Center for Research on
Genomics and Global Health

Precision Medicine and Health Disparities: The Promise and Perils of Emerging Technologies

Charles N. Rotimi, PhD

Director: Center for Research on Genomics and Global Health

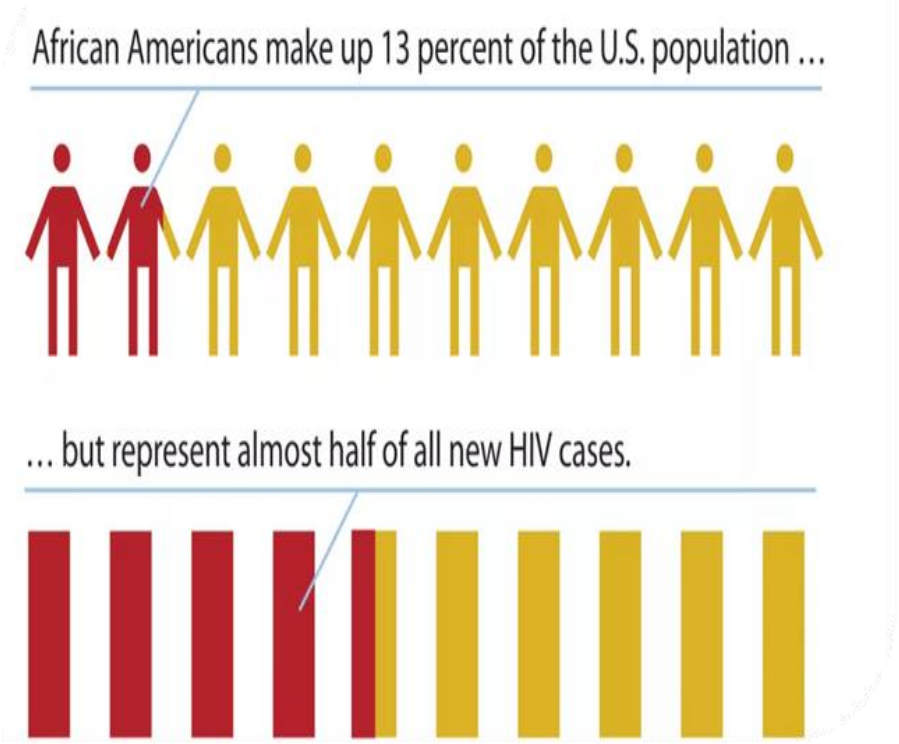
Chief and Senior Investigator: Metabolic, Cardiovascular and Inflammatory Disease Genomics Branch

What is a health disparity?

A disproportionate number of health conditions and deaths compared with the general population

Many forms of Health Disparities

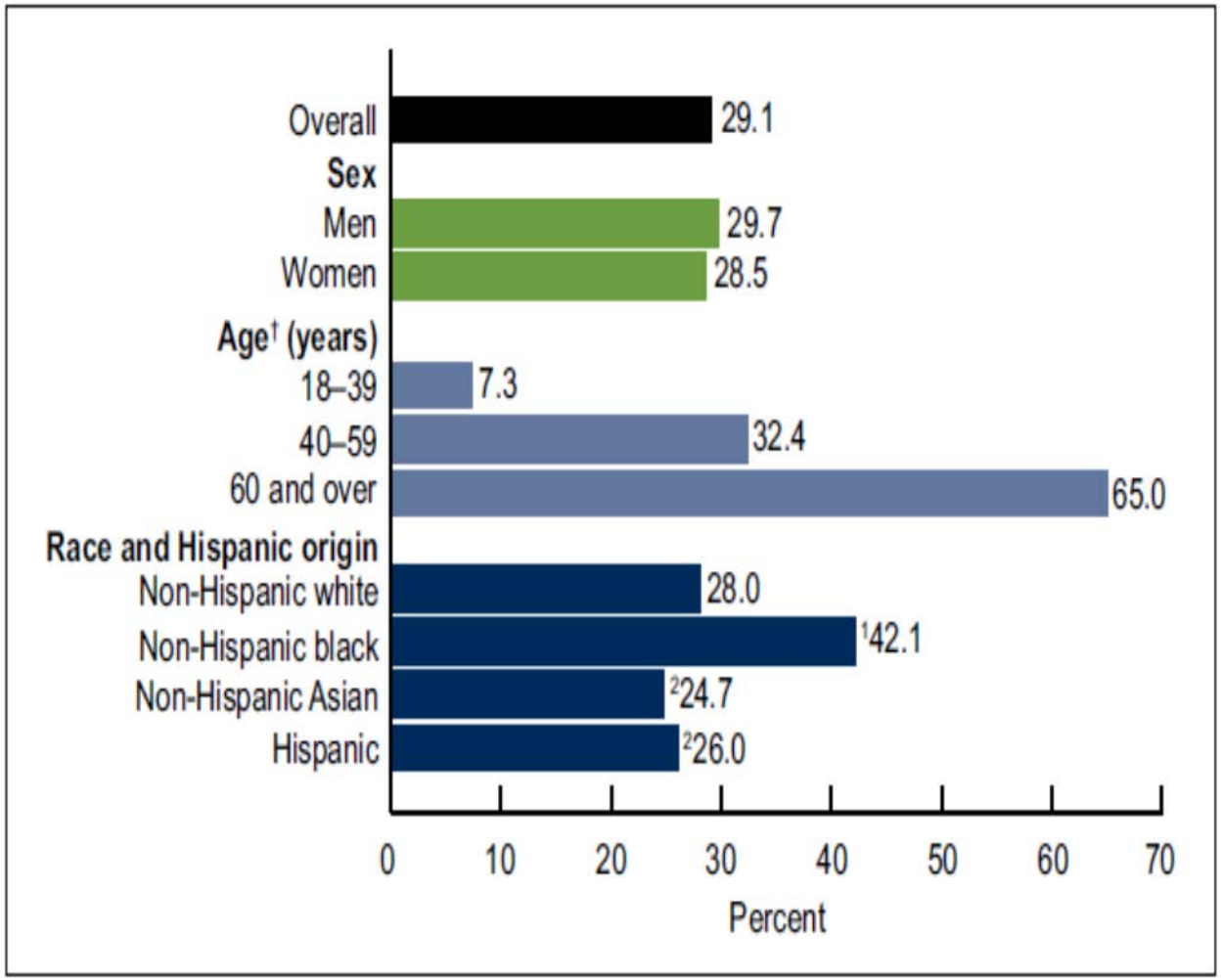
1. Ethnicity/Ancestry



http://lygeia.com/2015/11/19/leveraging-digital-strategies-to-address-health-disparities-part-1-measure-what-you-want-to-manage/

2. Age, gender & ancestry

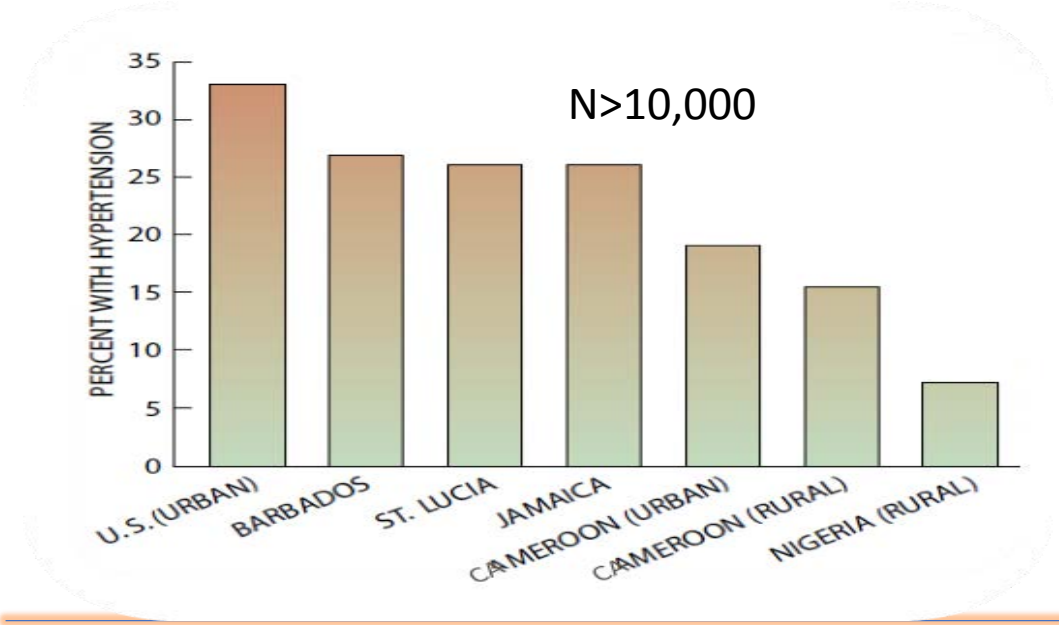
Prevalence of Hypertension – Aged 18 and over, US 2011-2012



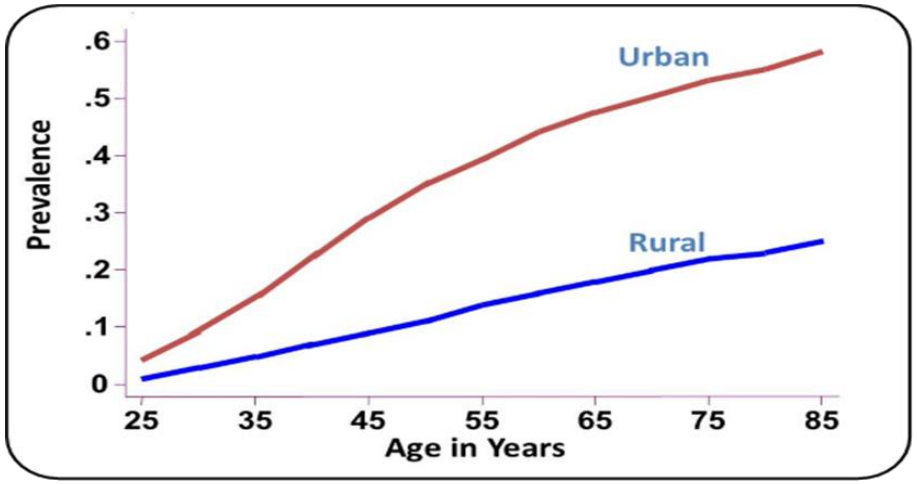
https://www.cdc.gov/nchs/data/databriefs/db133.pdf

3. Geography & ancestry

Prevalence of hypertension – Seven populations of West African origin

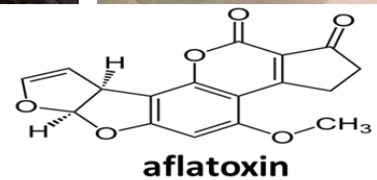


Prevalence of hypertension among urban and rural Yoruba individuals in Nigeria



4. Socioeconomic (poor vs rich)

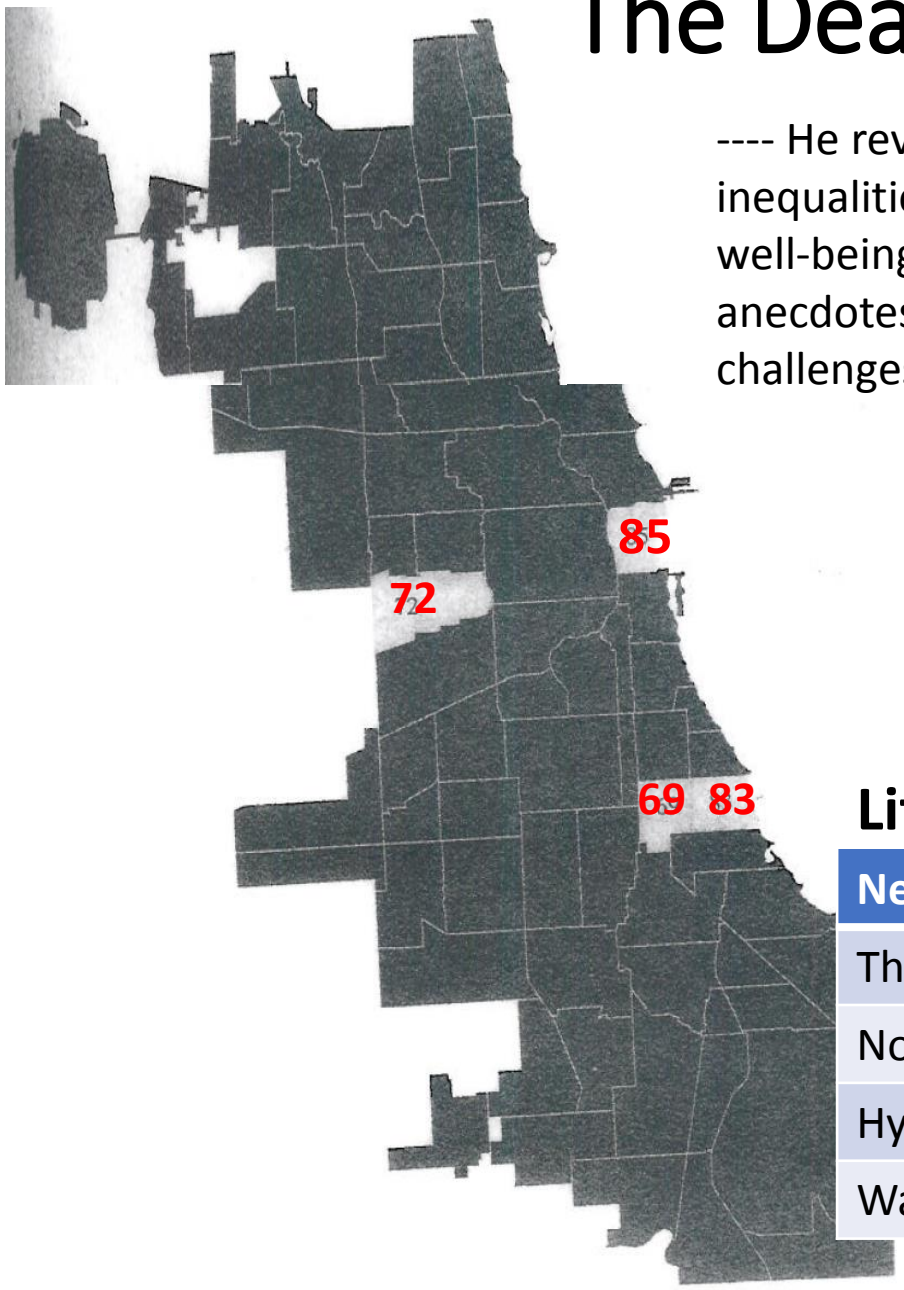
Production of aflatoxin by Aspergillus flavus in some Nigerian indigenous beverages and foodstuffs. *Mycopathologia* 1980



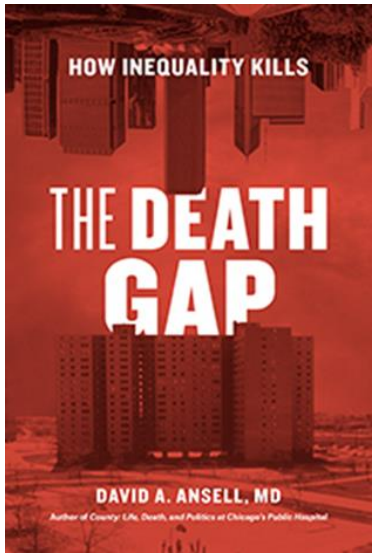
aflatoxin

Rotimi C et al., 1980

The Death Gap – David A Ansell, MD



---- He reveals the profound inequalities, particularly racial inequalities, that generate tremendous differences in lifespan and well-being across neighborhoods, and he provides powerful patient anecdotes that provide a human face to otherwise abstract challenges." Harold Pollack, University of Chicago



Location, Location, Location – real estate
These are also the three most important words in understanding health and wealth inequality in America

Life Expectancy varies greatly by neighborhoods in Chicago

Neighborhoods	Income	Life expectancy	comments
The Loop	$80,000	85yrs	Affluent downtown
North Lawndale	$25,000	72yrs	91% AA (5miles from the Loop)
Hyde Park	$40,000	83yrs	Racially diverse
Washington Park	$22,000	69yrs	Almost entirely AA

AA – African Americans

http://www.press.uchicago.edu/ucp/books/book/chicago/D/bo25081418.html

The major drivers of health disparities (inequalities) at the national and global levels are not genetic

The wages and benefits we're paid, the neighborhoods we live in, the schools we attend and our tax policies are health issues every bit as critical as diet, smoking and exercise.

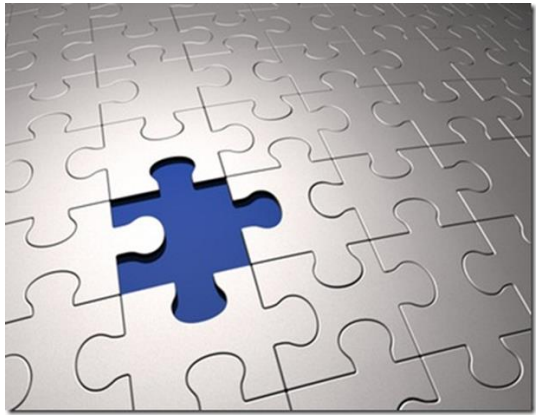
The unequal distribution of social factors that drive health disparities are **not natural or inevitable**. They are the result of choices that we as a community, as states, and as a nation have made, and can make differently

Larry Adelman, Unnatural Causes March 27, 2008

"If the misery of our poor be caused not by the laws of nature, but by our institutions, great is our sin."

- Charles Darwin

Why study genetics/genomics in the context of health disparities?



Our Genomes – A history book that has unbiasedly capture human experiences over thousands of years.

What is this book teaching us about human history & Health?

Reducing the Global Genomic Inequity Gap: Development of an African Genome Project

Melanie J. Newport[a] Charles N. Rotimi[b]

Public Health Genomics 2009;12:251–252

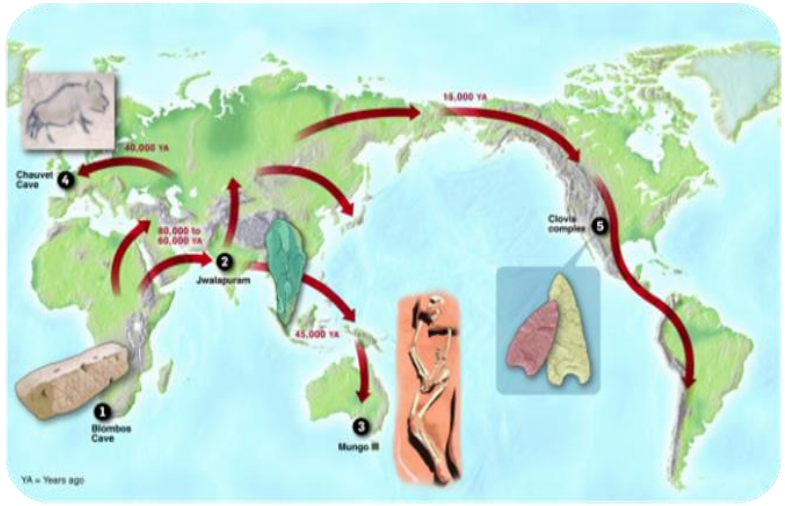
Concern that the equity gap that already exists between developed and developing countries will be widened if developing country populations, their scientists and health practitioners are not fully engaged in the application of genomic tools to address global problems including health and food production.

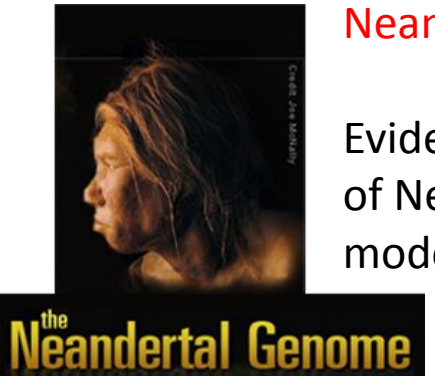
Tomorrow's Medicine and Technology may not work for all human populations

Yoruba community

Luyha & Maasai Kenya - 2005

Human Migrational History





Neanderthal genetic legacy

Evidence for introgression of Neanderthal genes into modern human gene pool

Any phenotypic effects on modern humans?

Human ancestry correlates with language and reveals that race is not an objective genomic classifier

Jennifer Baker, Charles Rotimi, Daniel Shriner

SCIENTIFIC REPORTS
www.nature.com/scientificreports
May 2017

1. Studied ancestry of 5,966 humans from 30 language families
2. Identified 21 ancestries; Majority (97.3%) have mixed ancestry
3. **Ubiquity of mixed ancestry emphasizes the importance of accounting for ancestry in history, forensics, and health.**

Using genetics to define racial group is like slicing soup. You can cut wherever you want, but the soup stays mixed. *Nature Biotechnology 2001*

Although "race" and thus racial groups may be difficult to define genetically, the impact of racism is real

Racism is a fundamental driver of inequalities in societies where it exists.

Benefits of Including Diverse Populations in Genomic Research

Understanding human biology

Mutations common in African Americans (2%); Rare in European Americans (<0.1%) Associated with 40% reduction in LDL-C level

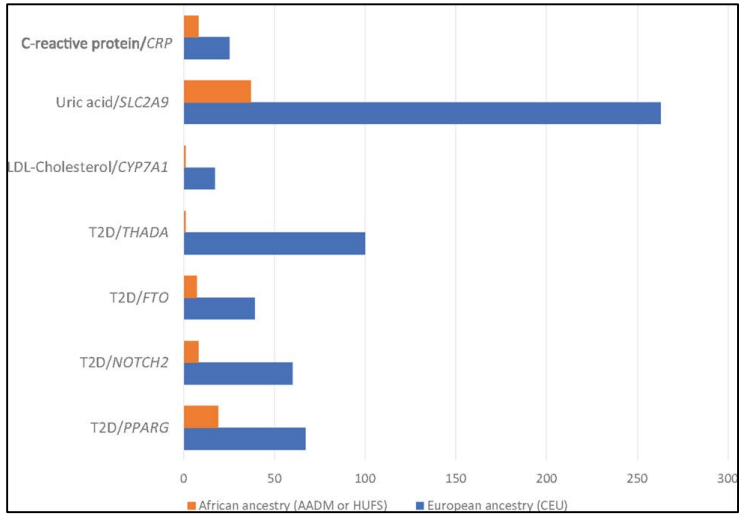
The New York Times

SCIENCE

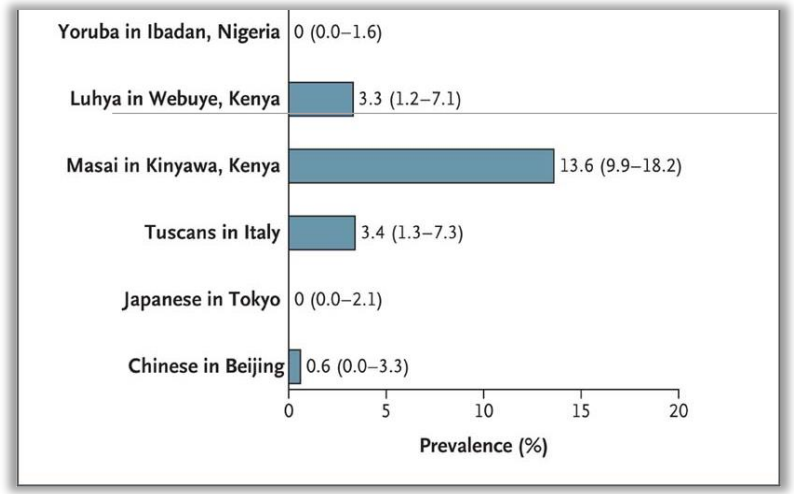
Genetic Tests for a Heart Disorder Mistakenly Find Blacks at Risk

By DENISE GRADY AUG. 17, 2016

Mistakes have been more common in blacks because they are more likely than whites to carry certain mutations that, in earlier studies, were thought to cause the disease



Genetic Screening to Prevent Abacavir Hypersensitivity Reaction



Rotimi CN and Jorde L, *NEJM,* 2010

The label "Africans" or "Blacks" renders radically different **HLA-B*5701** allele frequencies invisible.

Fine-Mapping: showing how smaller haplotype blocks in African ancestry populations helped refine genome-wide significant loci

Rotimi et al. Hum Mol Genet. 2017

African-Americans, Kidney Failure and APOL1

African-Americans are **13%** of the US population but account for **32%** of kidney failure in the US[1]

African-Americans are almost **4 times** more likely to develop kidney failure than caucasians.[1]

About **1 in 5** people with two copies of APOL1 renal risk variants will develop kidney disease[2]

These APOL1 variants account for **70%** of non-diabetic kidney failure in African-Americans[2]

About **4 in 10** African-Americans on dialysis have kidney failure caused by APOL1[2]

SOURCES

Geography, evolutionary biology, ancestry

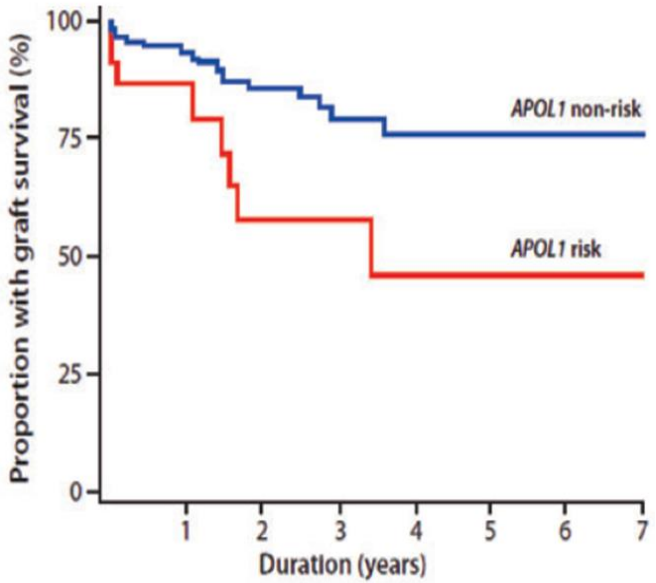
American Journal of Transplantation 2011; 11: 1025–1030
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03513.x

The *APOL1* Gene and Allograft Survival after Kidney Transplantation

Graft survival shorter in donor kidneys with 2 APOL1 risk variants (HR 3.8, p=0.008)

No difference by overall African ancestry



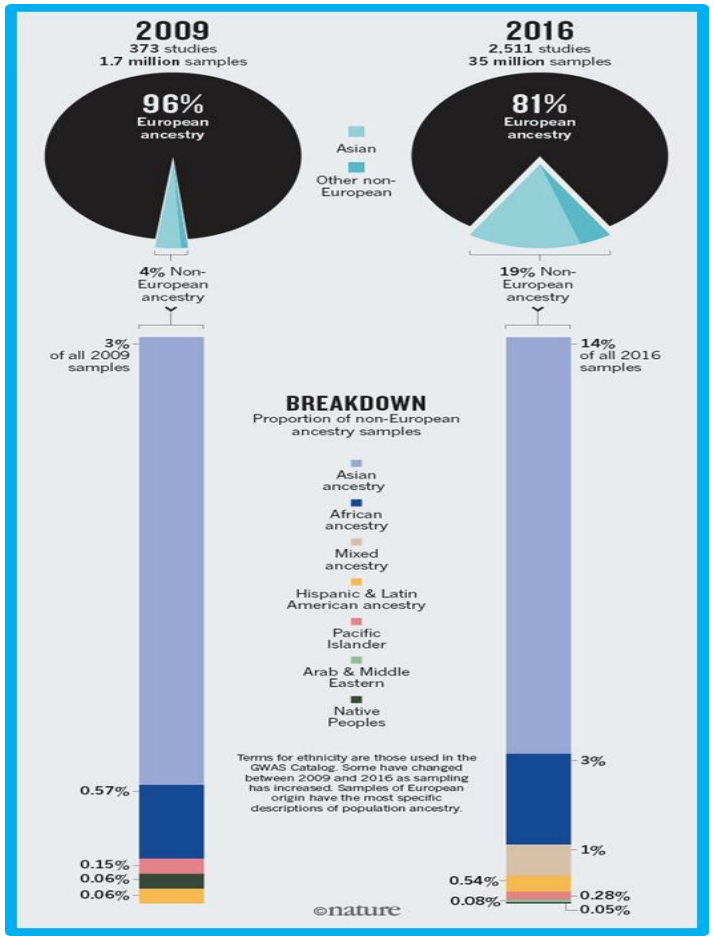
"Anytime different outcomes exist for kidney disease in African-Americans and European-Americans, an APOL1 influence needs to be investigated," says Barry Freedman.

http://www.wakeforestinnovations.com/discover-innovation/charting-new-waters/

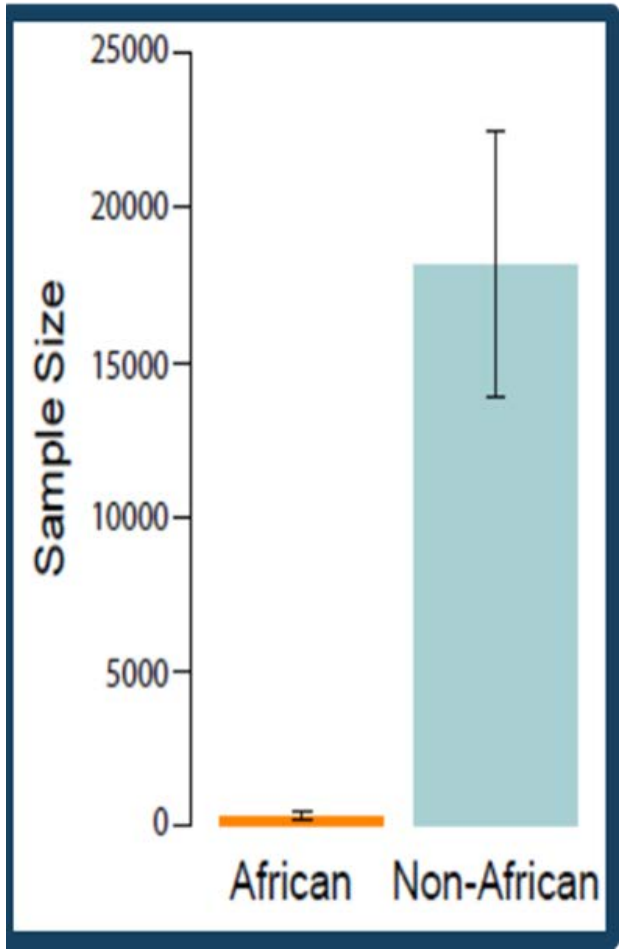
Health disparities in the genomic era: the case for diversifying ethnic representation

Charles N Rotimi*

Genome Medicine 2012, 4:65



Popejoy and Fullerton, *Nature*, 2016

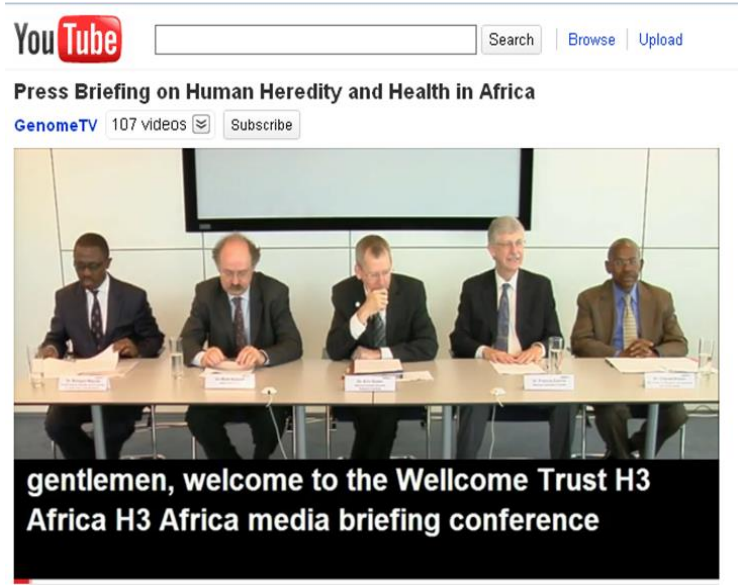


Rotimi C et al.
Human Molecular Genetics, 2017

The African Society of Human Genetics

The Africa Society of Human Genetics (AfSHG) was formed to ensure that Africa is not left out of the genomic revolution.

Annual meeting of the African Society of Human Genetics - Nov 2007, Cairo, Egypt



Human Heredity and Health in Africa (H3Africa)

London, England; June 22, 2010

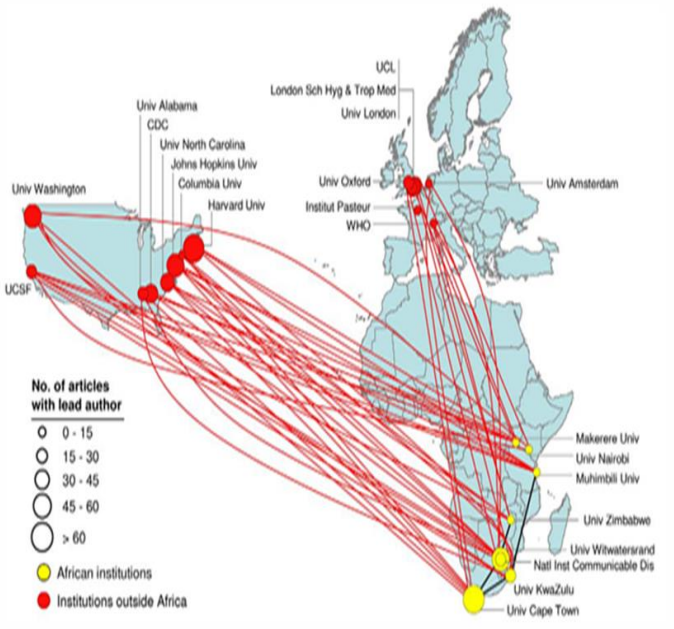
Vision for H3Africa

To enhance capacity for using contemporary research approaches, in Africa by African scientists, to understand the genetic and environmental factors that determine disease susceptibility and drug responses in Africans.

A key aspect of H3Africa - Awards are made directly to African Institutes & PIs

Before H3Africa:

Minimum Collaboration Between African Scientists



RESEARCH CAPACITY

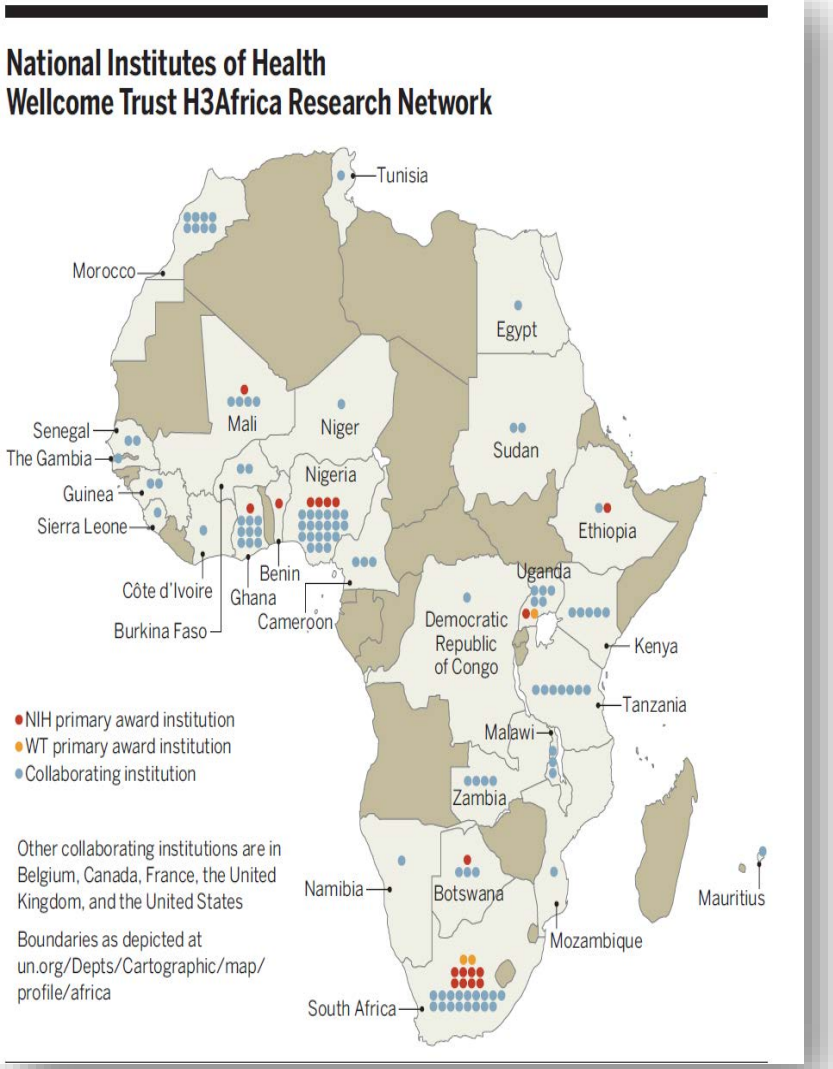
Enabling the genomic revolution in Africa

H3Africa is developing capacity for health-related genomics research in Africa

By **The H3Africa Consortium*†**

Our understanding of genome biology, genomics, and disease, and even human history, has advanced tremendously with the completion of the Human Genome Project. Technological advances coupled with significant cost reductions in genomic research have yielded novel insights into disease etiology, diagnosis, and therapy for some of the world's most intractable and devastating diseases—including malaria, HIV/AIDS, tuberculosis, cancer, and diabetes. Yet, de-

POLICY



Rotimi C et al. *Science.* 2014 Jun 20;344(6190):1346-8.

>$76 million of funding 27 African countries

>75,000 research participants >500 investigators 25 research projects

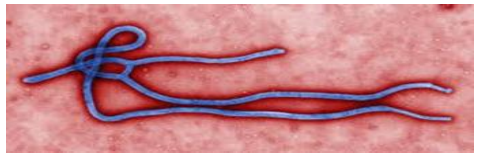
African Center of Excellence for of Infectious diseases Genomics
Redeemer's University, Nigeria

Establishing research programs for African scientists to pursue high-impact projects
Funded by H3Africa & World Bank

Christian Happi
Prof Molecular Biology & Genomics

Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak

Science
AAAS



"Because we have sophisticated genomics research laboratories at the African Centre of Excellence for Genomics of Infectious Diseases, in Redeemer's University, we were able to quickly diagnose the virus within hours of receiving the sample of the first Ebola index case in Nigeria"

The most diverse people in the world will finally get medicine made for them with a new genetic chip --- *Quartz Africa 2016*

A second generation human haplotype map of over 3.1 million SNPs

The International HapMap Consortium*

NATURE|Vol 449|18 October 2007

Table 4 | Estimated coverage of commercially available fixed marker arrays

Platform*	YRI		CEU		CHB+JPT	
	$r^2 \geq 0.8$ (%)	Mean maximum r^2	$r^2 \geq 0.8$ (%)	Mean maximum r^2	$r^2 \geq 0.8$ (%)	Mean maximum r^2
Affymetrix GeneChip 500K	46	0.66	68	0.81	67	0.80
Affymetrix SNP Array 6.0	66	0.80	82	0.90	81	0.89
Illumina HumanHap300	33	0.56	77	0.86	63	0.78
Illumina HumanHap550	55	0.73	88	0.92	83	0.89
Illumina HumanHap650Y	66	0.80	89	0.93	84	0.90
Perlegen 600K	47	0.68	92	0.94	84	0.90

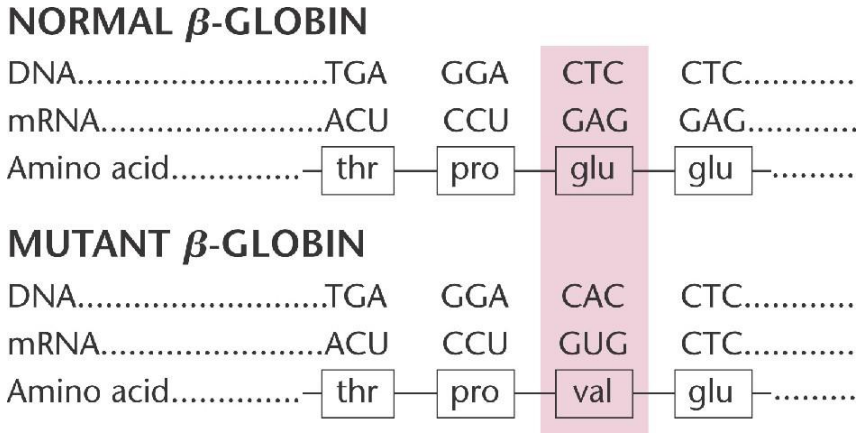
* Assuming all SNPs on the product are informative and pass QC; in practice these numbers are overestimates.

H3Africa Pan-African 2.5M Consortium Array

1. Extensive African-enriched reference panel
2. Based on sequencing of thousands of diverse individuals across Africa
3. 8 populations that have not been previously sequenced
4. Substantial improvement in sensitivity for African GWAS
5. H3Africa & Illumina collaboration

Sickle Cell Disease

- The first “molecular” disease
  - Caused by point mutation in the β-globin chain of hemoglobin
  - {VM Ingram 1956 Nature 178:792}



“the point mutation in the β-globin chain of hemoglobin, causes the hydrophilic amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position


Normal red blood cells


Sickled red blood cells

Epidemiology

- 1 in 5000 Americans, 1 in 500 African Americans
- 1 in 36,000 Hispanic Americans
- Disparity solely due to genetics

Treatment

- 1970s: opioids for pain management
- 1990s: hydroxyurea (increases HbF levels)
- 2017: L-glutamine second FDA-approved drug (“to reduce severe complications”)
- Blood transfusions
- Inactivation of BCL11A reactivates HbF (no therapeutic way to achieve this) {J Xu et al. *Science 2011*


The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Gene Therapy in a Patient with Sickle Cell Disease

Jean-Antoine Ribeil, M.D., Ph.D., Salima Hacein-Bey-Abina, Pharm.D., Ph.D.,

1st case - gene therapy trial 2017
No crises or adverse events after 15 months

Whole genome sequence-based haplotypes reveal single origin of the sickle allele during the Holocene Wet Phase

Daniel Shriner, Charles N. Rotimi

1. Five classical designations of sickle haplotypes are based on the presence/absence of restriction sites; named after ethnic groups or geographic origin of patients

2. Two models of the origin of the sickle allele
    a. **Multicentric** - five independent occurrences of the same mutation
    b. **Unicentric** - single older occurrence

3. Analyzed Whole Genome Sequence data from 1000 Genomes Project, African Genome Variation Project, and Qatar Genome project
4. Infer a single origin of the sickle allele ~ 7,300 years ago during Holocene Wet Phase or Green Sahara
5. We established a new haplotypic classification based on three clusters
    a. Central African Republic/Bantu + Cameroon
    b. Senegal
    c. Benin + Senegal
6. Senegal designation is substructured into two clusters, one shared with the Benin designation
7. Substructuring of haplotypes potentially confounded previous assessments of clinical phenotype or disease severity

https://www.biorxiv.org/content/early/2017/09/12/187419

The Medicalization of Race: Scientific Legitimization of a Flawed Social Construct.

Serious negative consequences of a physician's assumptions about a patient's race

8-year-old boy, phenotypically European, presented with acute abdominal pain and anemia (hematocrit, 0.21).

Although his body temperature was only 37.9 °C, surgery was considered. A technician found red corpuscles with hemolytic characteristics on a smear.

Surgery was canceled after the results of a subsequent sickle preparation were found to be positive, and the child was treated for previously undiagnosed sickle cell anemia.

His parents were from Grenada and were of Indian, northern European, and Mediterranean ancestry.

Ritchie Witzig – Ann Int Med 1996;125:675-679

The population genetics of chronic kidney disease: insights from the *MYH9–APOL1* locus

APOL1 genetic variants

Hispanic American			
Diabetes-unrelated ESRD (not biopsy-proven)	*MYH9* E1	3.7	6.88×10^{-03}
	APOL1 G1	15.5	8.80×10^{-04}

NATURE REVIEWS | NEPHROLOGY VOLUME 7 | JUNE 2011

http://usa.publiboda.com/hispanic_customs_traditions/social_customs.html

The Era of Precision Medicine

We must all go to the tailor so that our genomic clothing (precision medicine) will fit properly as we use genetics/genomics to understand disease etiology and develop new treatment strategies

Tomorrow's Medicine and Technology may not work for all human populations

Who is Black?

Naomi Osaka –
Haitian father and Japanese mother

Vijay Singh –
Nationality: Fijian

African Diaspora Populations
Range of individual African admixture proportion- 0% to 97.8%
Range of Native American ancestry - 0% to 100%

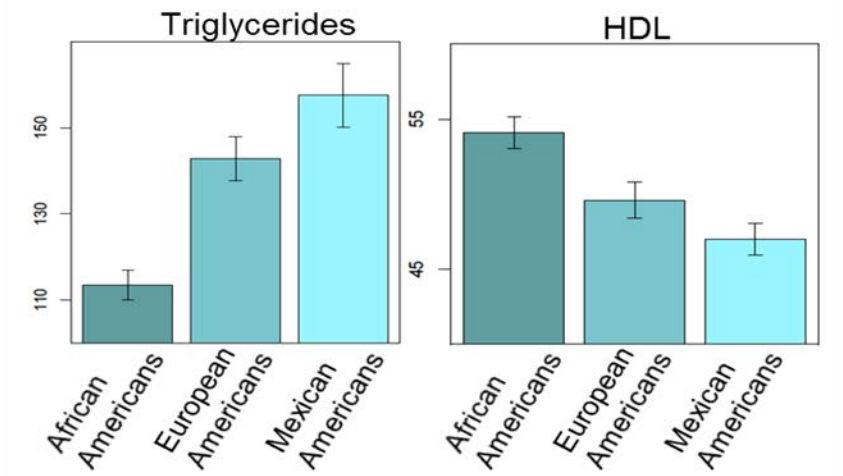
How do we interpret differential drug response by "groups" when "group" definition is imprecise, fluid and time dependent?

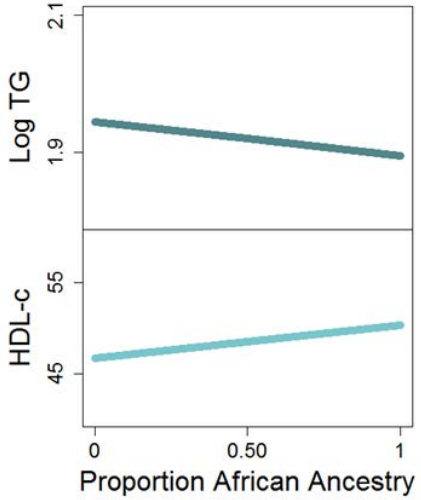
Gene-Based Sequencing Identifies Lipid-Influencing Variants with Ethnicity-Specific Effects in African Americans

PLOS | GENETICS

March 2014 | Volume 10 | Issue 3 | e1004190

Amy R. Bentley[1]*, Guanjie Chen[1], Daniel Shriner[1], Ayo P. Doumatey[1], Jie Zhou[1], Hanxia Huang[1], James C. Mullikin[2], Robert W. Blakesley[2], Nancy F. Hansen[3], Gerard G. Bouffard[2], Praveen F. Cherukuri[4], Baishali Maskeri[2], Alice C. Young[2], Adebowale Adeyemo[1], Charles N. Rotimi[1]*

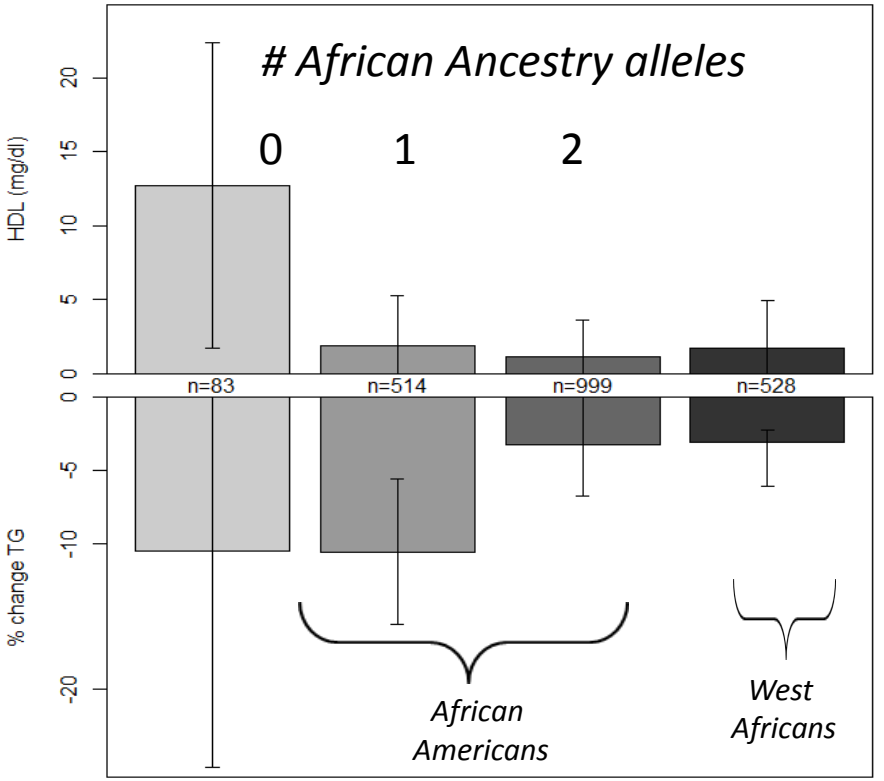




Sequenced 5 genes (*ABCA1*, *LCAT*, *LPL*, *PON1*, and *SERPINE1*) for variant discovery in African Americans with extreme lipids.

Follow-up in population-based sample of African Americans (n=1694)

Association of *LPL* variants (rs328) depended on ancestry at that locus.

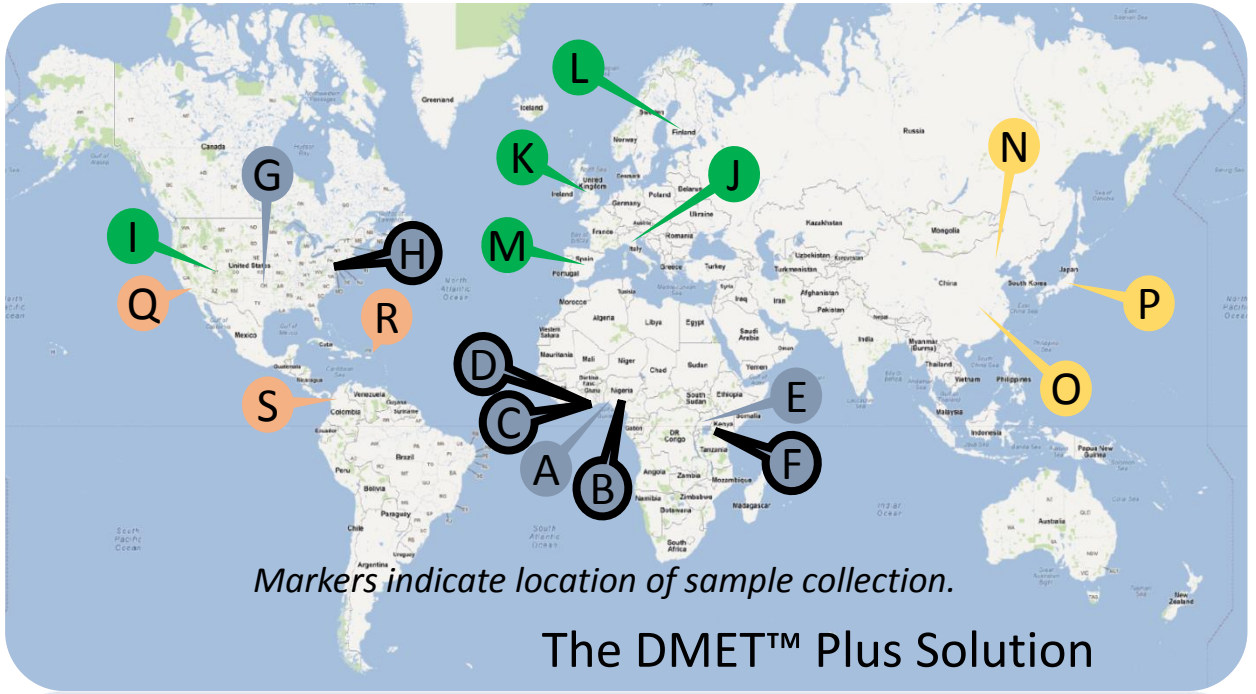


Pharmacogenomics, ancestry and clinical decision making for global populations

E Ramos[1], A Doumatey[1], AG Elkahloun[2], D Shriner[1], H Huang[1], G Chen[1], J Zhou[1], H McLeod[3], A Adeyemo[1] and CN Rotimi[1]

The Pharmacogenomics Journal

The Pharmacogenomics Journal (2014) 14, 217–222



Markers indicate location of sample collection.

The DMET™ Plus Solution

Warfarin Dosing

		Non-African Ancestry			*African Ancestry*			
Mean dose	Haplotype	CEU	CHB	JPT	YRI	MKK	LWK	ASW
40.15	TTGGC	0.36	0.05	0.10	0.54	0.51	0.44	0.50
35.24	TCGGC	0.24	--	--	0.34	0.27	0.37	0.32
26.41	TCAAT	0.37	0.11	0.15	0.02	0.16	0.06	0.10
23.86	CCAAT	0.03	0.83	0.75	--	--	--	--
??	TCAGC	--	--	--	0.14	0.07	0.12	0.08

Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance

Dongliang Ge[1], Jacques Fellay[1], Alexander J. Thompson[2], Jason S. Simon[3], Kevin V. Shianna[1], Thomas J. Urban[1], Erin L. Heinzen[1], Ping Qiu[3], Arthur H. Bertelsen[3], Andrew J. Muir[2], Mark Sulkowski[4], John G. McHutchison[2] & David B. Goldstein[1]

Nature. Sept 2009.

Nature – Oct 8, 2009

1. Hepatitis C virus infection affects 170 million people worldwide; leading cause of cirrhosis.

2. Treatment - 48-week course of peginterferon-alpha-2b or -alpha-2a combined with ribavirin

3. Patients of European ancestry have higher probability of being cured compared to patients of African ancestry.

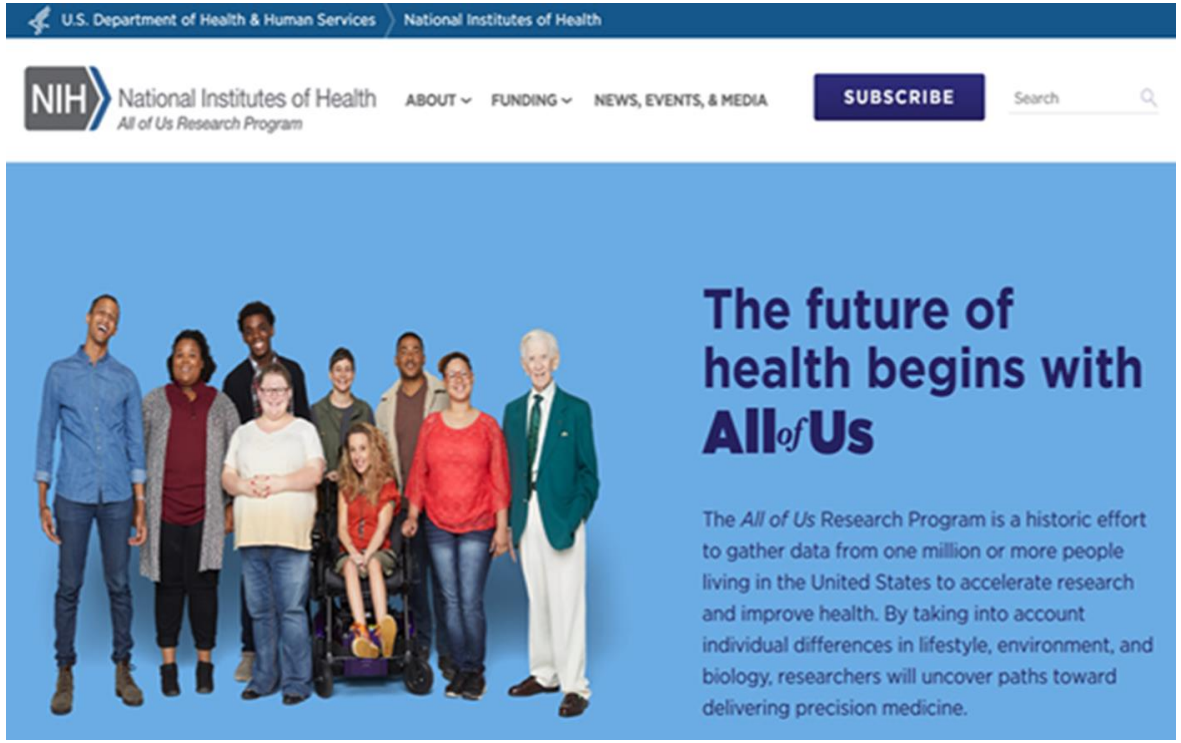
4. Finding - SNP rs12979860 near the IL28B gene, encoding interferon-lambda-3, is associated with ~2-fold change in response to treatment in patients of European ancestry and African-Americans.

Population Groups	# individuals (# populations)	Mean Frequency	Frequency Range
Africa	428 (10)	36.2	23.1 – 54.8
Europe	761 (13)	68.35	52.8 – 85.7
East Asia	380 (8)	94.93	90.0 – 100

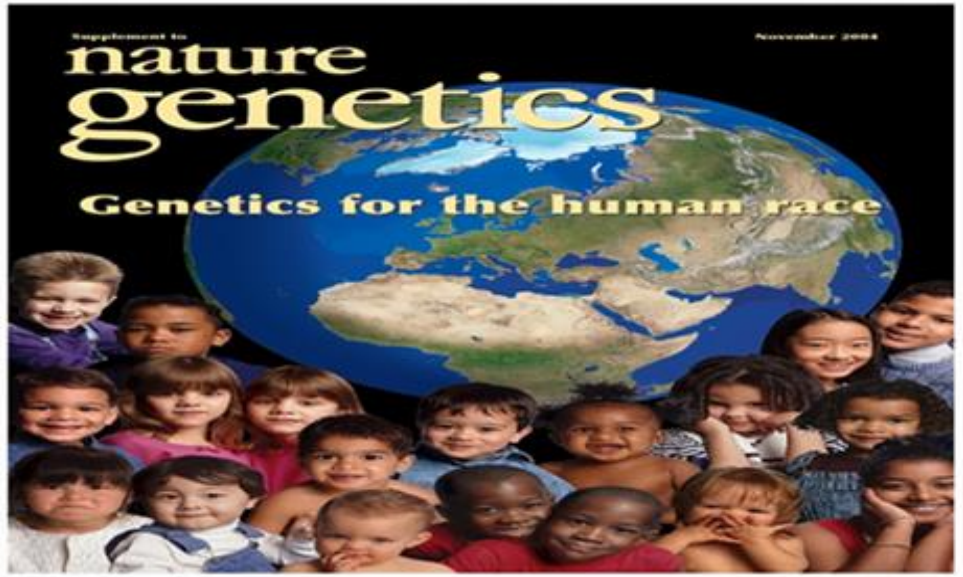
Because the genotype leading to better response is in substantially greater frequency in European than African populations, this genetic polymorphism also explains approximately half of the difference in response rates between African-Americans and patients of European ancestry

Precision Medicine

More Precise Accounting for Individual Variability



Most guide against over promise especially in the context of health disparities



Our Diversity is not an illusion.

We need to study how our genetic backgrounds increase our susceptibility/resistance to disease

This may shed novel insight into Health Disparities

Many persons contributed to this presentation

Special thanks to Daniel Shriner for the sickle cell slides

Thanks

Glad to take questions