Race, Clinical Algorithms, and Health Justice

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McDonald-Merrill-Ketcham Award Lecture
2/24/2023

Disclaimer

The speaker declares no financial or other conflicts of interest

Opinions expressed are my own and should not be construed as the views of my affiliate institutions or collaborators

Agenda

1. Race-based clinical algorithms in medicine
2. The barriers to overcoming race-based medicine and delivering precision medicine
3. The role of the law
   A. How can law and policy promote inclusive genomics inquiries?
   B. Do current research policies promote or hinder our scientific understanding of the complex interactions of biology, environment, and health?
4. Conclusion
   A. Genomics discoveries should influence law & policy more frequently and vice versa

Frameworks:
Law, Genomics Research
Policy, Bioethics

The NEW ENGLAND JOURNAL of MEDICINE

MEDICINE AND SOCIETY

Race and Genetic Ancestry in Medicine — A Time for Reckoning with Racism

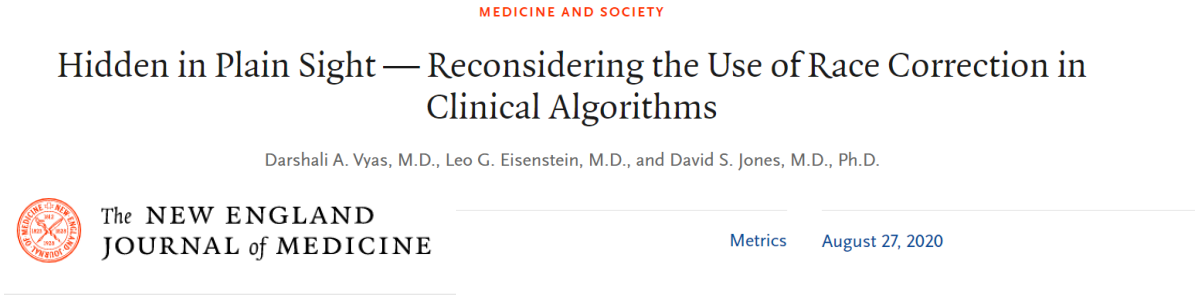
Luisa N. Borrell, D.D.S., Ph.D., Jennifer R. Elhawary, M.S., Elena Fuentes-Afflick, M.D., M.P.H., Jonathan Witonsky, M.D., Nirav Bhakta, M.D., Ph.D., Alan H.B. Wu, Ph.D., Kirsten Bibbins-Domingo, Ph.D., M.D., José R. Rodríguez-Santana, M.D., Michael A. Lenoir, M.D., James R. Gavin, III, M.D., Ph.D., Rick A. Kittles, Ph.D., Noah A. Zaitlen, Ph.D., et al.

2021

"The largest genetic clusters of people correspond to geographic regions and specific populations in Africa, Europe, Asia, Oceania, and the Americas, suggesting that continental-level ancestry captures the greatest population differences in genetic variation. **Ancestry assessment within continents can provide information on a finer scale"**

"However, before ancestry adjustment is widely adopted, it is important to demonstrate that it provides results at least as accurate as those of race adjustment."

Race Correction – Example Definition



MEDICINE AND SOCIETY

Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms

Darshali A. Vyas, M.D., Leo G. Eisenstein, M.D., and David S. Jones, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

Metrics August 27, 2020

"…involves diagnostic algorithms and practice guidelines that adjust or 'correct' their outputs on the basis of a patient's race or ethnicity. Physicians use these algorithms to individualize risk assessment and guide clinical decisions. By embedding race into the basic data and decisions of health care, these algorithms propagate race-based medicine."

Race Correction – Example Definition

From race-based to race-conscious medicine: how anti-racist uprisings call us to act

Jessica P Cerdeña, Marie V Plaisime*, Jennifer Tsai**

THE LANCET

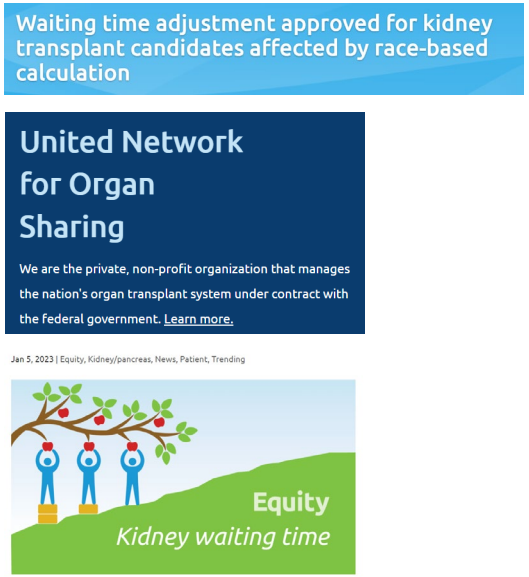
Volume 396, Issue 10257, 10–16 October 2020, Pages 1125-1128

". . . . the system by which research characterising race as an essential, biological variable, translates into clinical practice, leading to inequitable care."

Race Correction

Report
GLUCOSE
BUN
CREATININE
EGFR IF NONAFRICN AM
EGFR IF AFRICN AM

```
**In accordance with recommendations from
the NKF-ASN Task force,**
  Labcorp is in the process of updating
its eGFR calculation to the
  2021 CKD-EPI creatinine equation that
estimates kidney function
  without a race variable.
```



Jan 5, 2023 | Equity, Kidney/pancreas, News, Patient, Trending

Race Correction

https://www.hollywoodreporter.com/

Bias in Algorithms

Science

INSIGHTS

POLICY FORUM

HEALTH DISPARITIES

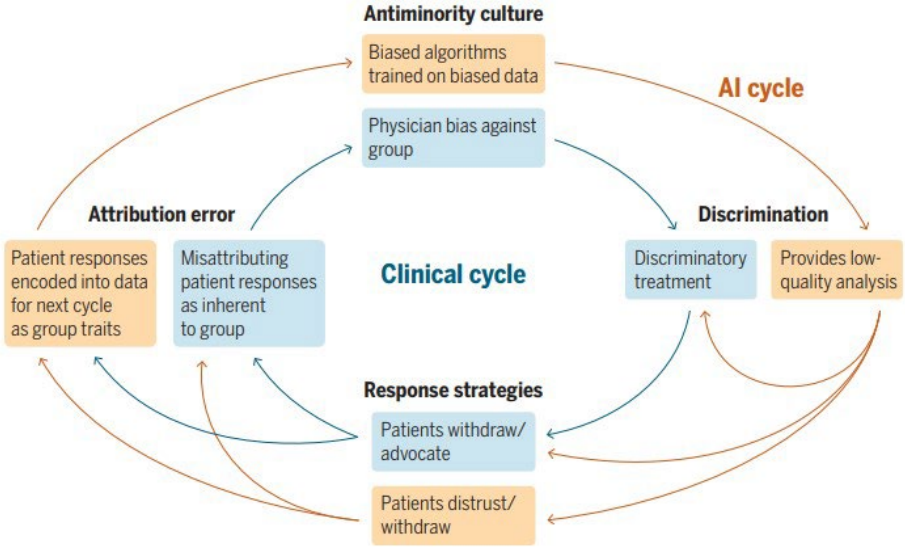
Exclusion cycles: Reinforcing disparities in medicine

By Ana Bracic[1], Shawneequa L. Callier[2,3], W. Nicholson Price II[4,5]

Clinical practice, data collection, and medical AI constitute self-reinforcing and interacting cycles of exclusion

Medical practice and AI create overlapping exclusion cycles

Around a generalized structure of the four-step cycle, we depict two interacting exclusion cycles: clinical encounters (blue) and artificial intelligence (AI) products that result from, and influence, data surrounding those clinical encounters (orange). Each cycle self-perpetuates, but the cycles also interact at various points.



What is race?

“Race is a concept without a generally agreed upon definition.”

“Racial groups have no defined boundaries, but have a blurry and imprecise relationship with human genetic variation and population groups across the world.”

-Vence Bonham, JD

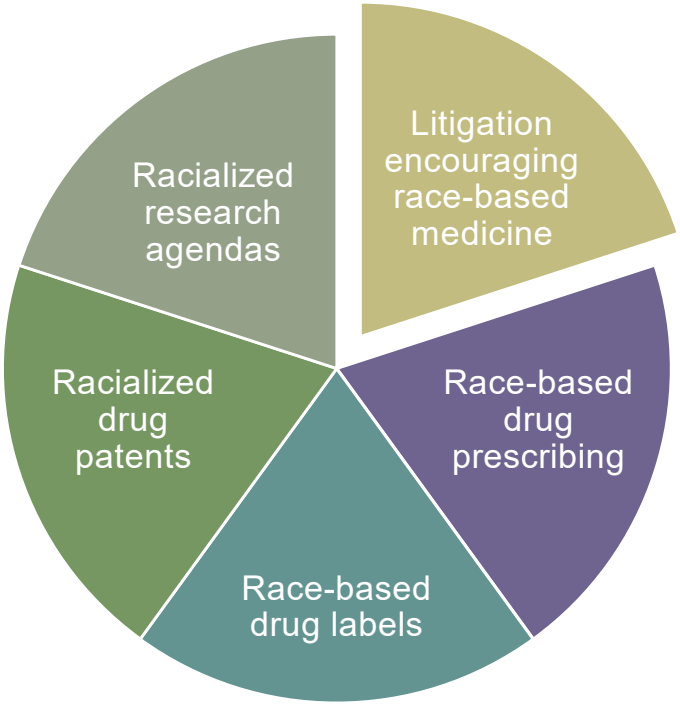
What is race?

Racial categories in the United States

- Free, white or other, slave (1790)
- White, black, mulatto (1860)
- White, black, Mulatto, Chinese, Indian, Quadroon Octoroon, Japanese (1890)
- White, Black (of Negro Descent), Chinese, Indian, Japanese (1900)

OMB CENSUS CATEGORIES

Role of the law



Race & Patent Protection

Race is used as a genetic category to obtain patent protection and drug approval.

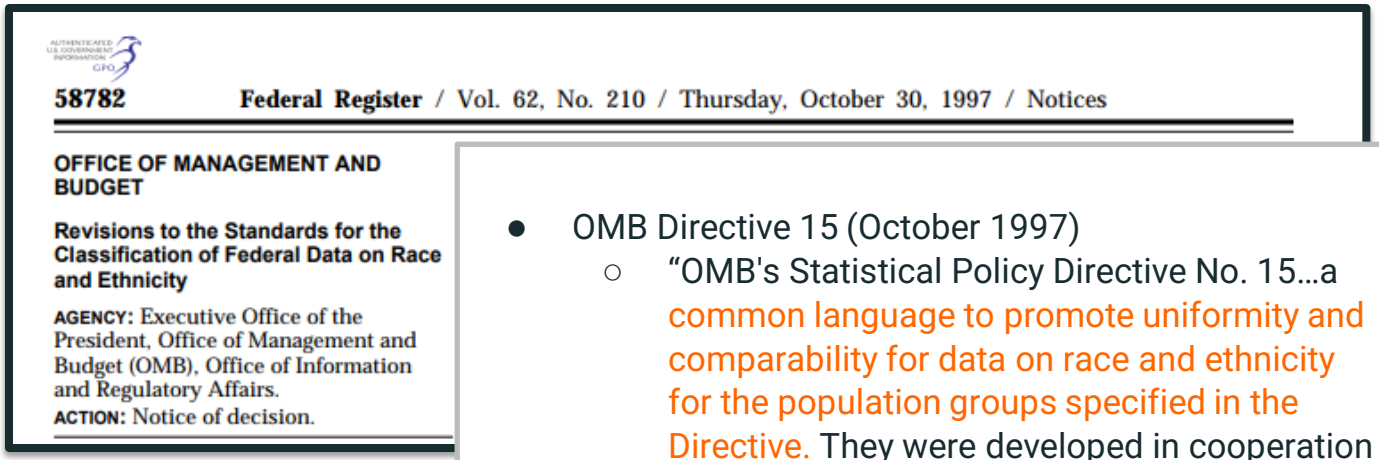
Race-specific patent language has served as a foundation for conducting clinical trials, developing and marketing drugs, and raising capital.

Table 1 Racial and ethnic categories mentioned in US patent filings, 1976–present

From: Patenting race

	Issued patents		Patent applications filed since 2001
Category	**1976–1997**	**1998–2005**	
Race	0	2	15
Ethnic	0	0	2
African-American/black	0	4	11
Alaska native	0	0	0
Asian	0	0	13
Caucasian/white	0	6	18
Hispanic/Latino	0	0	3
Native American	0	0	2
Pacific Islander	0	0	1
Total	0	12	65

Kahn, J. Patenting race. *Nat Biotechnol* **24,** 1349–1351 (2006).



58782 Federal Register / Vol. 62, No. 210 / Thursday, October 30, 1997 / Notices

OFFICE OF MANAGEMENT AND BUDGET

Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity

AGENCY: Executive Office of the President, Office of Management and Budget (OMB), Office of Information and Regulatory Affairs.

ACTION: Notice of decision.

- OMB Directive 15 (October 1997)
  - "OMB's Statistical Policy Directive No. 15…a common language to promote uniformity and comparability for data on race and ethnicity for the population groups specified in the Directive. They were developed in cooperation with Federal agencies to provide consistent data on race and ethnicity throughout the Federal Government. Development of the data standards stemmed in large measure from new responsibilities to enforce civil rights laws."
  - Household surveys, administrative forms (e.g., school registration, mortgage lending)
  - Monitor equal access in housing, education and employment

"These standards generally reflect a social definition of race and ethnicity recognized in this country, and they do not conform to any biological, anthropological, or genetic criteria."

Law & Policy

The NIH Revitalization Act of 1993 (Pub. L. No. 103-43)

"NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research."

"...that women and members of minority groups and their subpopulations **must be included in all NIH-funded clinical research**, unless a **clear and compelling rationale and justification** establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research."

Law & Policy

- The Food and Drug Administration Modernization Act of 1997 (Pub. L. No. 105-115)
  - "Collection of Race and Ethnicity Data in Clinical Trials," updated in 2016.
  - "a standardized approach for collecting and reporting race and ethnicity data in submissions for clinical trials for FDA-regulated medical products."
- Race and Ethnicity Diversity Plan (FDA Draft Guidance April 2022)

Pharmacogenomics and Personalized Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Inconsistency in race and ethnic classification in pharmacogenetics studies and its potential clinical implications

Frederick Zhang[1]
Joseph Finkelstein[2]

[1]Center for Bioinformatics and Data Analytics, Columbia University Irving Medical Center, New York, NY, USA; [2]Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY, USA

- Ali-Khan, Sarah E., Tomasz Krakowski, Rabia Tahir, and Abdallah S. Daar. "The use of race, ethnicity and ancestry in human genetic research." The HUGO journal 5, no. 1-4 (2011): 47-63.
  - ". . . no article using 'race', 'ethnicity' or 'ancestry' defined or discussed the meaning of these concepts in context; a third of articles still do not provide a rationale for their use, with those using 'ancestry' being the least likely to do so."
  - ". . . there remains a clear imperative for highlighting the importance of consistent and comprehensive reporting on human populations to the genetics/genomics community globally, to generate explicit guidelines for the uses of ancestry and genetic ancestry, and importantly, to ensure that guidelines are followed."

Drug Labels - Complexity

"The addition of ancestry information to the warning creates a deceptively, complex task for clinicians—determining the ancestry of patients." Perry Payne 2014

The Pharmacogenomics Journal (2014) 14, 473–480

www.nature.com/tpj

ORIGINAL ARTICLE

Ancestry-based pharmacogenomics, adverse reactions and carbamazepine: is the FDA warning correct?

PW Payne[1,2,3]

In an effort to prevent potentially fatal adverse reactions to carbamazepine, the US Food and Drug Administration (FDA) issued an alert in 2007 containing pharmacogenomic information, which is still in effect today. The alert states that carbamazepine-induced skin reactions are significantly more common in patients with the human leukocyte antigen (HLA)-B*1502 allele and that these people are almost exclusively from 'broad areas of Asia, including South Asian Indians.' This study reviews the medical evidence relied upon by the FDA and finds that the alert does not accurately reflect the medical evidence relied upon in 2007 or evidence that has been generated over the last 5 years since the label was created. The FDA drug labeling should be modified to reflect current medical evidence.

The Pharmacogenomics Journal (2014) **14,** 473–480; doi:10.1038/tpj.2014.14; published online 22 April 2014

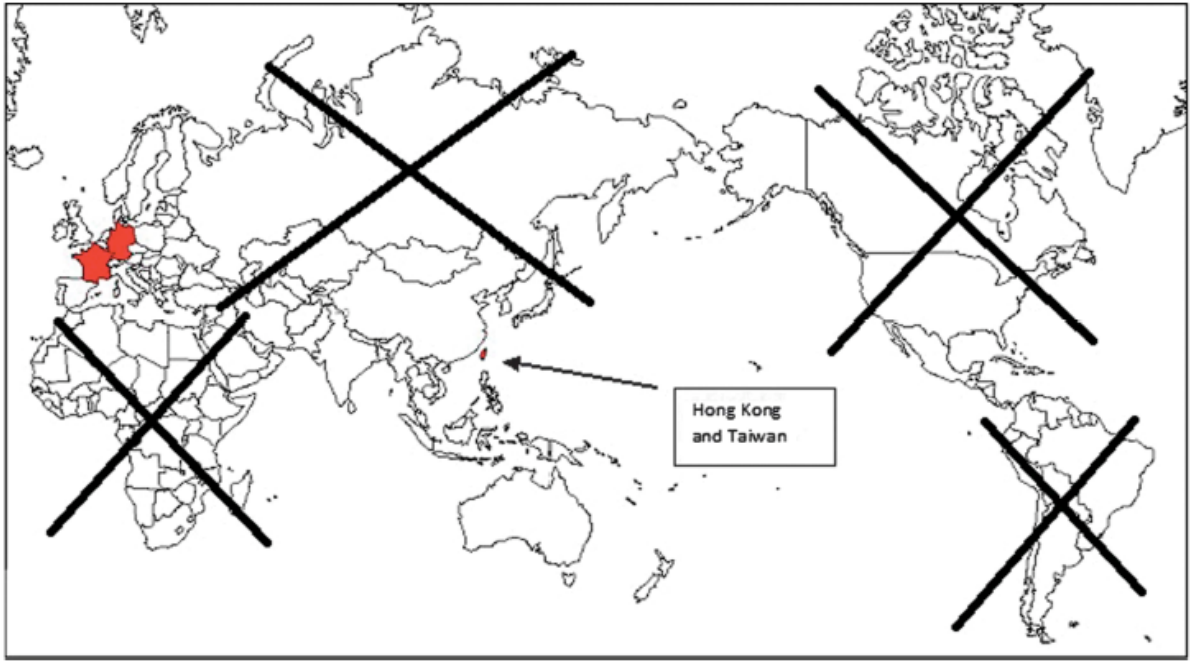
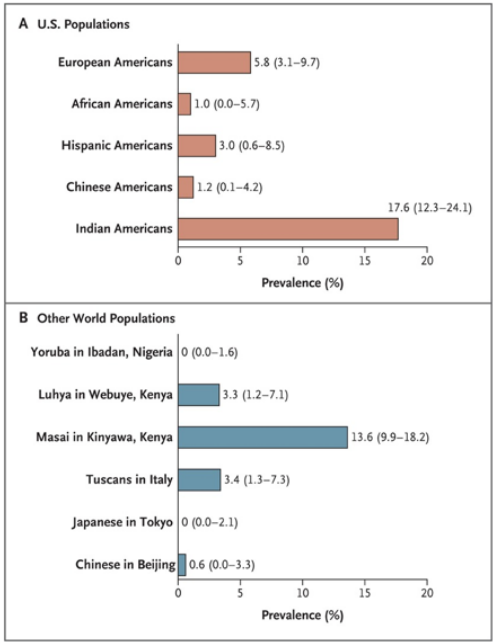


Figure 3. Map of region covered by medical evidence relied upon by the Food and Drug Administration (FDA) for pharmacogenomic warning for carbamazepine (area covered by medical evidence in red).

Payne PW. Ancestry-based pharmacogenomics, adverse reactions and carbamazepine: is the FDA warning correct?. The pharmacogenomics journal. 2014;14(5):473.

Genomic Variation



Rotimi CN, Jorde LB. N Engl J Med 2010;363:1551-1558.

REVIEW ARTICLE

GENOMIC MEDICINE

W. Gregory Feero, M.D., Ph.D., and Alan E. Guttmacher, M.D., *Editors*

Ancestry and Disease in the Age of Genomic Medicine

Charles N. Rotimi, Ph.D., and Lynn B. Jorde, Ph.D.

Public Health Implications

Genetic Screening to Prevent Hypersensitivity Reaction to Abacavir

Labels such as Black or African "obscure biomedically relevant variation and could lead to less vigilance among physicians . . ."

The NEW ENGLAND JOURNAL of MEDICINE

Figure 1. Variation in the HLA-B*5701 Locus in 11 HapMap Samples.

Box 1 What do we mean by ancestry?

In the context of this paper, ancestry is defined using genetic variants based on the distribution of those variants in worldwide populations. An individual's genome is a mosaic of segments from different ancestral populations. By comparing segments of DNA with the distribution of genetic variants in worldwide populations, it is possible to determine the likely "parental" or source population for each segment of DNA, indicating a component of the individual's overall ancestry. Using this process to interrogate an individual's entire genome, the proportion of an individual's genomic inheritance from specific ancestral populations can be estimated. Importantly, someone's genetic ancestry may have little to do with their identity in terms of race or culture. An individual with a relatively small proportion of African ancestry may not self-identify as "Black" or "African American", yet they may have African ancestry at a specific region of the genome where that ancestry may confer risk, for instance, by carrying a pharmacogenomic risk allele that is more prevalent among those with African ancestry. Based on our most recent analysis of 282 global samples, there are at least 21 ancestries.[139] Notably, mixed ancestry is the norm across samples and continents, and the vast majority of individuals (an estimated 97.3%) show ancestral heterogeneity.[139] Finally, individuals' ancestry estimates may change over time as our reference datasets become more diverse.

npj | Genomic Medicine

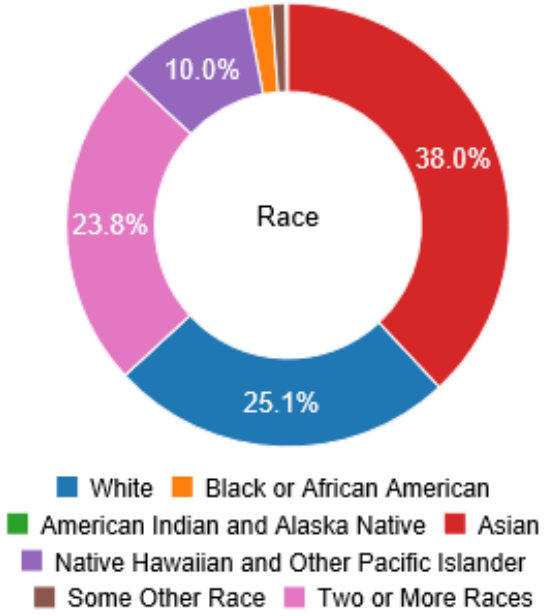
www.nature.com/npjgenmed

REVIEW ARTICLE OPEN

Evaluating the promise of inclusion of African ancestry populations in genomics

Amy R. Bentley[1], Shawneequa L. Callier[1,2] and Charles N. Rotimi[1*]

Litigation

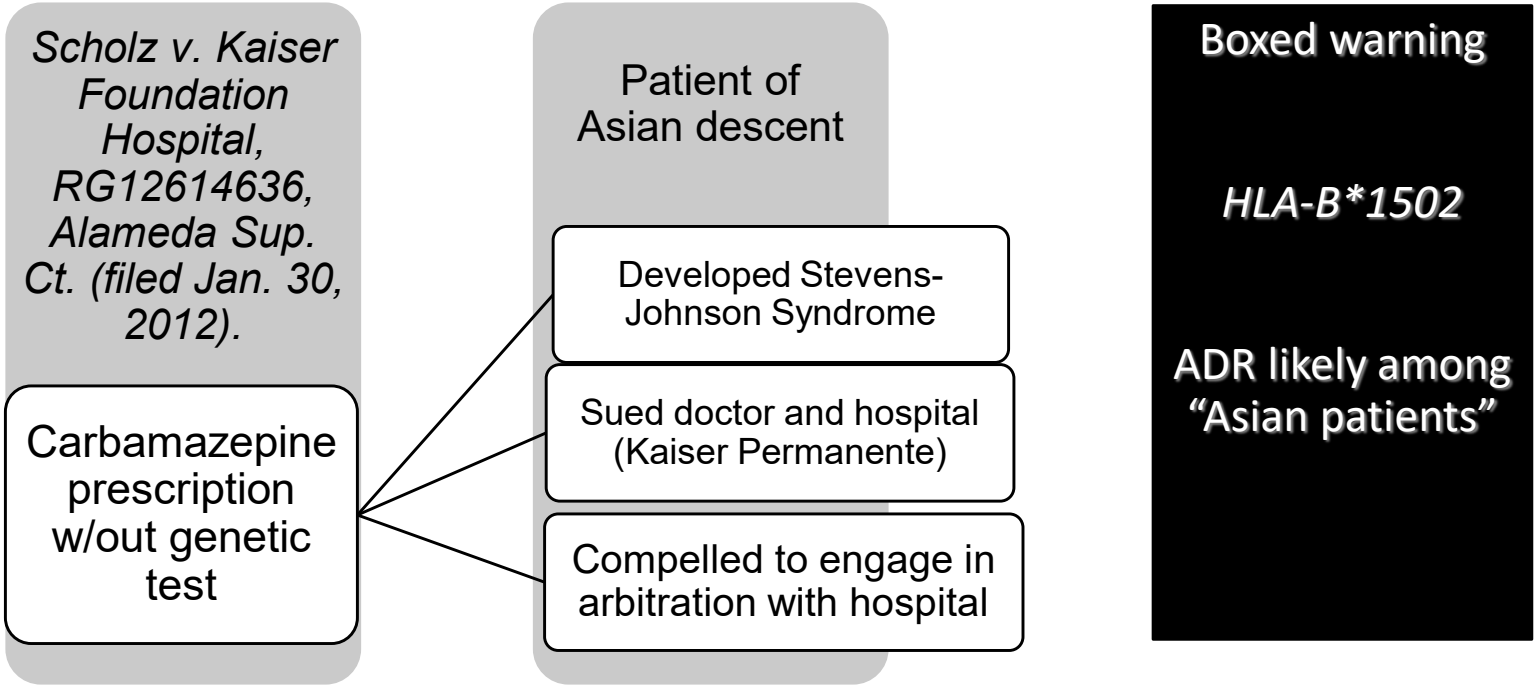


Hawaii AG Complaint (2014)

- False, deceptive, unfair marketing
- Higher and more expensive marketing to poor responders
- Sought to replace aspirin

Hawaii ex rel. Louie v. Bristol-Myers Squibb Co. et al., case number 14-1-0708-03 (2014)

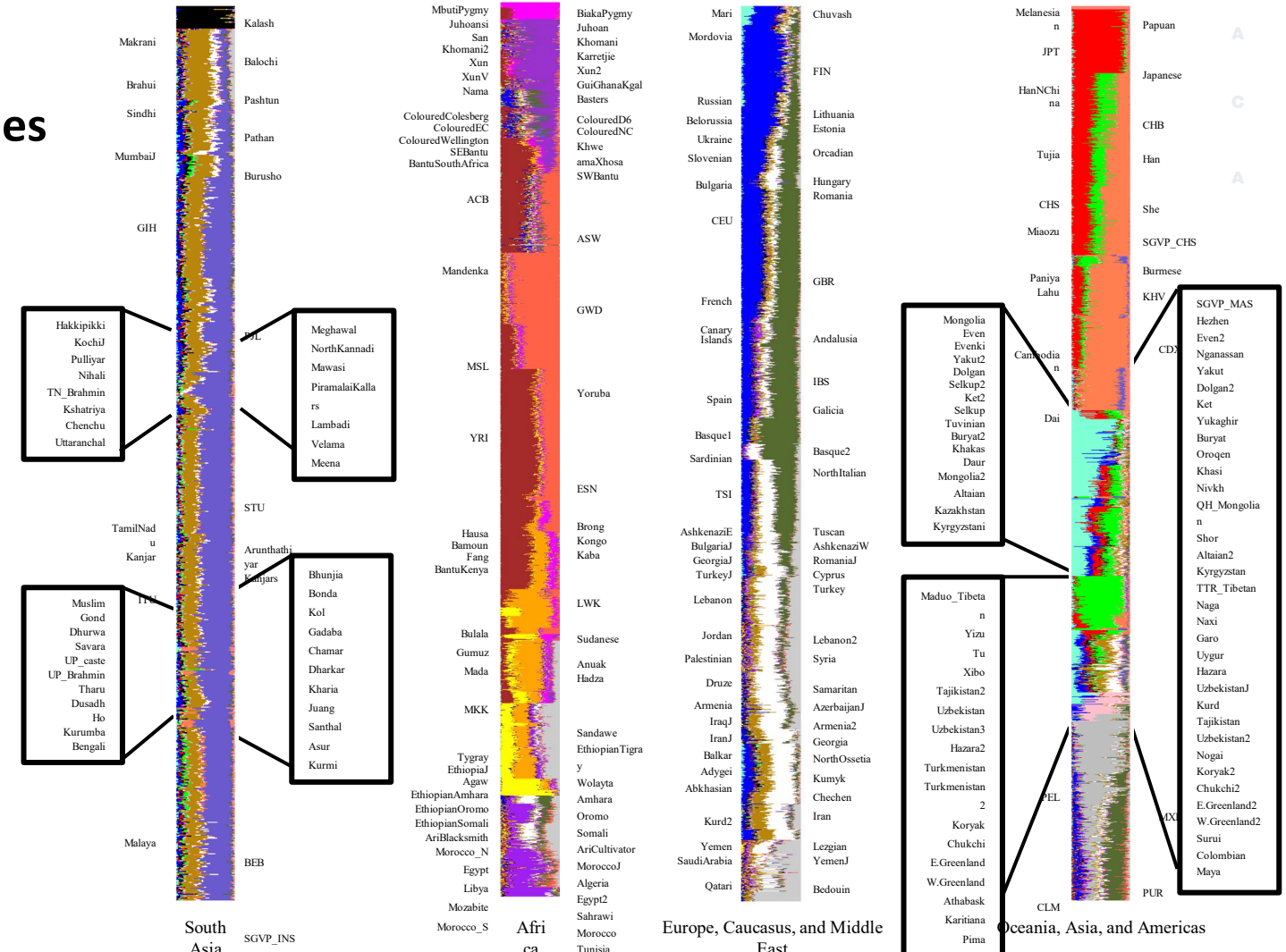
Litigation


Scholz v. Kaiser Foundation Hospital, RG12614636, Alameda Sup. Ct. (filed Jan. 30, 2012).
Carbamazepine prescription w/out genetic test
Patient of Asian descent
Developed Stevens-Johnson Syndrome
Sued doctor and hospital (Kaiser Permanente)
Compelled to engage in arbitration with hospital
Boxed warning
*HLA-B*1502*
ADR likely among "Asian patients"

20. Carbamazapine, also known as and referred to herein as Carbatrol, is a drug known to have an increased potential to cause life-threatening disease to persons of Asian heritage. Specifically, it was and is known in the medical community that persons of Asian descent who take the drug have a much greater tendency to develop Stevens-Johnson Syndrome. Stevens-Johnson Syndrome is a life threatening toxic skin condition in which cell

Scholz v. Kaiser Foundation Hospital, RG12614636,
Alameda Sup. Ct. (filed Jan. 30, 2012)

Race vs Ancestries



Baker, J.L., Rotimi, C.N. & Shriner, D. Human ancestry correlates with language and reveals that race is not an objective genomic classifier. *Sci Rep* **7,** 1572 (2017).

NIH NHGRI

Genomics Research Landscape

Perspective

Box 5

Bold predictions for human genomics by 2030

"Research in human genomics will have moved beyond population descriptors based on historic social constructs such as race."

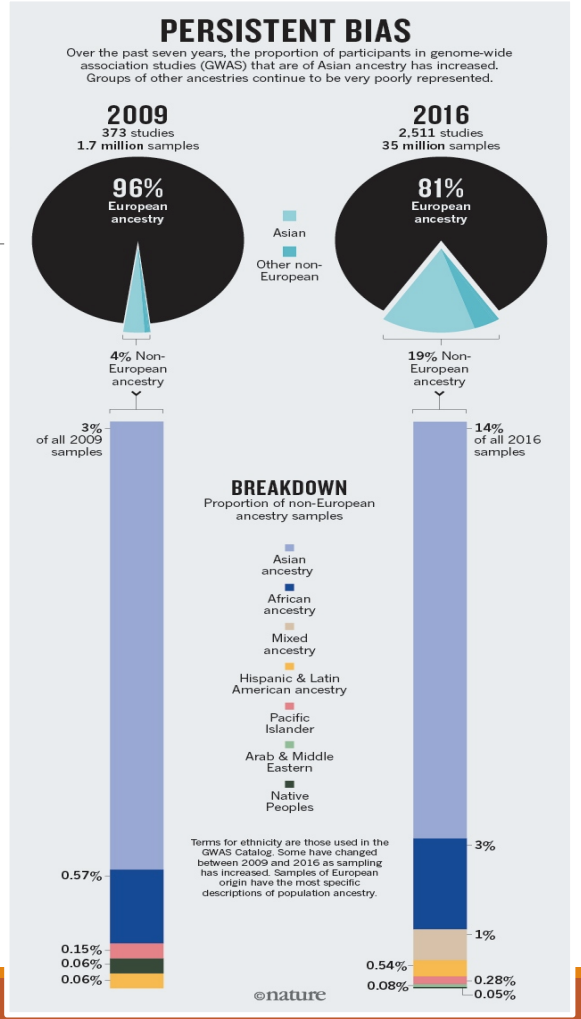
Green, E.D., Gunter, C., Biesecker, L.G. *et al.* Strategic vision for improving human health at The Forefront of Genomics. *Nature* **586,** 683–692 (2020). https://doi.org/10.1038/s41586-020-2817-4

Use of Race, Ethnicity, and Ancestry as Population Descriptors in Genomics Research

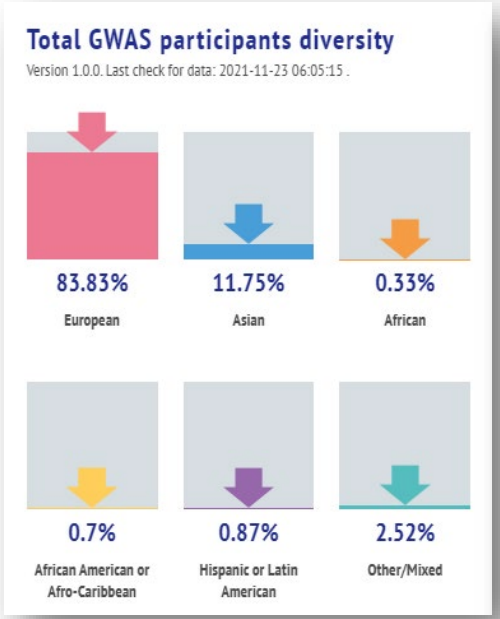
National Academies of Sciences, Engineering, and Medicine ad hoc committee (2022)

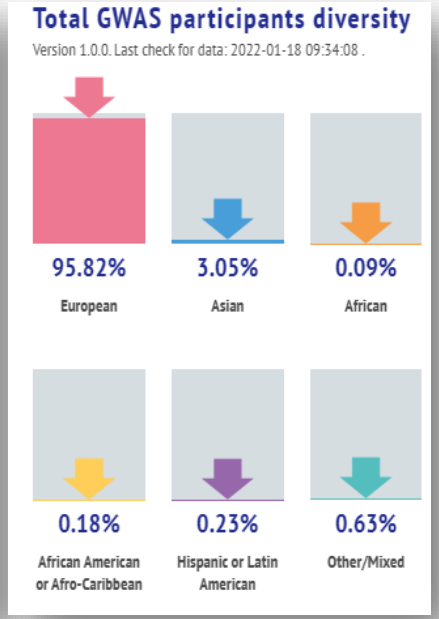
Genomics Research Landscape

Popejoy, Alice B., and Stephanie M. Fullerton. "Genomics is failing on diversity." *Nature News* 538.7624 (2016): 161.



Genomics Research Landscape





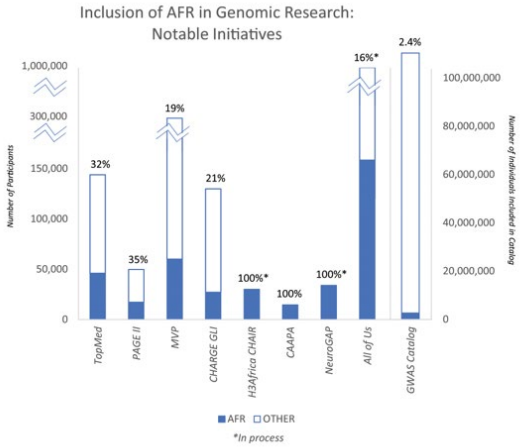
Mills, Melinda C., and Charles Rahal. 2020. The GWAS diversity monitor tracks diversity by disease in real time. *Nature genetics* 52, (3) (03): 242-2

Genomics Discovery

Evaluating the promise of inclusion of African ancestry populations in genomics

Amy R. Bentley, Shawneequa L. Callier & Charles N. Rotimi

npj Genomic Medicine **5**, Article number: 5 (2020) | Cite this article



J Community Genet (2017) 8:255–266
DOI 10.1007/s12687-017-0316-6

ORIGINAL ARTICLE

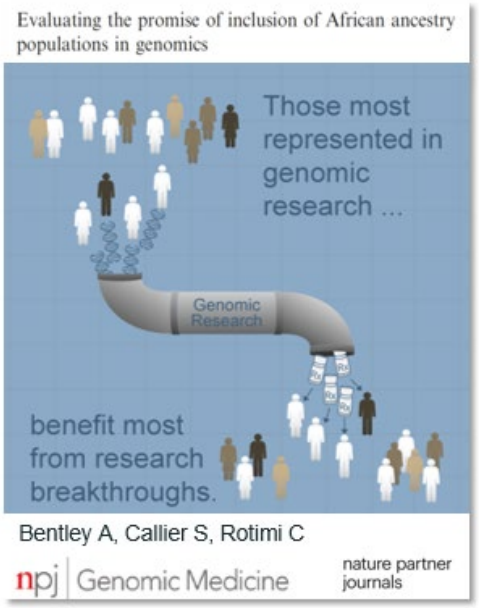
Diversity and inclusion in genomic research: why the uneven progress?

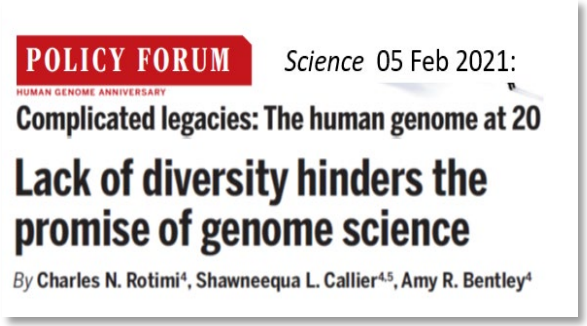
Amy R. Bentley [1] · Shawneequa Callier [1,2] · Charles N. Rotimi [1]

Table 1 Key challenges and recommendations for promoting genomic research in diverse populations

Challenge
Lagging diversity within the scientific community
Limited engagement
Preference by researchers to analyze data from well-characterized, well-powered, predominantly European ancestry cohorts
Difficulty in publication/funding due to relatively smaller sample sizes in diverse populations
Limitations in current genotyping technology to adequately capture variation among diverse individuals
Analytical challenges of diversity

Genomics Discovery

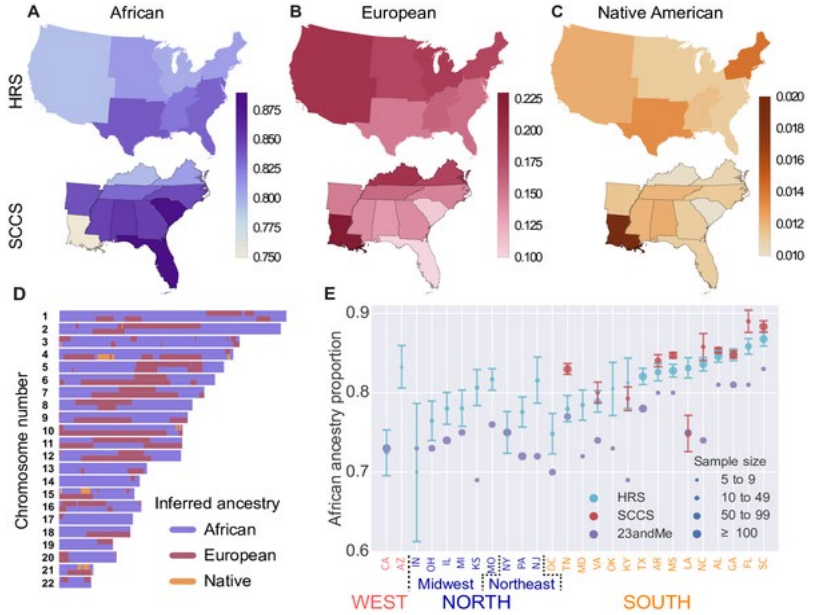




"Any two sub-Saharan Africans are more likely to be genetically different from each other than from an individual of European or Asian ancestry"

". . . African-Americans have been under-represented in genetic studies, and relatively little is known about nation-wide patterns of genomic diversity in the population."

Fig 1. Inferred regional ancestry proportions for the HRS and SCCS cohorts: (A) African, (B) European, and (C) Native American ancestries.



Baharian S, Barakatt M, Gignoux CR, Shringarpure S, Errington J, et al. (2016) The Great Migration and African-American Genomic Diversity. PLOS Genetics 12(5): e1006059. https://doi.org/10.1371/journal.pgen.1006059
https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1006059

PLOS | GENETICS

Genomics Discovery

nature

COMMENT · 08 SEPTEMBER 2020

Don't ignore genetic data from minority populations

Efforts to build representative studies are defeated when scientists discard data from certain groups. Instead, researchers should work to balance statistical needs with fairness.

(Ben-Eghan, et al., 2020; Melchionna, 2021; Wickland et al., 2022)

J Natl Cancer Inst. 2022 Mar 17;djac054. doi: 10.1093/jnci/djac054. Online ahead of print.

Lower Exome Sequencing Coverage of Ancestrally African Patients in the Cancer Genome Atlas

Daniel P Wickland [1], Mark E Sherman [1], Derek C Radisky [2], Aaron S Mansfield [3] [4], Yan W Asmann [1]

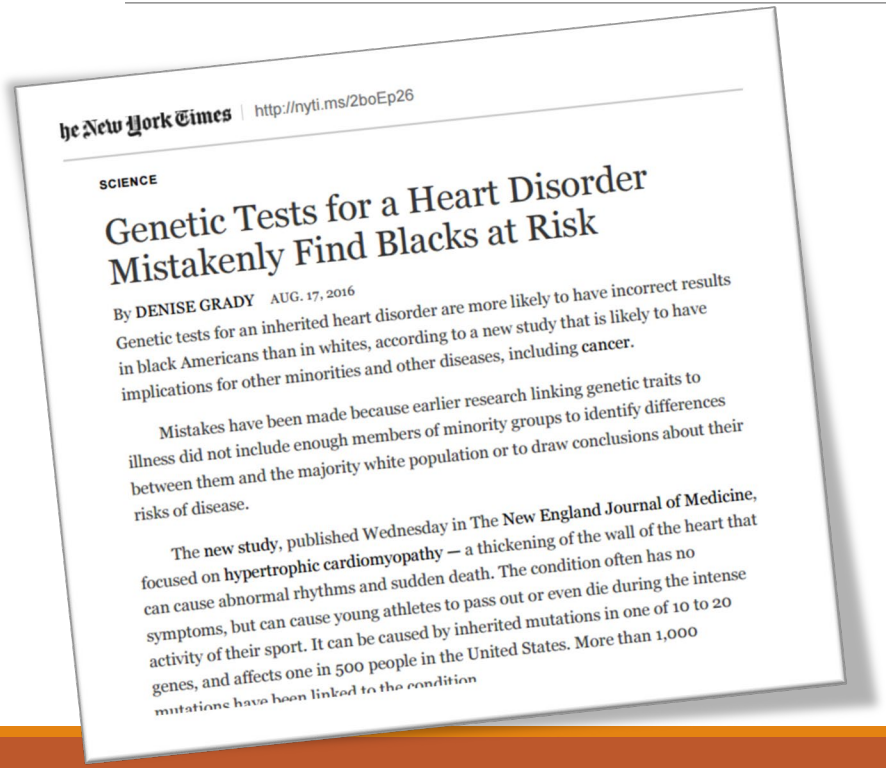
HEALTH IT ANALYTICS

ANALYTICS IN ACTION NEWS

Black Cancer Patients Have Lower Quality Genomic Sequencing Data

Mayo Clinic found significant differences in genomic sequencing data among racial groups, specifically lower quality data for Black patients in one of most used cancer research datasets.

Clinical Implications



The New York Times | http://nyti.ms/2boEp26

SCIENCE

Genetic Tests for a Heart Disorder Mistakenly Find Blacks at Risk

By DENISE GRADY AUG. 17, 2016

Genetic tests for an inherited heart disorder are more likely to have incorrect results in black Americans than in whites, according to a new study that is likely to have implications for other minorities and other diseases, including cancer.

Mistakes have been made because earlier research linking genetic traits to illness did not include enough members of minority groups to identify differences between them and the majority white population or to draw conclusions about their risks of disease.

The new study, published Wednesday in The New England Journal of Medicine, focused on hypertrophic cardiomyopathy — a thickening of the wall of the heart that can cause abnormal rhythms and sudden death. The condition often has no symptoms, but can cause young athletes to pass out or even die during the intense activity of their sport. It can be caused by inherited mutations in one of 10 to 20 genes, and affects one in 500 people in the United States. More than 1,000 mutations have been linked to the condition

HealthAffairs

Lack Of Diversity In Genomic Databases Is A Barrier To Translating Precision Medicine Research Into Practice

Latrice G. Landry, Nadya Ali, David R. Williams, Heidi L. Rehm, and Vence L. Bonham

AFFILIATIONS

PUBLISHED: MAY 2018 No Access https://doi.org/10.1377/hlthaff.2017.1595

(Grady, 2016 & Landry, et al., 2018)

Lack of Diversity and Inclusion + Biologizing race prevents patients from realizing the benefits of precision medicine.

What does health justice require?

"Justice may require more than securing greater inclusion of women, minorities, and other groups in research to derive benefits from research."

-Law Professor, Patricia King, May 2007

Race and Racism

2022

Socioeconomic disparities rank Iowa as third worst state for Black Americans

A recent study ranked Iowa as the third worst state in the U.S. for Black Americans on an index of various socioeconomic factors.

The Daily Iowan

THE INDEPENDENT NEWSPAPER OF THE UNIVERSITY OF IOWA COMMUNITY SINCE 1868

RACE

A new study examines Black life expectancy and well-being in the U.S.

October 2, 2022 · 4:53 PM ET
Heard on All Things Considered

"But when you look at life expectancy in the aggregate, always comparing it to white people, you miss the diversity of those places that are winning, that are actually taking charge in spite of that constant - of racism that is a pall across the country."

Summary

1. Race-based clinical algorithms cause people who could benefit from a therapy or intervention to not receive it.
2. Lack of DEI in research leadership and participation hinders the realization of precision medicine and the overcoming of race-based medicine.
3. Laws and policies should reflect understanding about genomics and hold researchers accountable for overstating the role of race in medicine.

Recommendations

1. Explain limits of broad population labels (“African ancestry”) when reporting genomic results
2. Study and report genetic diversity within continental and regional groups
3. Describe and justify reasons for using social variables in the analysis, including race and ethnicity
    A. Clearly articulate reasons for stratifying groups based on race/ethnicity
    B. Explain how social labels contribute to the analysis

Develop new laws that encourage the genomic and pharmacogenomic study of diverse groups with input from research, medical, and commercial stakeholders