES

Local, national, international

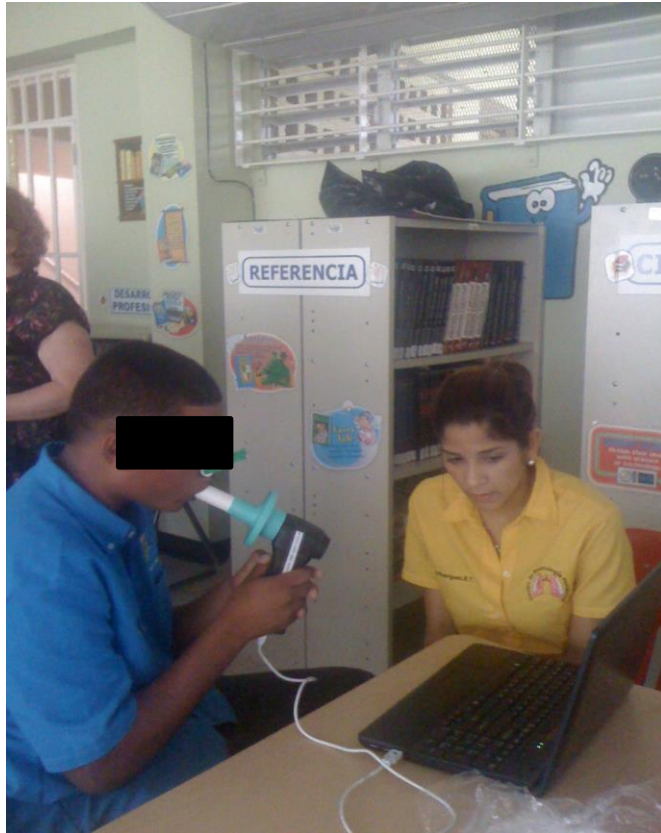


1998 - present

UCSF

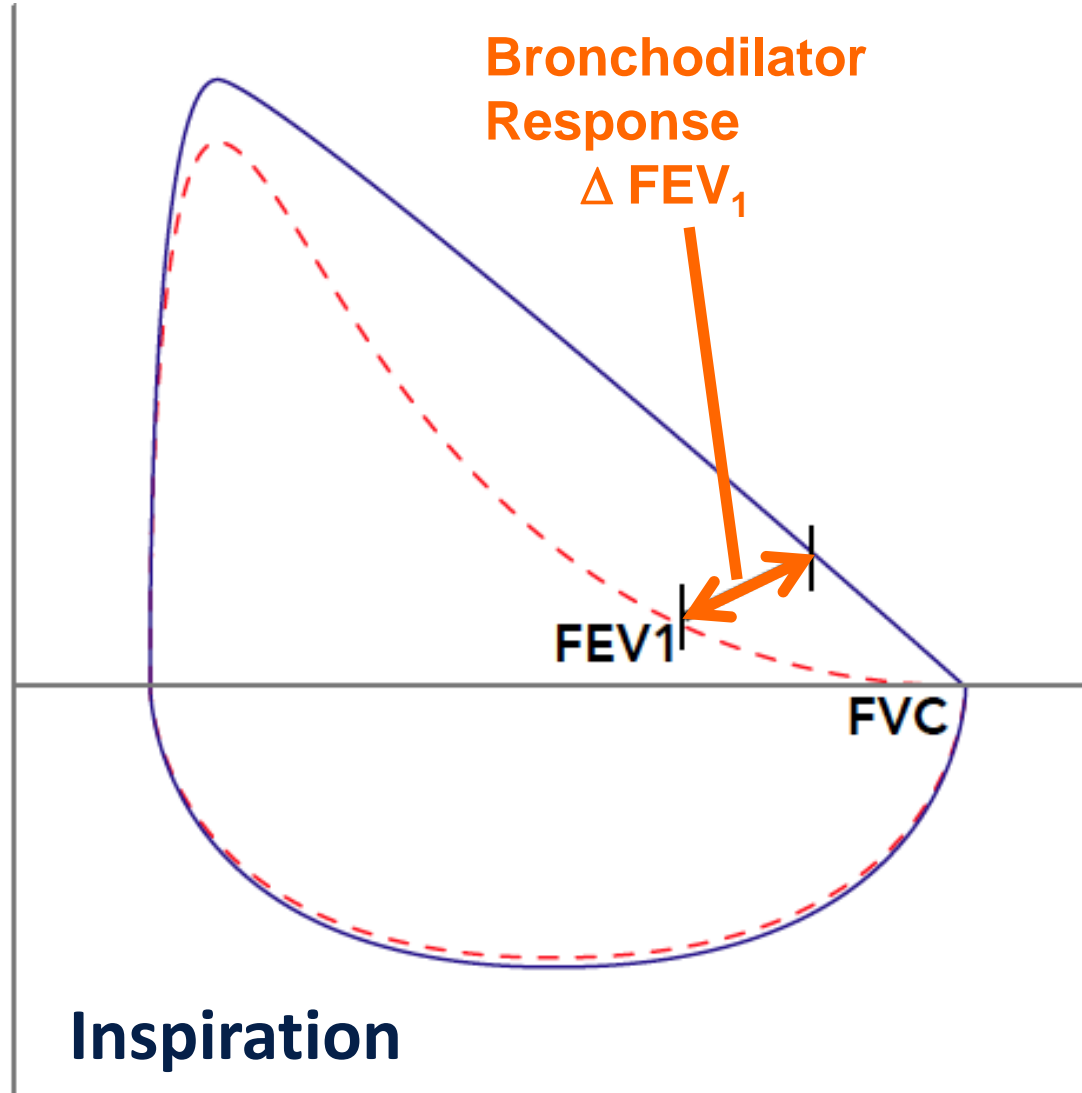
**Recruited > 10,000 minority
participants**

Measuring Bronchodilator Response

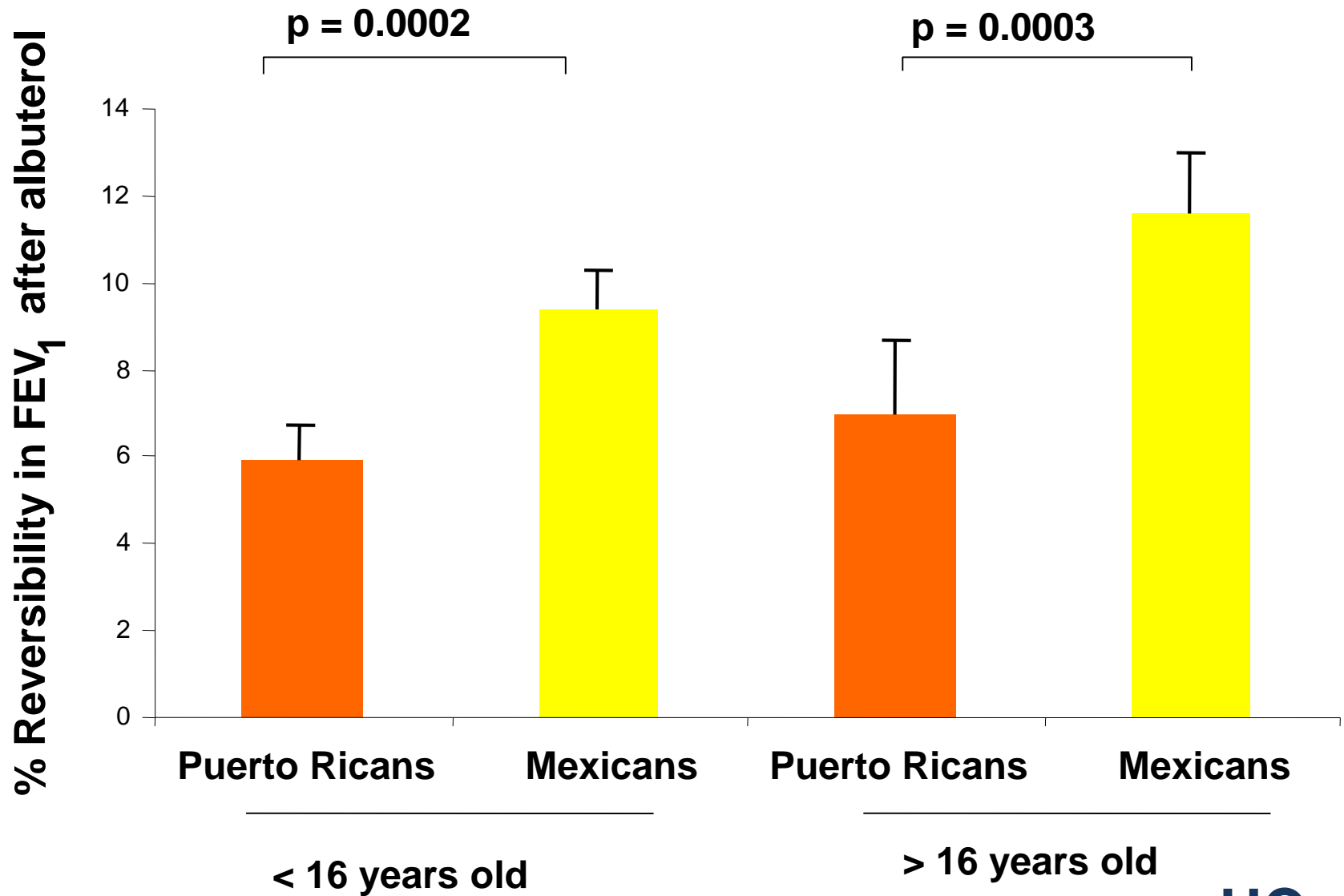


Exhalation

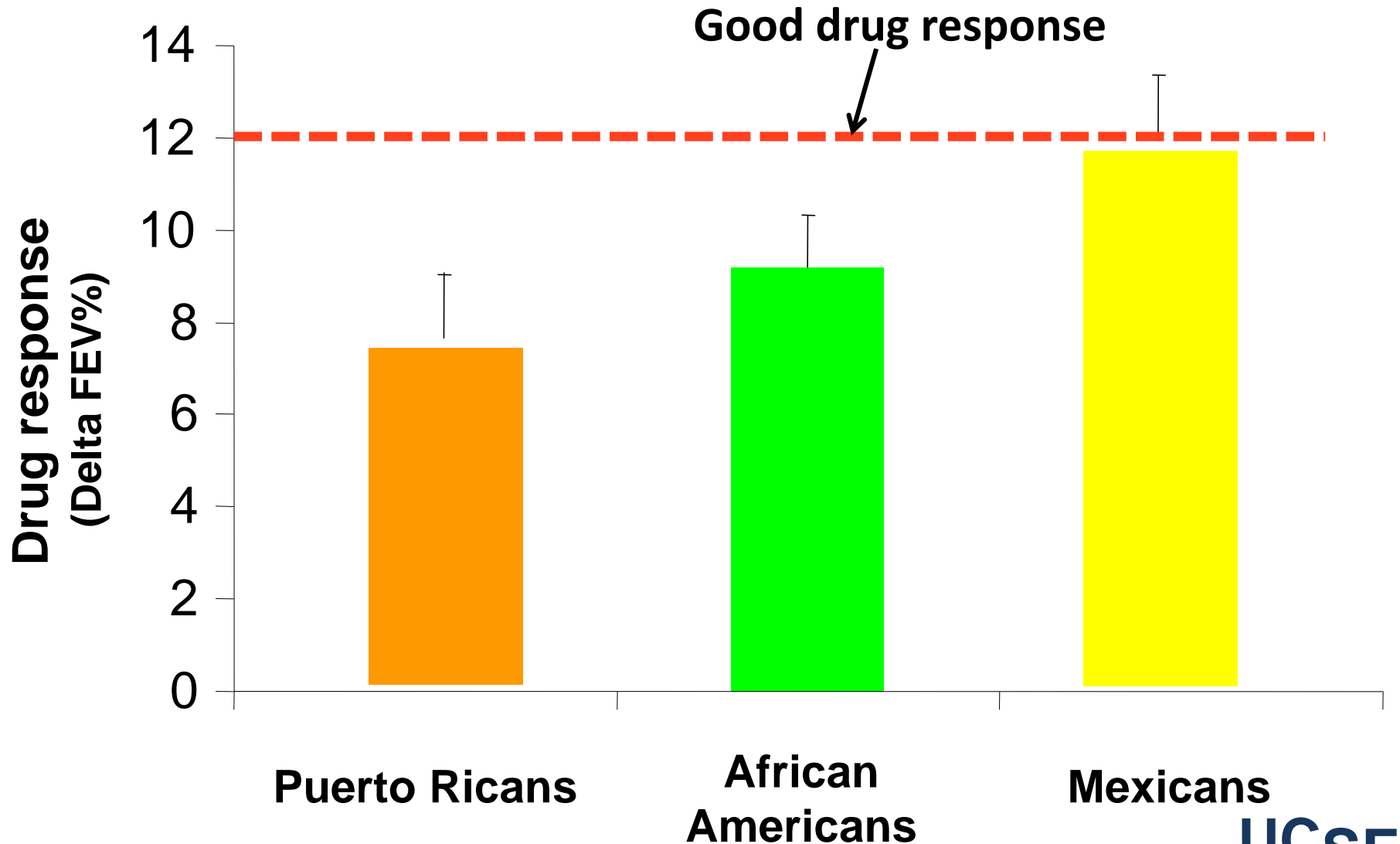
Flow (L/s)



Ethnicity & Drug Response



Children with Moderate-to-Severe Asthma

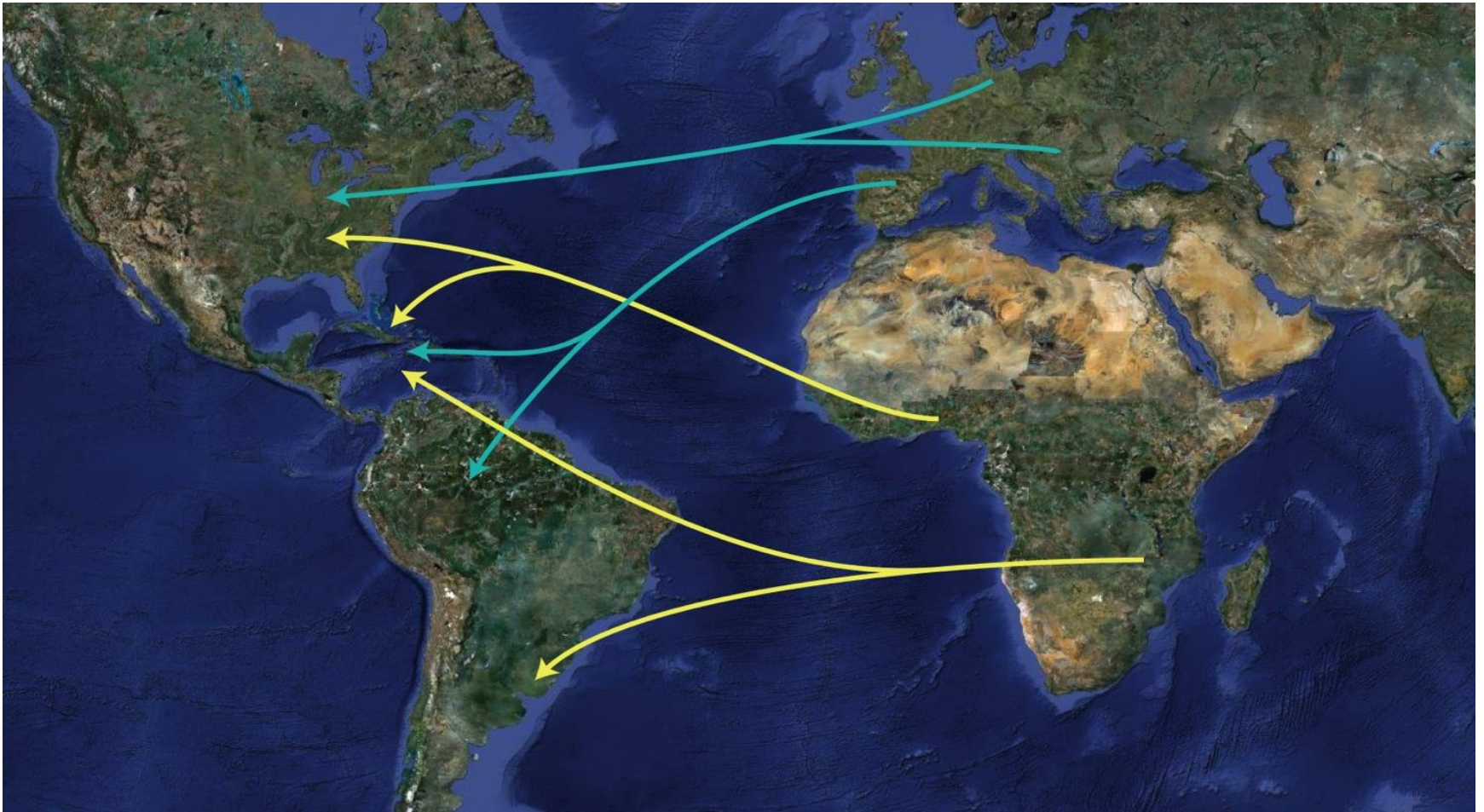


Black Box Warning

**“In African Americans,
asthma-related deaths occurred at a
higher rate in patients treated with
Salmeterol than those treated with
placebo (..relative risk: 7.26..)...”**

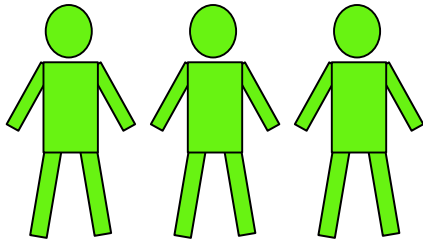
Racially Mixed Populations

Rich resource for study of complex diseases

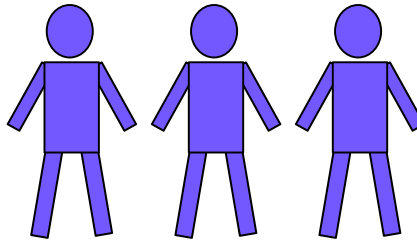


Ancestry of Latinos & African Americans

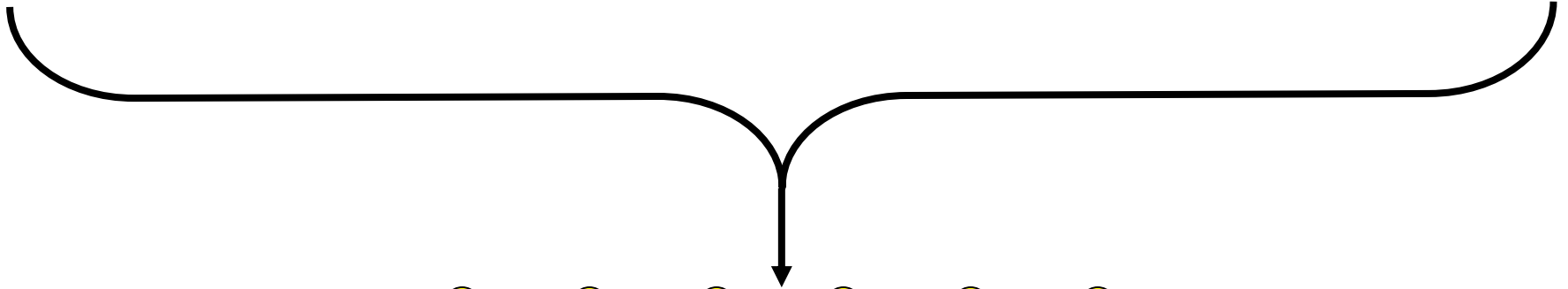
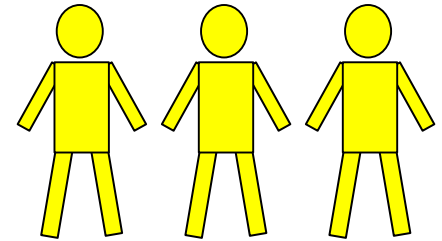
African



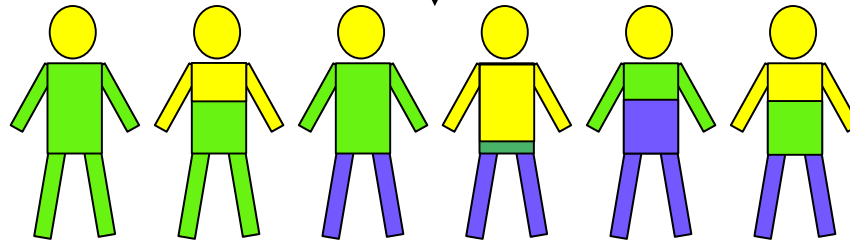
Native American

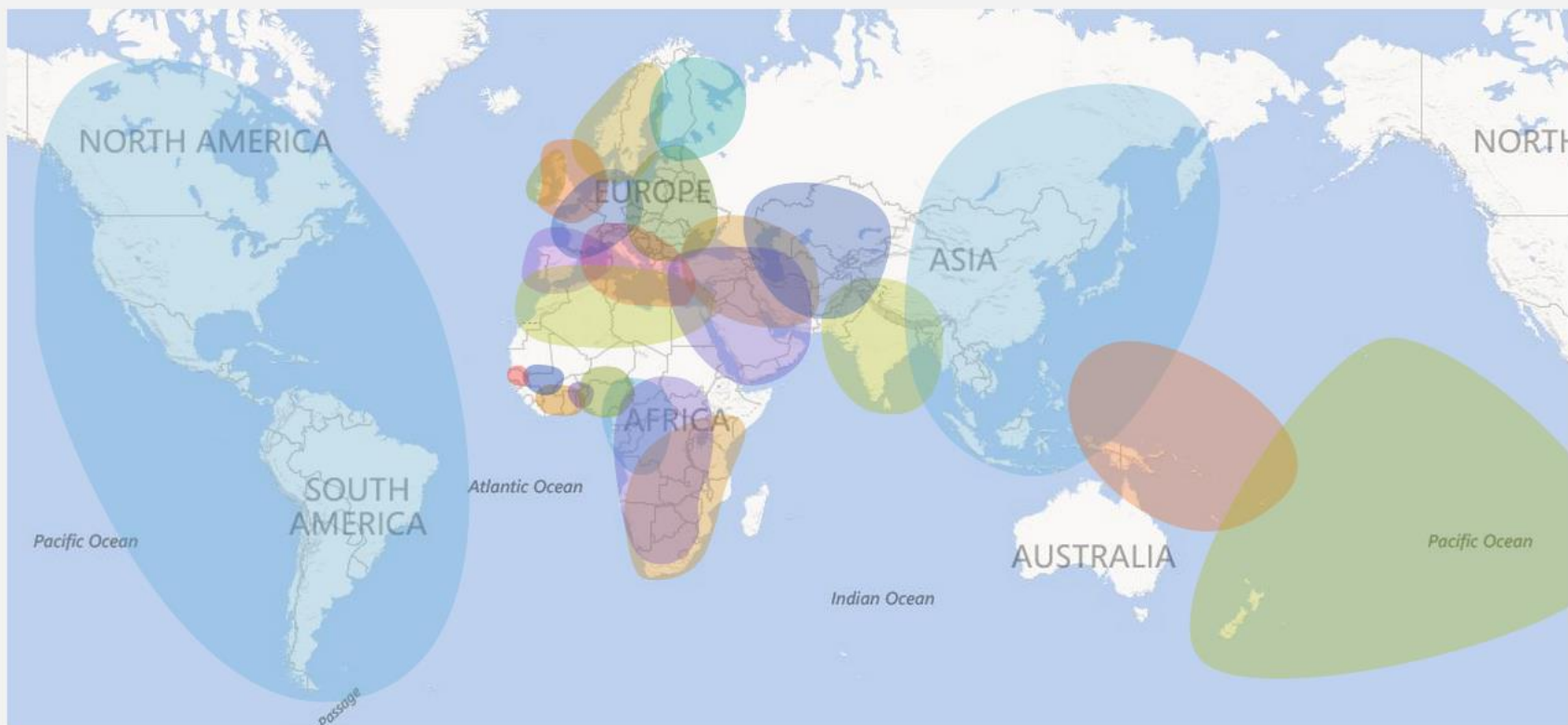


European



Admixed





AFRICA

- Africa North
- Africa South-Central
- Hunter-Gatherers
- Africa Southeastern Bantu
- Benin/Togo
- Cameroon/Congo
- Ivory Coast/Ghana
- Mali
- Nigeria
- Senegal

AMERICA

- Native American

ASIA

- Asia Central
- Asia East
- Asia South

EUROPE

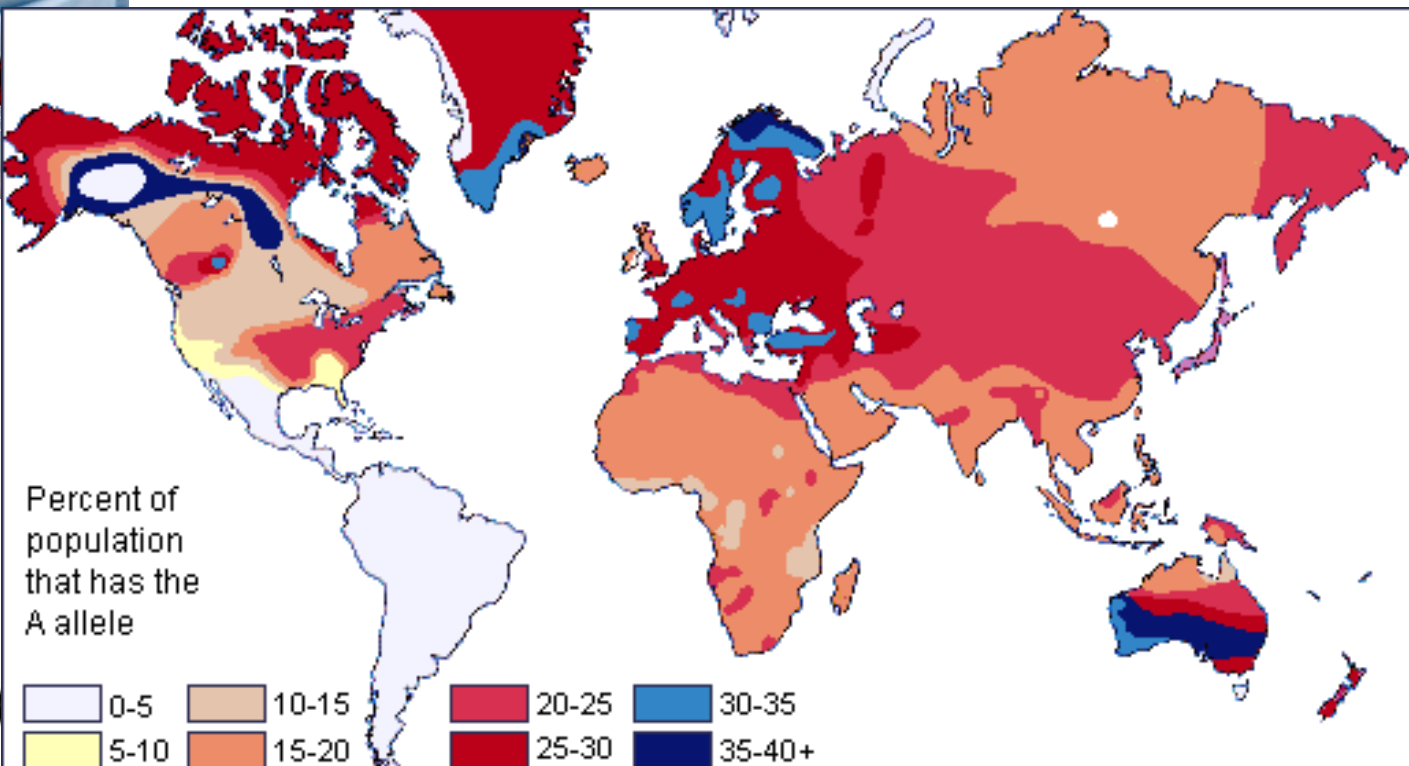
- Europe East
- Europe West
- European Jewish
- Finland/Northwest Russia
- Great Britain
- Iberian Peninsula
- Ireland
- Italy/Greece
- Scandinavia

PACIFIC ISLANDER

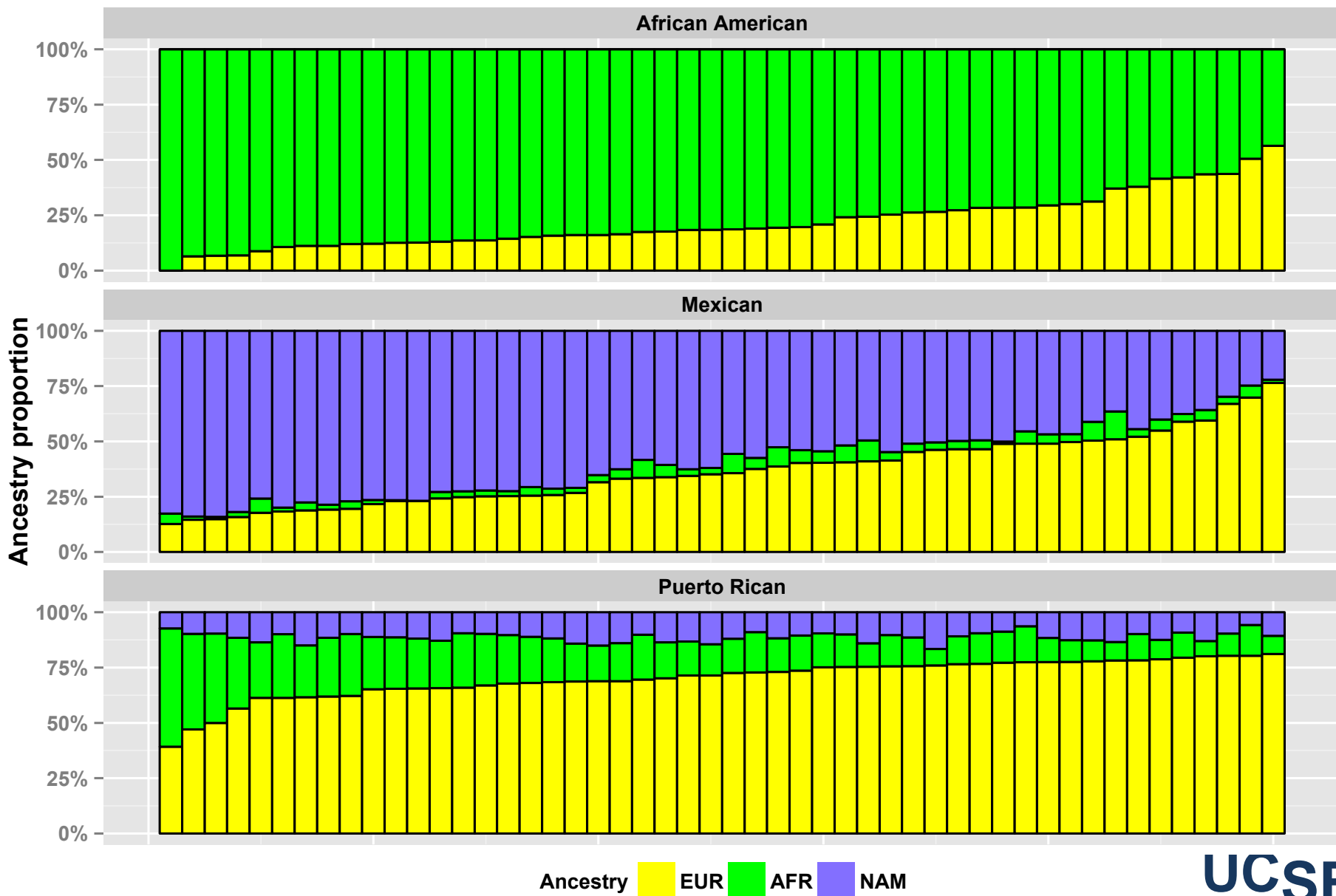
- Melanesia
- Polynesia

WEST ASIA

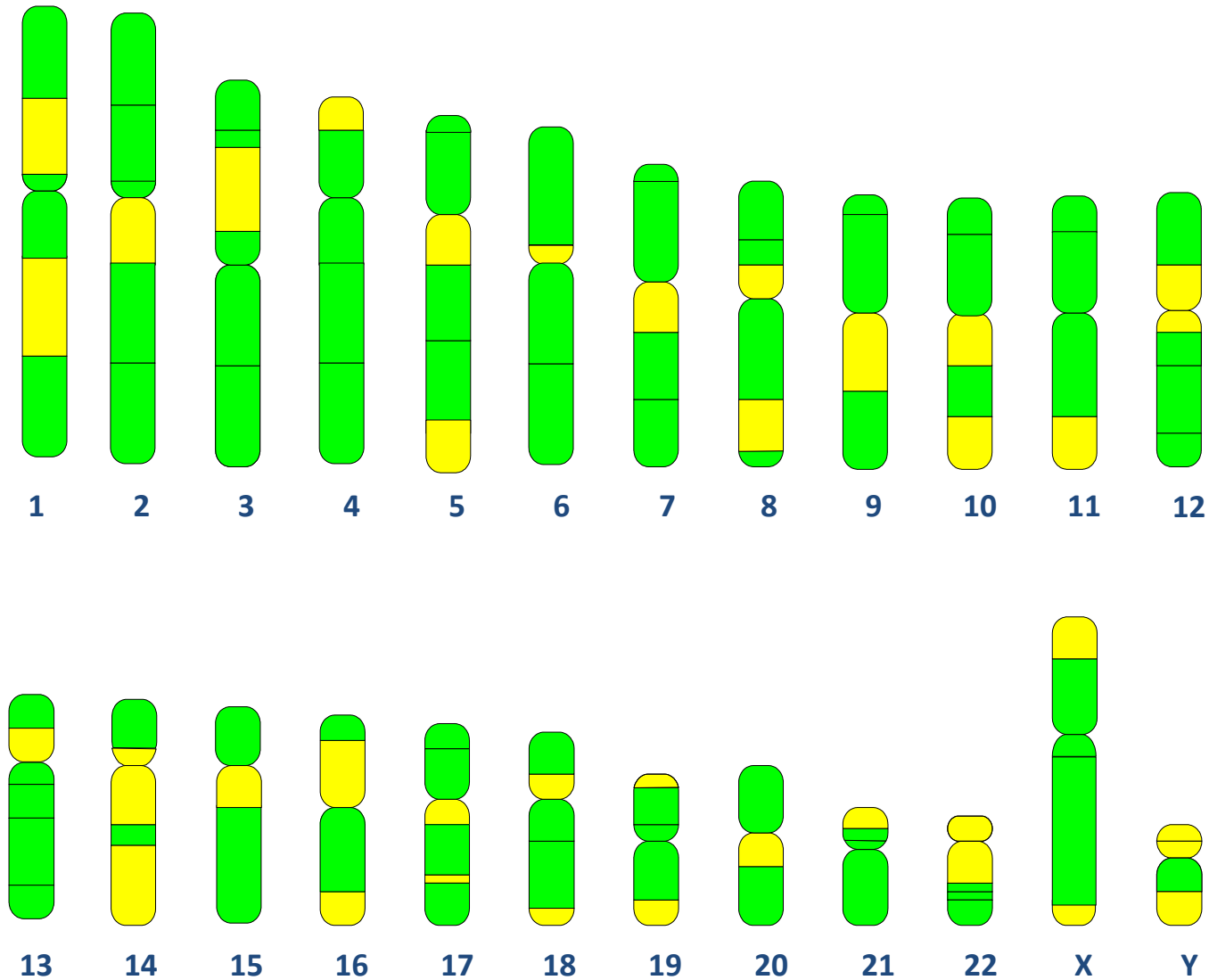
- Caucasus
- Middle East



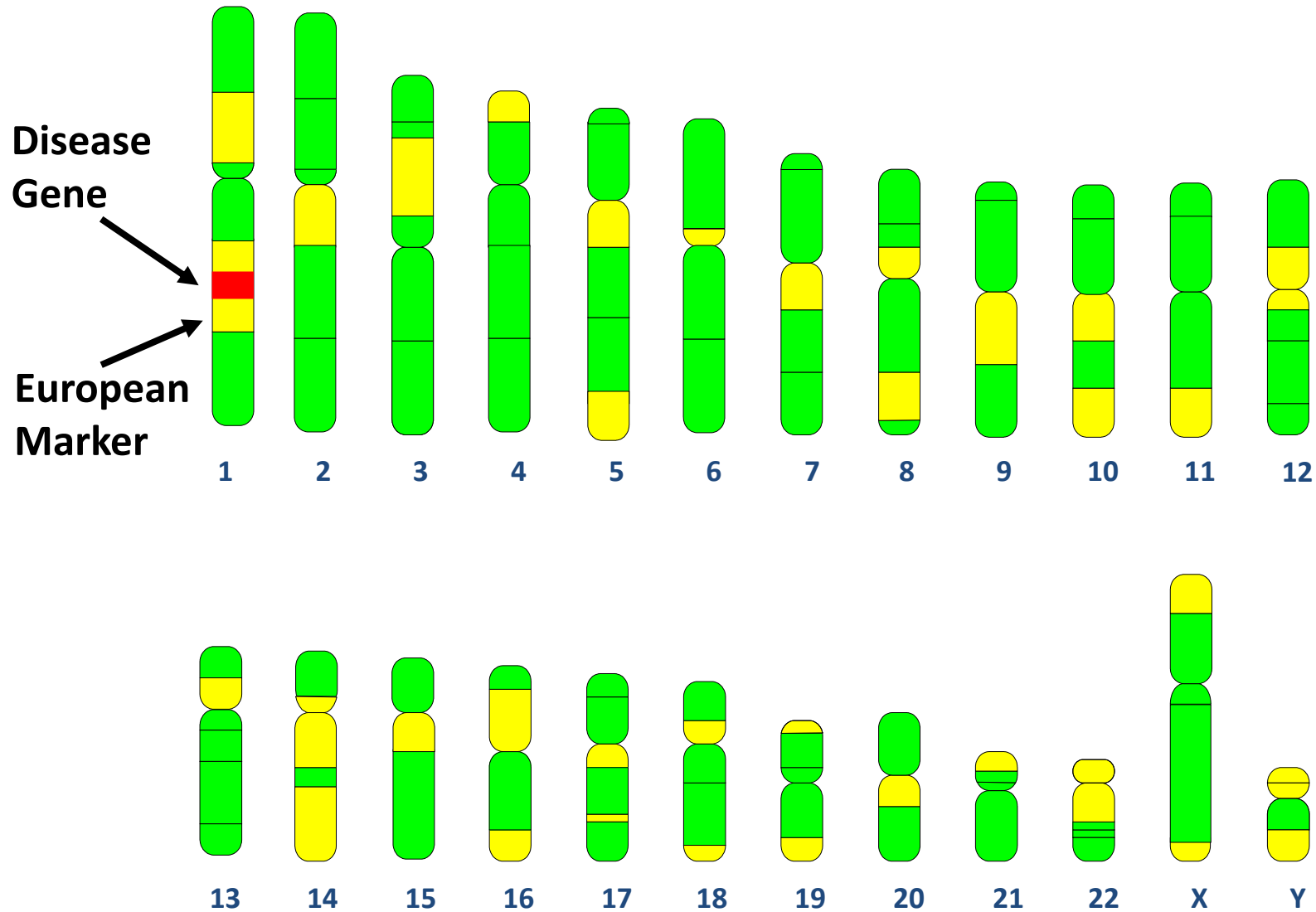
Genetic Ancestry



African Americans & Multiple Sclerosis



African Americans & Multiple Sclerosis

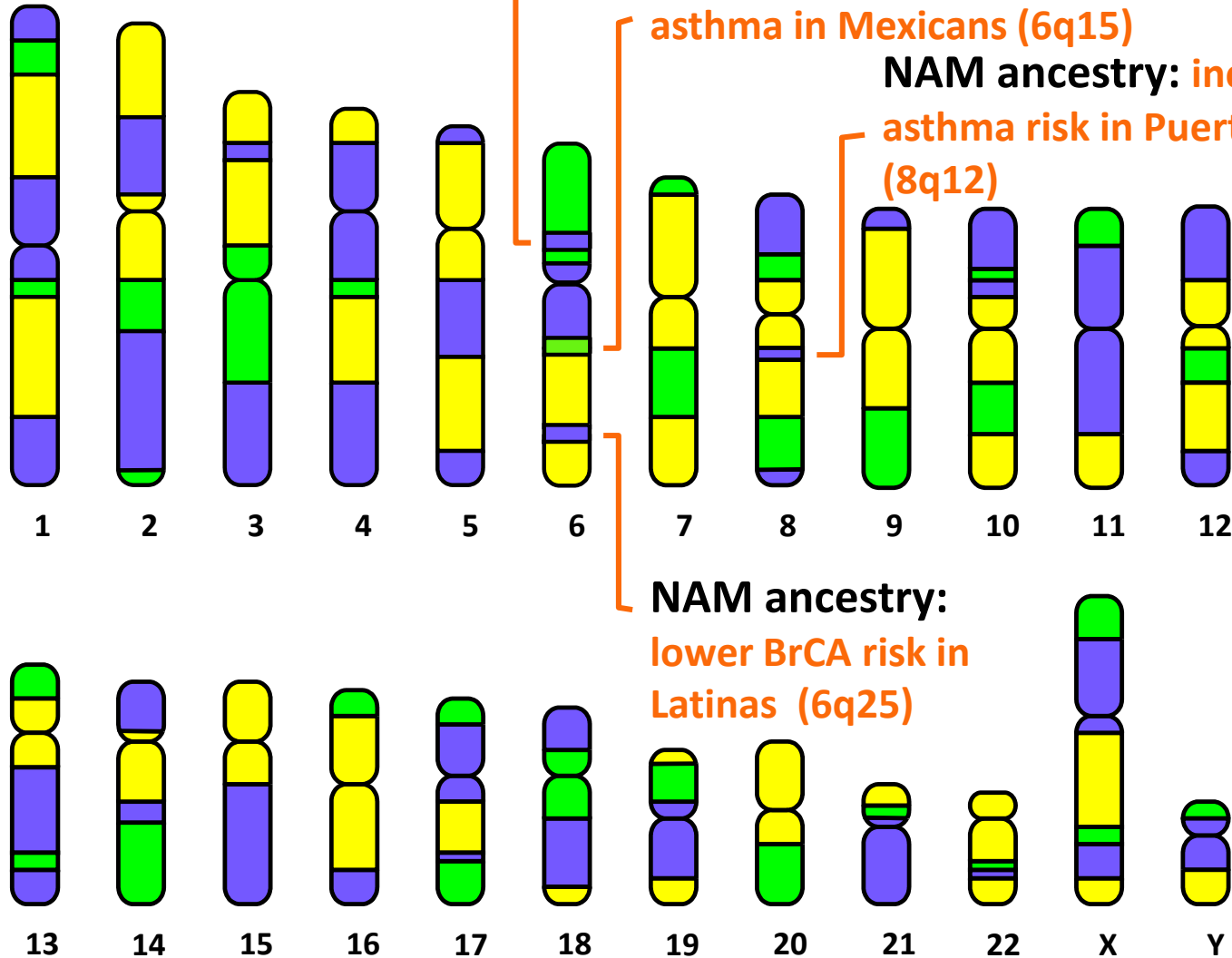


Locus Specific Ancestry

NAM ancestry: lower IgE levels in Latinos (6p21)

AFR ancestry: protective for asthma in Mexicans (6q15)

NAM ancestry: increases asthma risk in Puerto Ricans (8q12)





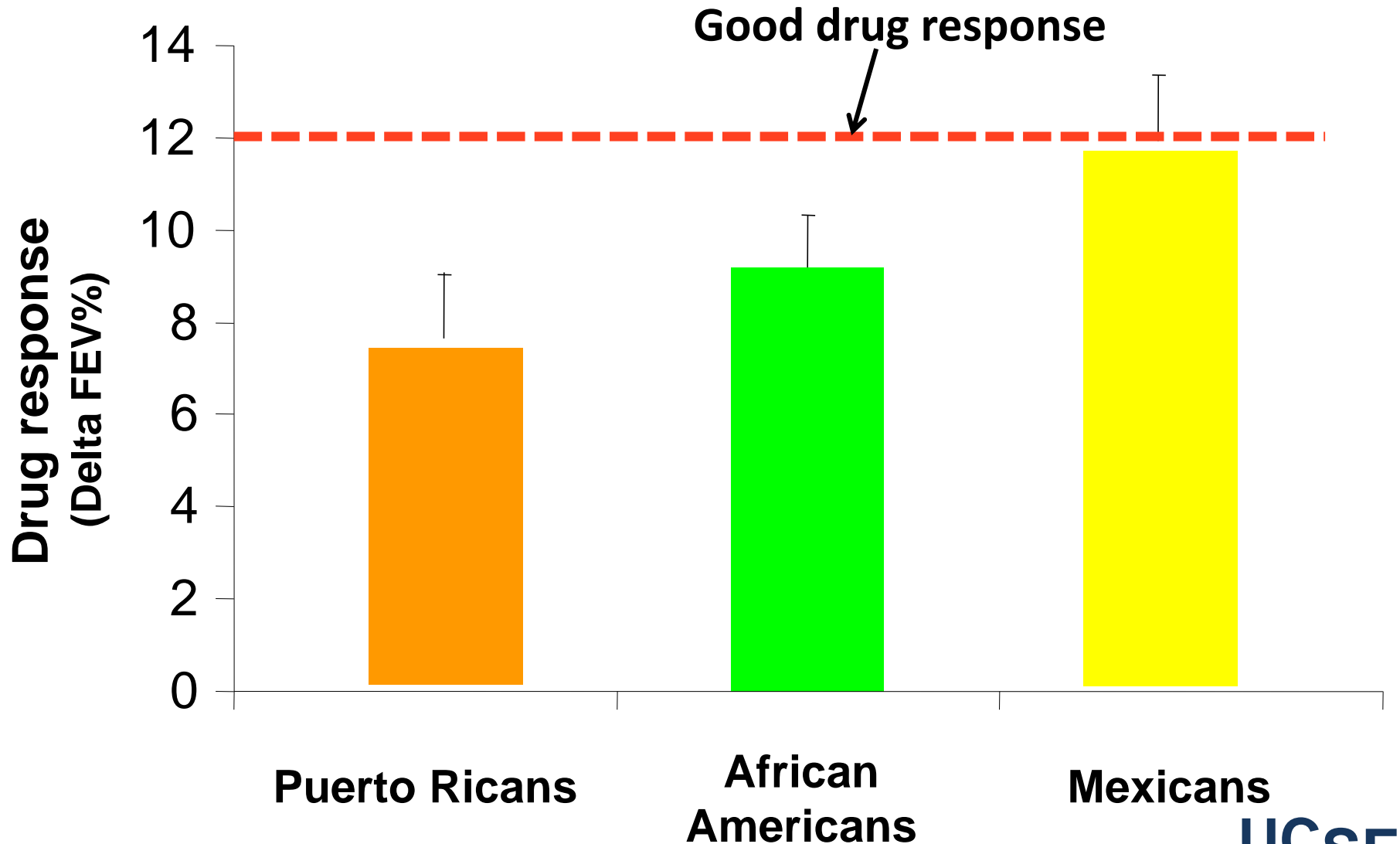
National Heart, Lung,
and Blood Institute

Whole genome sequencing

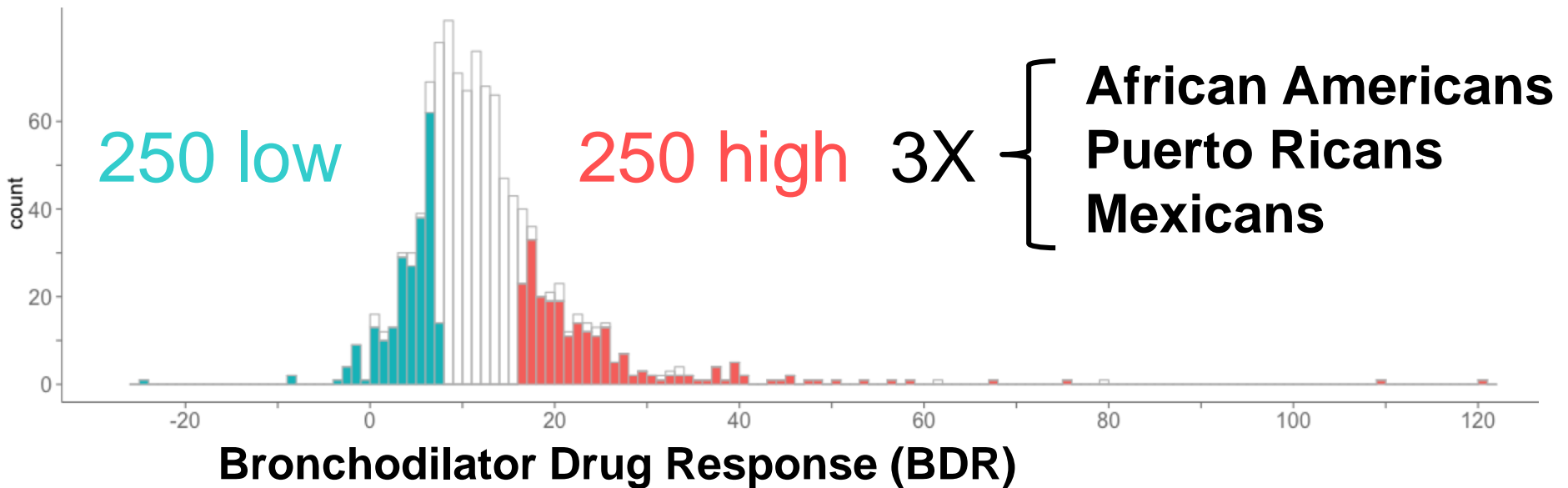
1,500 minority children

Albuterol response

Children with Moderate-to-Severe Asthma



1,500 Subjects, Extremes of Drug Response



BDR Association

$$\mathbf{BDR} = \text{Variants} + \text{Age} + \text{Sex} + \text{BMI} + \begin{matrix} \text{Global} \\ \text{Ancestry} \end{matrix}$$

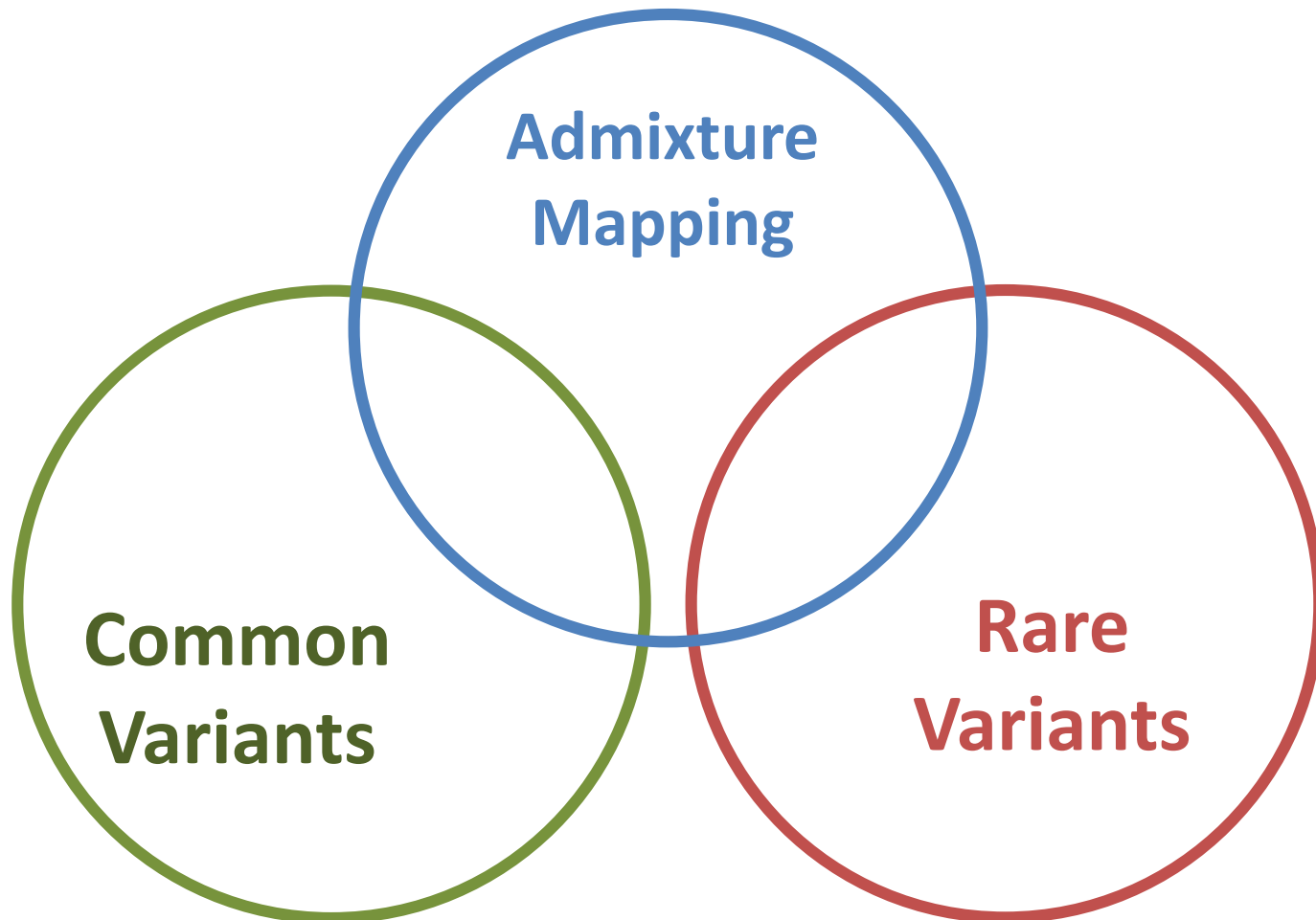
Individual effects

- PLINK
- Common variants
 - $\text{MAF} > 1\%$
- Logistic regression

Combined effects

- SKAT-O
- Rare variants
- Group variants by sliding windows

WGS Value-Added

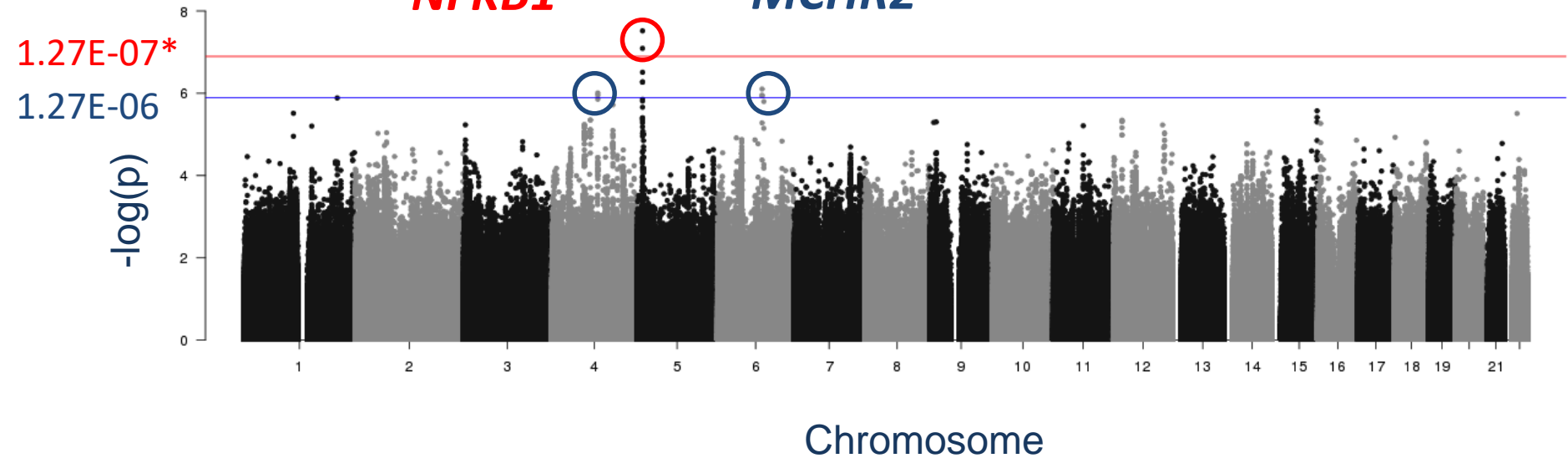


Cosmopolitan, Common variants

LINC01194, DNAH5

NFKB1

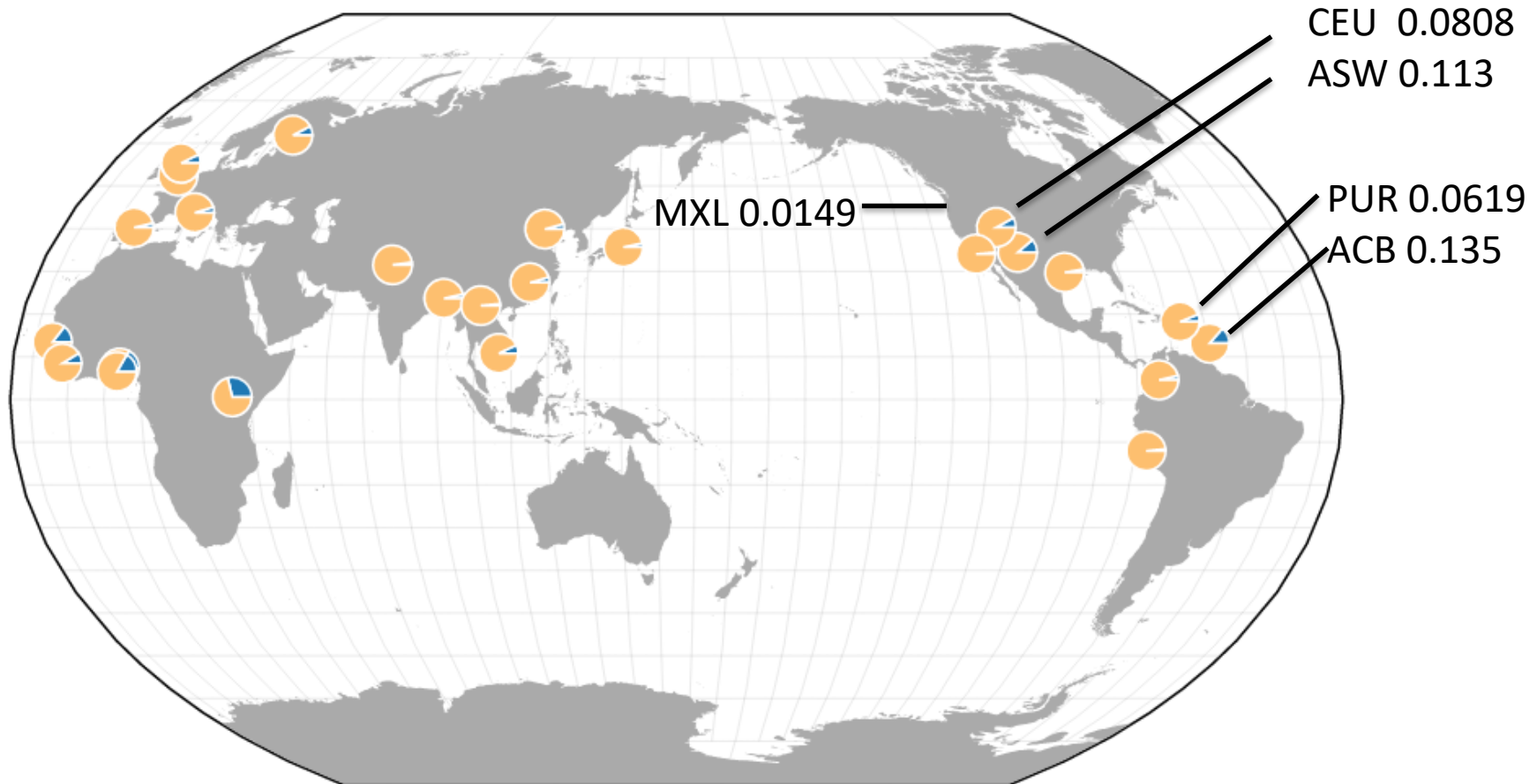
MCHR2



*Genome-wide significance threshold adjusted by coda R package (estimate the effective number of test using autocorrelation of association p-value)

The low BDR allele tracks with African ancestry

chr4:103453535 T/C



The minor allele is the low BDR allele

The low BDR allele tracks with African ancestry

Puerto Ricans



African Americans

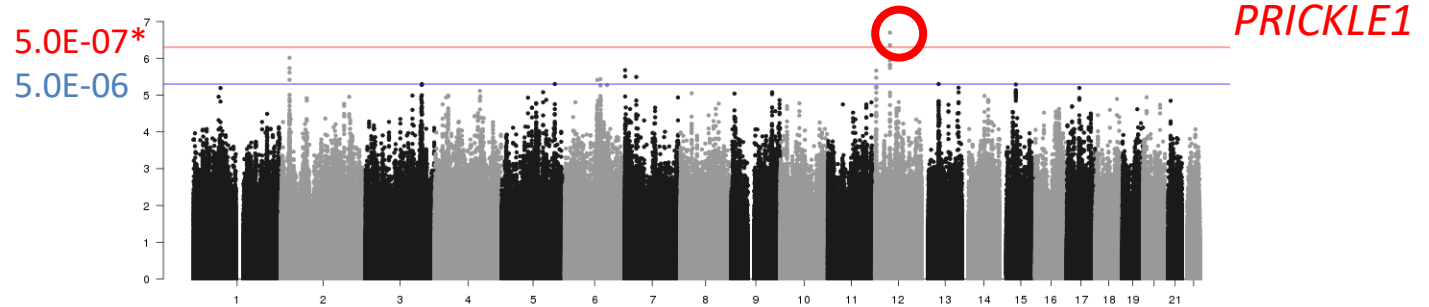
Lower BDR

Higher asthma prevalence

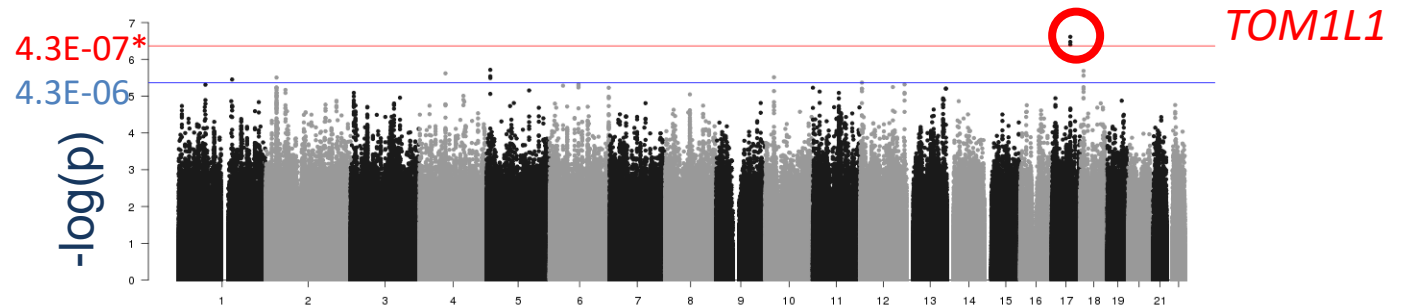
Higher asthma mortality

Combined Effects of Rare Variants, Ethnic-specific

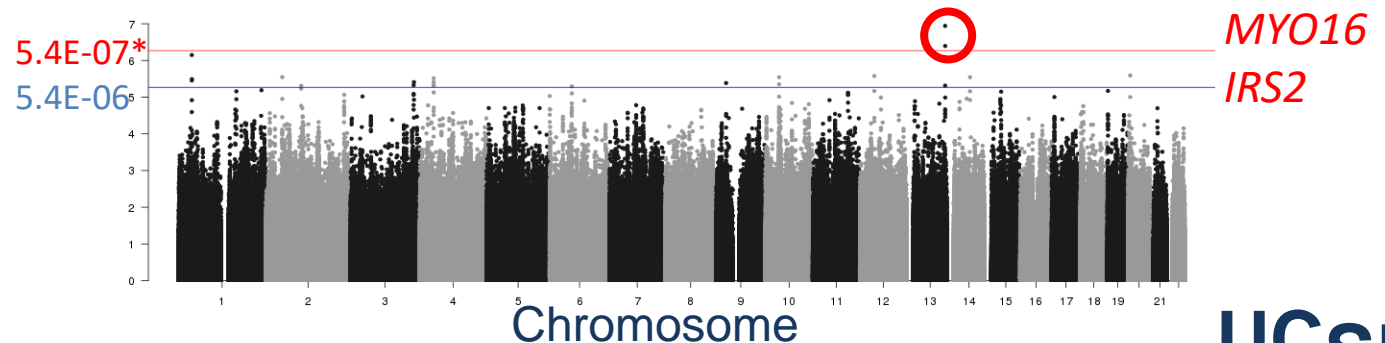
Puerto Ricans



African Americans

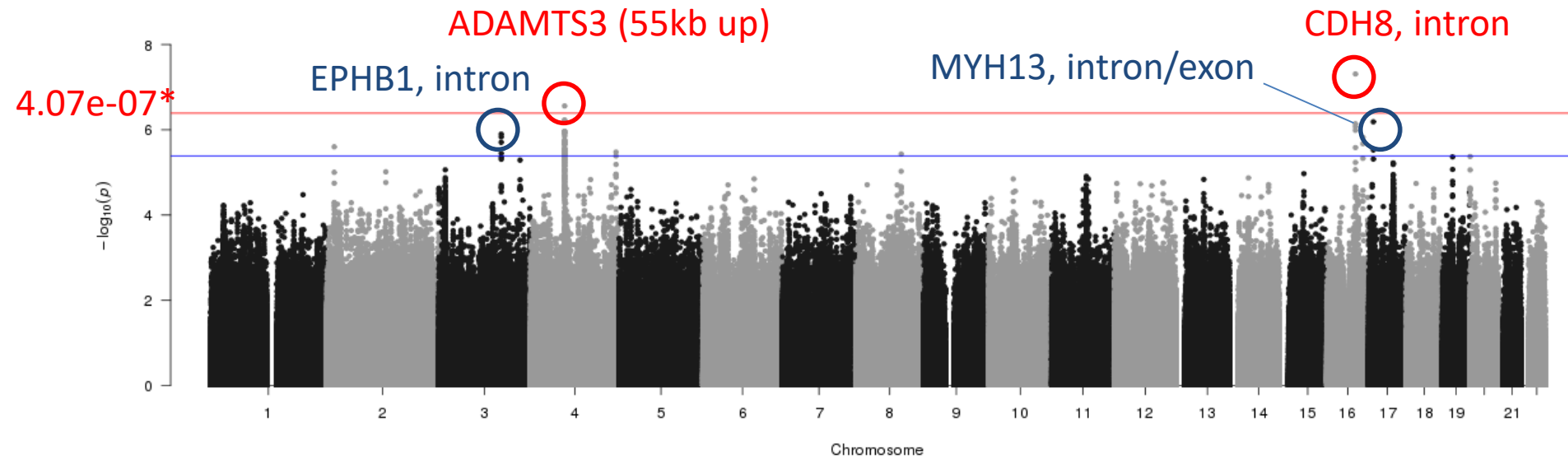


Mexican



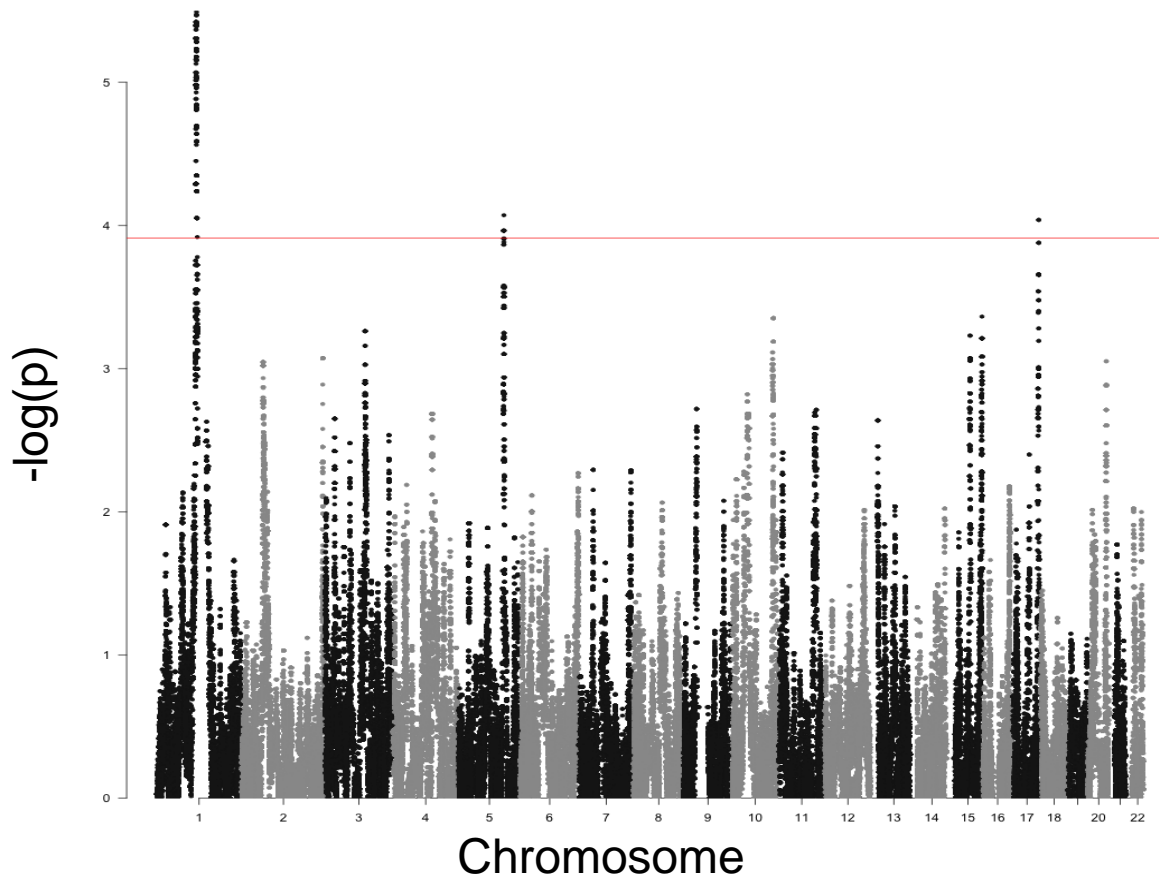
UCSF

Combined Effects of Rare Variants, Shared



Ancestry-specific BDR Association

Native American Ancestry (Puerto Ricans)



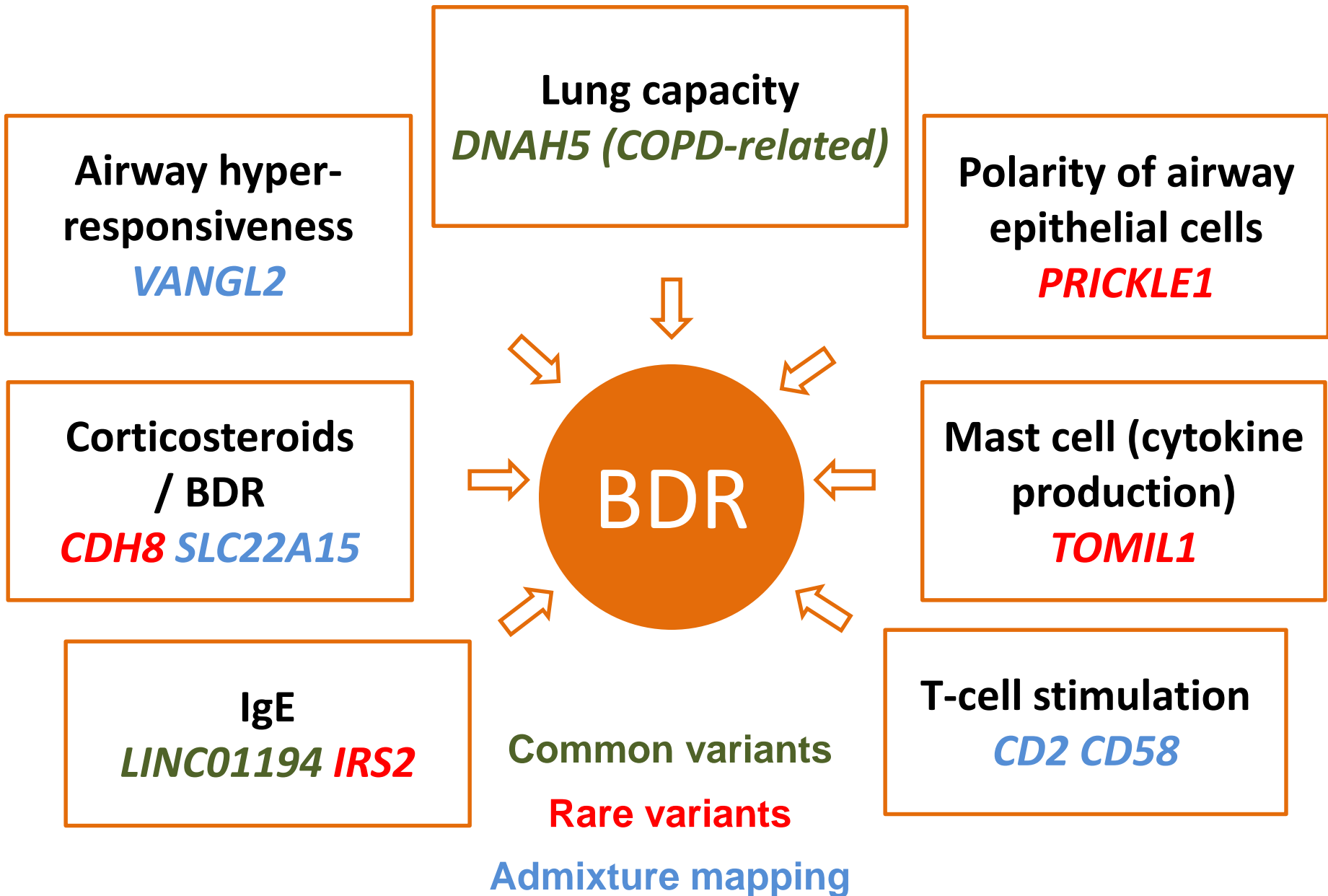
Chr1

CD2

CD58

SLC22A15

VANGL1



Challenges

- Matching cohorts for replication
- Sample size
- Need tools for WGS data from admixed population
- Despite challenges, big step forward to improve diversity





Over \$9 billion global sales in 2010



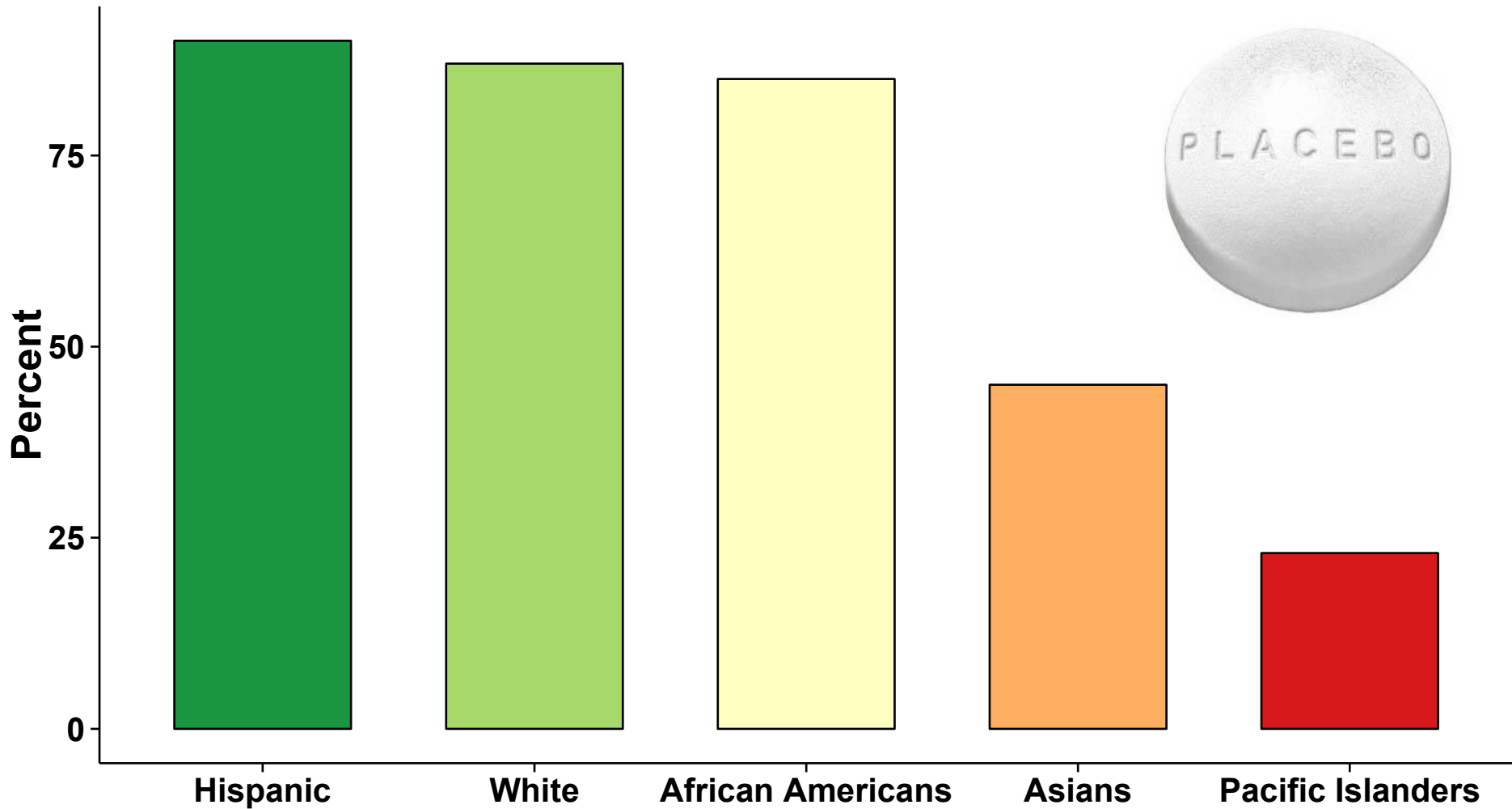
Bristol-Myers Squibb

UCSF

Drug Companies Gambling with Your Life?



Who Responds to Plavix?



Attorney General Of Hawaii Sues BMS

The Washington Times

Hawaii attorney general sues maker of drug Plavix

BloombergBusiness

Bristol-Myers, Sanofi Sued by Hawaii Over Plavix Labeling

**PACIFIC
BUSINESS NEWS**

Hawaii attorney general sues makers of drug Plavix alleging unfair and deceptive marketing

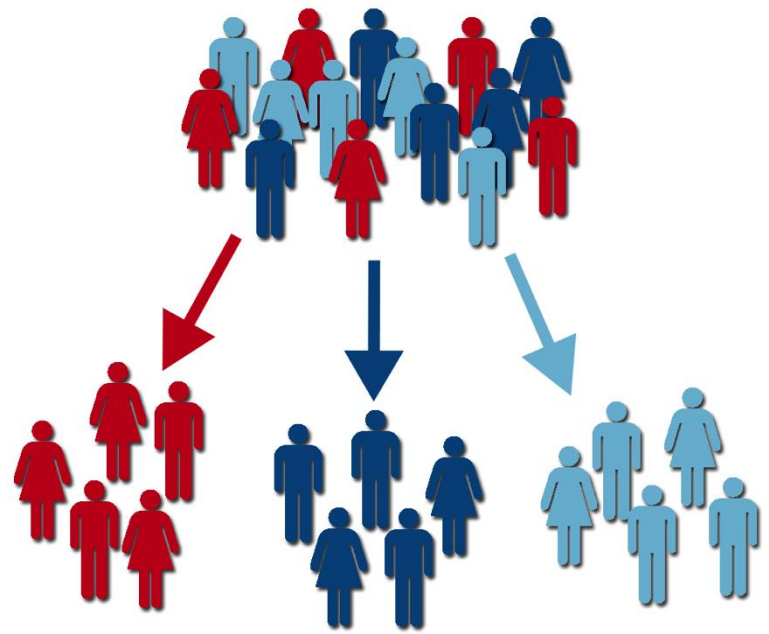


Mayo Clinic CIM
@MayoClinicCIM

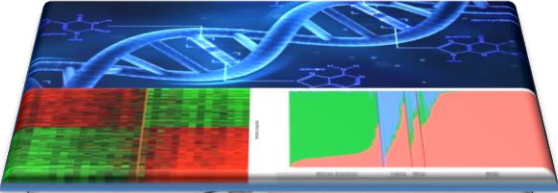


Lawsuit in Hawaii against Plavix Sponsors
Alleges Burden is on Pharma to Market PGx
Information - ow.ly/vZfhH

THE WALL STREET JOURNAL. States Take Drug Makers to Court
Over Marketing



Genomic



Clinical



Behavioral



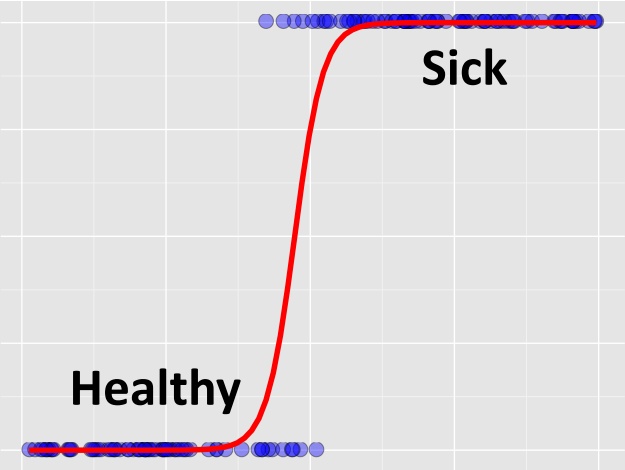
Socio-demographic



Built environment



Geographic





“And that’s why we’re here today.

Because something called ***Precision Medicine*** ... gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen.”

State of the Union Address
January 20, 2015

The U.S. Precision Medicine Initiative® Cohort Program



PMI Goals

- **One million or more volunteers**
 - Reflect the diversity of the U.S.
- **Longitudinal cohort with close interactions**
 - Collect EHR data, biospecimens, survey, complete baseline physical evaluation
- **Two methods of recruitment**
 - Direct volunteers
 - Healthcare provider organizations (incl. FQHCs)



Why We Do What We Do



Moral Compass



Life's most persistent and urgent question is,
"What are you doing for others?"
- Martin Luther King, Jr.



Once social change begins,
it cannot be reversed.
- Cesar Chavez

Where Do YOU Fit?



Stand UP !!! - Be Counted !!!



Team Science



Angel Mak
Marquitta White
Zachary Szpiech
Sam Oh
Ryan Hernandez
Noah Zaitlen
Donglei Hu
Scott Huntsman
Celeste Eng
Sandra Salazar
Walter Eckalbar
Dara Torgerson



Soren Germer
Karen Bunting
Robert Darnell
NYGC team

**Hospital
Universitario N.S. de
Candelaria**

María Pino-Yanes



TOPMed



Max Seibold