The role of other population descriptors

Or: Where not to look for answers to the use of race and ethnicity in biomedical research

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G2P GENOMES TO PEOPLE

Structure and Take homes

1. Existing guidelines for the use of population descriptions align on several core themes, but disagree on definitions of these categories and appropriate contexts for use
2. “Ancestry” is seen by some as part of the solution to the use of race and ethnicity
3. Appealing to “Ancestry” would compound issues, not solve them
4. “Genetic ancestry” is a precisely defined concept, but seldom the one called for in applications
5. Two golden rules: get the right concept of difference for a specific use case; appreciate that most use cases involve multiple relevant dimensions of difference

Edmond and Lily Safra Center for Ethics Project

1. Existing guidelines for the use of population descriptions align on several core themes, but disagree on definitions of these categories and appropriate contexts for use

AJHG

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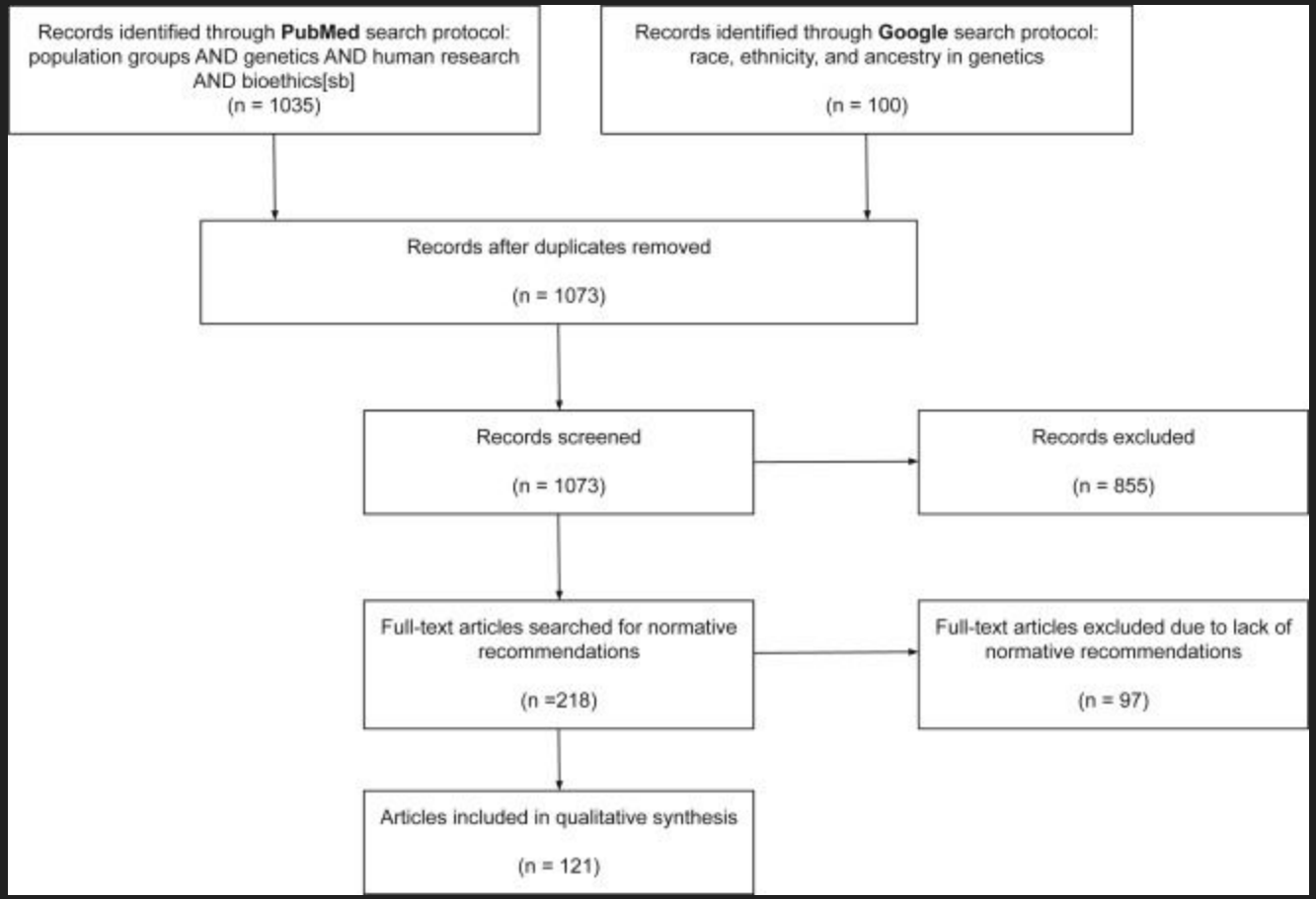
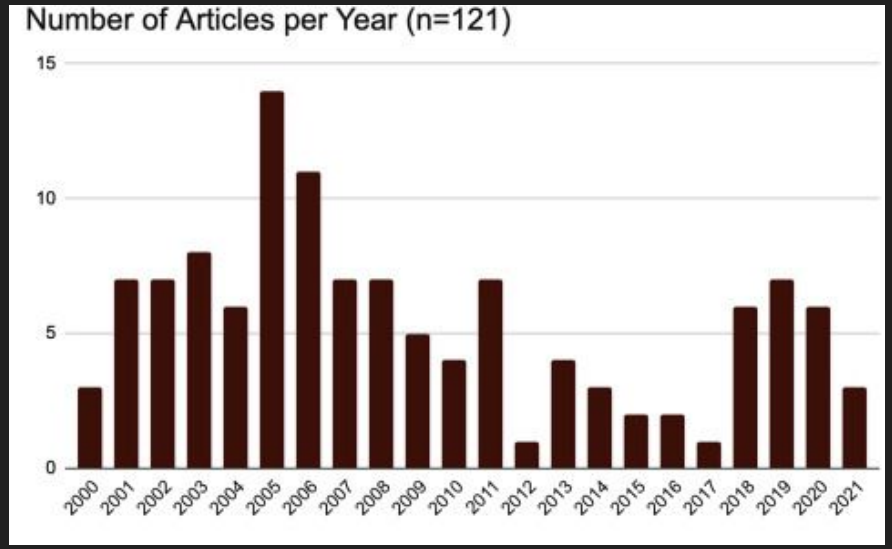
Review

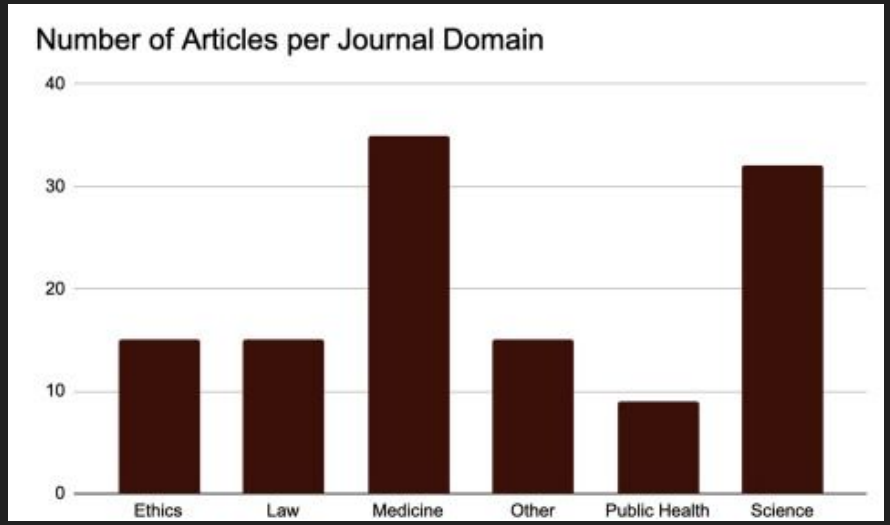
A scoping review of guidelines for the use of race, ethnicity, and ancestry reveals widespread consensus but also points of ongoing disagreement

Madelyn Mauro [1], Danielle S. Allen [1], Bege Dauda [2 3], Santiago J. Molina [4], Benjamin M. Neale [5 6 7], Anna C.F. Lewis [1 8]


Records identified through **PubMed** search protocol: population groups AND genetics AND human research AND bioethics[sb] (n = 1035)
Records identified through **Google** search protocol: race, ethnicity, and ancestry in genetics (n = 100)
Records after duplicates removed (n = 1073)
Records screened (n = 1073)
Records excluded (n = 855)
Full-text articles searched for normative recommendations (n =218)
Full-text articles excluded due to lack of normative recommendations (n = 97)
Articles included in qualitative synthesis (n = 121)

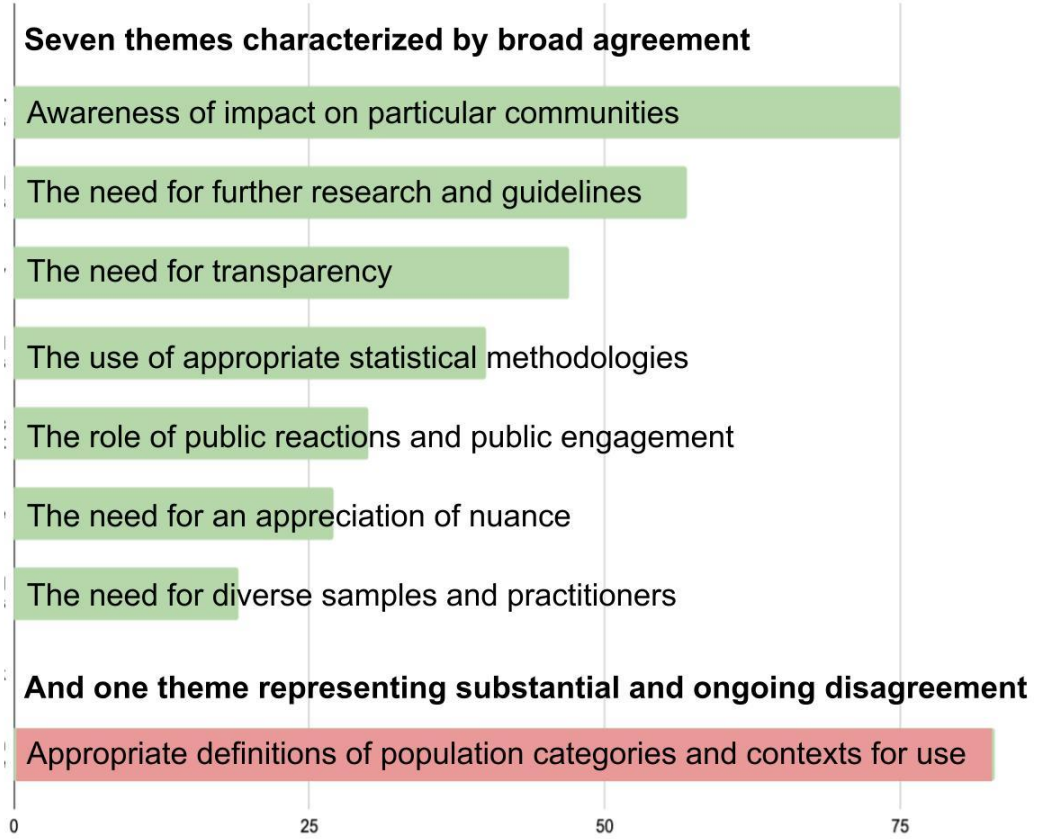
Articles included





Most, if not all, contributing authors for 102 articles (84% of total article yield) were affiliated with the US.

Thematic analysis of 384 guidelines published in 121 articles for the use of race, ethnicity, and ancestry in science, medicine and public health with a focus on genetics research, identified:



2. “Ancestry” is seen by some as part of the solution to the use of race and ethnicity

Little reflection on the use of “ancestry”

“This begs the question: is ancestry being touted as a cure-all to the problems raised by the use of race and ethnicity in science and medicine?”

Why?

> “Ancestry” viewed as a more objective and less sensitive concept than race or ethnicity

> Expertise needed for the inference of genetic ancestry categories makes this process non-transparent to many/harder to challenge

Focus on ways race is inappropriately baked into health algorithms

A partial list of race-adjusted algorithms: “Given their potential to perpetuate or even amplify race-based health inequities, they merit thorough scrutiny.”

Vyas et al, *Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms,* NEJM, 2020

“[T]he appraisal of whether the use of race or ethnicity is appropriate in algorithms that include race correction will require further research into the complex interactions among ancestry, race, racism, socioeconomic status, and environment”

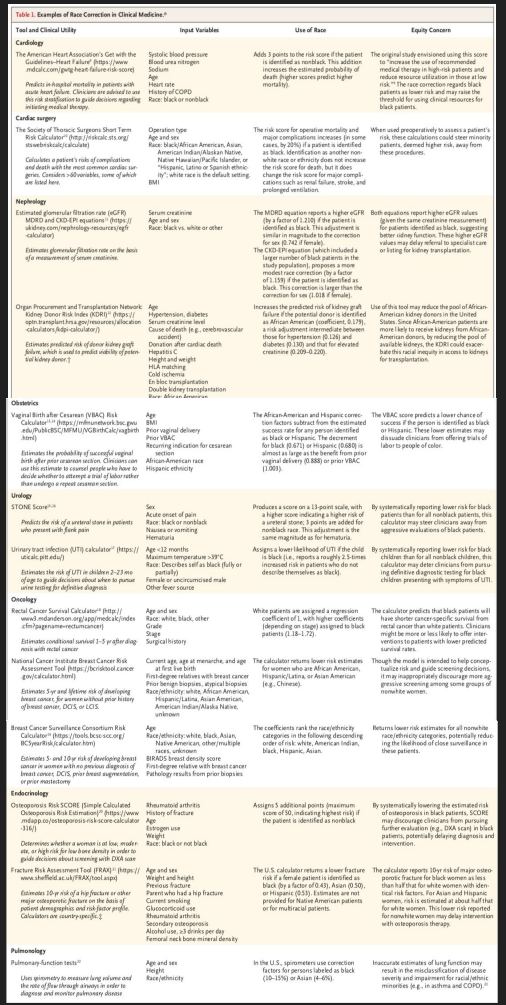


Table 1. Examples of Race Correction in Clinical Medicine.*

Tool and Clinical Utility	Input Variables	Use of Race	Equity Concern
Cardiology			
The American Heart Association's Get with the Guidelines–Heart Failure† (https://www.mdcalc.com/gwtg-heart-failure-risk-score) *Predicts in-hospital mortality in patients with acute heart failure. Clinicians are advised to use this risk stratification to guide decisions regarding initiating medical therapy.*	Systolic blood pressure Blood urea nitrogen Sodium Age Heart rate History of COPD Race: black or nonblack	Adds 3 points to the risk score if the patient is identified as nonblack. This addition increases the estimated probability of death (higher scores predict higher mortality).	The original study envisioned using this score to "increase the use of recommended medical therapy in high-risk patients and reduce resource utilization in those at low risk."[4] The race correction regards black patients as lower risk and may raise the threshold for using clinical resources for black patients.
Cardiac surgery			
The Society of Thoracic Surgeons Short Term Risk Calculator‡ (http://riskcalc.sts.org/stswebriskcalc/calculate) *Calculates a patient's risks of complications and death with the most common cardiac surgeries. Considers >80 variables, some of which are listed here.*	Operation type Age and sex Race: black/African American, Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, or "Hispanic, Latino or Spanish ethnicity"; white race is the default setting BMI	The risk score for operative mortality and major complications increases (in some cases, by 20%) if a patient is identified as black. Identification as another non-white race or ethnicity does not increase the risk score for death, but it does change the risk score for major complications such as renal failure, stroke, and prolonged ventilation.	When used preoperatively to assess a patient's risk, these calculations could steer minority patients, deemed higher risk, away from these procedures.
Nephrology			
Estimated glomerular filtration rate (eGFR) MDRD and CKD-EPI equations§ (https://akdhelp.com/nephrology-resources/egfr-calculator) *Estimates glomerular filtration rate on the basis of a measurement of serum creatinine.*	Serum creatinine Age and sex Race: black vs. white or other	The MDRD equation reports a higher eGFR (by a factor of 1.210) if the patient is identified as black. This adjustment is similar in magnitude to the correction for sex (0.742 if female). The CKD-EPI equation (which included a larger number of black patients in the study population), proposes a more modest race correction (by a factor of 1.159) if the patient is identified as black. This correction is larger than the correction for sex (1.018 if female).	Both equations report higher eGFR values (given the same creatinine measurement) for patients identified as black, suggesting better kidney function. These higher eGFR values may delay referral to specialist care or listing for kidney transplantation.
Organ Procurement and Transplantation Network: Kidney Donor Risk Index (KDRI)¶ (https://optn.transplant.hrsa.gov/resources/allocation-calculators/kdpi-calculator/) *Estimates predicted risk of donor kidney graft failure, which is used to predict viability of potential kidney donor.‖*	Age Hypertension, diabetes Serum creatinine level Cause of death (e.g., cerebrovascular accident) Donation after cardiac death Hepatitis C Height and weight HLA matching Cold ischemia En bloc transplantation Double kidney transplantation Race: African American	Increases the predicted risk of kidney graft failure if the potential donor is identified as African American (coefficient, 0.179), a risk adjustment intermediate between those for hypertension (0.126) and diabetes (0.130) and that for elevated creatinine (0.209–0.220).	Use of this tool may reduce the pool of African-American kidney donors in the United States. Since African-American patients are more likely to receive kidneys from African-American donors, by reducing the pool of available kidneys, the KDRI could exacerbate this racial inequity in access to kidneys for transplantation.
Obstetrics			
Vaginal Birth after Cesarean (VBAC) Risk Calculator¶,[19] (https://mfmunetwork.bsc.gwu.edu/PublicBSC/MFMU/VGBirthCalc/vgbirth.html) *Estimates the probability of successful vaginal birth after prior cesarean section. Clinicians can use this estimate to counsel people who have to decide whether to attempt a trial of labor rather than undergo a repeat cesarean section.*	Age BMI Prior vaginal delivery Prior VBAC Recurring indication for cesarean section African-American race Hispanic ethnicity	The African-American and Hispanic correction factors subtract from the estimated success rate for any person identified as black or Hispanic. The decrement for black (0.671) or Hispanic (0.680) is almost as large as the benefit from prior vaginal delivery (0.888) or prior VBAC (1.003).	The VBAC score predicts a lower chance of success if the person is identified as black or Hispanic. These lower estimates may dissuade clinicians from offering trials of labor to people of color.
Urology			
STONE Score[20,21] *Predicts the risk of a ureteral stone in patients who present with flank pain*	Sex Acute onset of pain Race: black or nonblack Nausea or vomiting Hematuria	Produces a score on a 13-point scale, with a higher score indicating a higher risk of a ureteral stone; 3 points are added for nonblack race. This adjustment is the same magnitude as for hematuria.	By systematically reporting lower risk for black patients than for all nonblack patients, this calculator may steer clinicians away from aggressive evaluations of black patients.
Urinary tract infection (UTI) calculator[22] (https://uticalc.pitt.edu/) *Estimates the risk of UTI in children 2–23 mo of age to guide decisions about when to pursue urine testing for definitive diagnosis*	Age <12 months Maximum temperature >39°C Race: Describes self as black (fully or partially) Female or uncircumcised male Other fever source	Assigns a lower likelihood of UTI if the child is black (i.e., reports a roughly 2.5-times increased risk in patients who do not describe themselves as black).	By systematically reporting lower risk for black children than for all nonblack children, this calculator may deter clinicians from pursuing definitive diagnostic testing for black children presenting with symptoms of UTI.
Oncology			
Rectal Cancer Survival Calculator[23] (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=rectumcancer) *Estimates conditional survival 1–5 yr after diagnosis with rectal cancer*	Age and sex Race: white, black, other Grade Stage Surgical history	White patients are assigned a regression coefficient of 1, with higher coefficients (depending on stage) assigned to black patients (1.18–1.72).	The calculator predicts that black patients will have shorter cancer-specific survival from rectal cancer than white patients. Clinicians might be more or less likely to offer interventions to patients with lower predicted survival rates.
National Cancer Institute Breast Cancer Risk Assessment Tool (https://bcrisktool.cancer.gov/calculator.html) *Estimates 5-yr and lifetime risk of developing breast cancer, for women without prior history of breast cancer, DCIS, or LCIS.*	Current age, age at menarche, and age at first live birth First-degree relatives with breast cancer Prior benign biopsies, atypical biopsies Race/ethnicity: white, African American, Hispanic/Latina, Asian American, American Indian/Alaska Native, unknown	The calculator returns lower risk estimates for women who are African American, Hispanic/Latina, or Asian American (e.g., Chinese).	Though the model is intended to help conceptualize risk and guide screening decisions, it may inappropriately discourage more aggressive screening among some groups of nonwhite women.
Breast Cancer Surveillance Consortium Risk Calculator[24] (https://tools.bcsc-scc.org/BCSyearRisk/calculator.htm) *Estimates 5- and 10-yr risk of developing breast cancer in women with no previous diagnosis of breast cancer, DCIS, prior breast augmentation, or prior mastectomy*	Age Race/ethnicity: white, black, Asian, Native American, other/multiple races, unknown BIRADS breast density score First-degree relative with breast cancer Pathology results from prior biopsies	The coefficients rank the race/ethnicity categories in the following descending order of risk: white, American Indian, black, Hispanic, Asian.	Returns lower risk estimates for all nonwhite race/ethnicity categories, potentially reducing the likelihood of close surveillance in these patients.
Endocrinology			
Osteoporosis Risk SCORE (Simple Calculated Osteoporosis Risk Estimation)[25] (https://www.mdapp.co/osteoporosis-risk-score-calculator-316/) *Determines whether a woman is at low, moderate, or high risk for low bone density in order to guide decisions about screening with DXA scan*	Rheumatoid arthritis History of fracture Age Estrogen use Weight Race: black or not black	Assigns 5 additional points (maximum score of 50, indicating highest risk) if the patient is identified as nonblack	By systematically lowering the estimated risk of osteoporosis in black patients, SCORE may discourage clinicians from pursuing further evaluation (e.g., DXA scan) in black patients, potentially delaying diagnosis and intervention.
Fracture Risk Assessment Tool (FRAX)[26] (https://www.sheffield.ac.uk/FRAX/tool.aspx) *Estimates 10-yr risk of a hip fracture or other major osteoporotic fracture on the basis of patient demographics and risk-factor profile. Calculators are country-specific.‖*	Age and sex Weight and height Previous fracture Parent who had a hip fracture Current smoking Glucocorticoid use Rheumatoid arthritis Secondary osteoporosis Alcohol use, ≥3 drinks per day Femoral neck bone mineral density	The U.S. calculator returns a lower fracture risk if a female patient is identified as black (by a factor of 0.43), Asian (0.50), or Hispanic (0.53). Estimates are not provided for Native American patients or for multiracial patients.	The calculator reports 10-yr risk of major osteoporotic fracture for black women as less than half that for white women with identical risk factors. For Asian and Hispanic women, risk is estimated at about half that for white women. This lower risk reported for nonwhite women may delay intervention with osteoporosis therapy.
Pulmonology			
Pulmonary-function tests[20] *Uses spirometry to measure lung volume and the rate of flow through airways in order to diagnose and monitor pulmonary disease*	Age and sex Height Race/ethnicity	In the U.S., spirometers use correction factors for persons labeled as black (10–15%) or Asian (4–6%).	Inaccurate estimates of lung function may result in the misclassification of disease severity and impairment for racial/ethnic minorities (e.g., in asthma and COPD).[27]

The perceived importance of genetic ancestry

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., David S. Wilkes, M.D., Neil R. Powe, M.D., M.P.H., M.B.A., Elad Ziv, M.D., and Esteban G. Burchard, M.D., M.P.H.

"The race/ethnicity categories used in biomedical research and clinical practice are broad and less precise than ancestry….. ancestry is a fixed characteristic of the genome"

MEDICINE AND SOCIETY

Embracing Genetic Diversity to Improve Black Health

Akinyemi Oni-Orisan, Pharm.D., Ph.D., Yusuph Mavura, M.S., Yambazi Banda, Ph.D., Timothy A. Thornton, Ph.D., and Ronnie Sebro, M.D., Ph.D.

"The ultimate goal, we believe, would be to replace race with genetic ancestry in an evidence-based manner."

3. Appealing to “Ancestry” would compound issues, not solve them

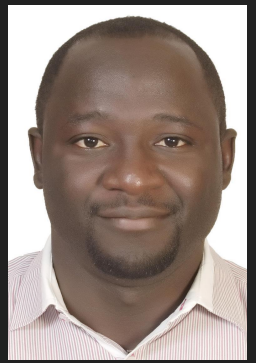
Frontiers in Genetics Sections Articles Research Topics Editorial Board About journal

ORIGINAL RESEARCH article

Front. Genet., 23 January 2023
Sec. ELSI in Science and Genetics
Volume 14 - 2023 | https://doi.org/10.3389/fgene.2023.1044555

Ancestry: How researchers use it and what they mean by it

Bege Dauda[1], Santiago J. Molina[2], Danielle S. Allen[3], Agustin Fuentes[4], Nayanika Ghosh[5], Madelyn Mauro[3], Benjamin M. Neale[6,7,8], Aaron Panofsky[9,10,11], Mashaal Sohail[12], Sarah R. Zhang[13] and Anna C. F. Lewis[3,14]*



What does ancestry mean to you?

We asked researchers for whom “ancestry” was a prominent concept in their work

- Most struggled to answer the question
- Many gave very personal answers

They differed as to

a) what ancestry is a property of (DNA, individual, family, population) and

b) what criteria are appealed to (biology, culture/ethnicity, genealogical connections, geographical origins)

Some quotes

- “Previously I used ethnicity. But then my mentor told me that nowadays people use ancestry.’’
- “instead of race, because we cannot use, like ‘mixed race’ because. . . the connotation is not good.”
- “But ancestry is in some ways, to be perfectly honest, a neutral term that that doesn't raise anybody's hackles whereas race, ethnicity is commonly used but bothers some people to hear, whereas nobody has a problem with the word ancestry. So you know I'm perfectly happy to tell you sometimes it's just a plain dodge”

How is “ancestry” operationalized?

Inn 26% of cases, no specification. In remaining:

- 52% genetic
- 35% non-genetic
- 14% both

Articles frequently slipped between terms. In some places using “European ancestry” and “African ancestry” and in others using, “European,” “Caucasian” or “Black African”

“Ancestry” not the hoped for objective counterpart to race/ethnicity

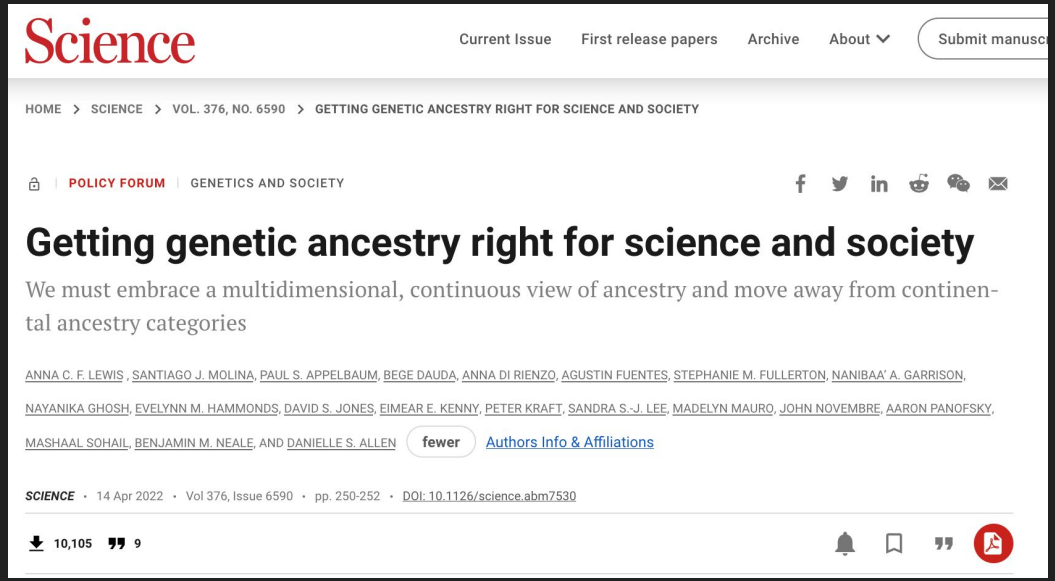
“Ancestry” as a bridge between the social and the genetic

- Ancestry can be about either social identity or genetics
- Ambiguity is taken advantage of, in the situation of genetically inferred categories alongside social categories
- Aided by the the dominance of continental ancestry categories, and the conflation of these with racial categories

Use of continental ancestry categories problematic for scientific and ethical reasons

They represent the same old typological thinking

This is a) has had damaging social consequences (ethically problematic), b) is hopelessly oversimplified (scientifically problematic)



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POLICY FORUM | GENETICS AND SOCIETY

Getting genetic ancestry right for science and society

We must embrace a multidimensional, continuous view of ancestry and move away from continental ancestry categories

ANNA C. F. LEWIS , SANTIAGO J. MOLINA, PAUL S. APPELBAUM, BEGE DAUDA, ANNA DI RIENZO, AGUSTIN FUENTES, STEPHANIE M. FULLERTON, NANIBAA' A. GARRISON, NAYANIKA GHOSH, EVELYNN M. HAMMONDS, DAVID S. JONES, EIMEAR E. KENNY, PETER KRAFT, SANDRA S.-J. LEE, MADELYN MAURO, JOHN NOVEMBRE, AARON PANOFSKY, MASHAAL SOHAIL, BENJAMIN M. NEALE, AND DANIELLE S. ALLEN fewer Authors Info & Affiliations

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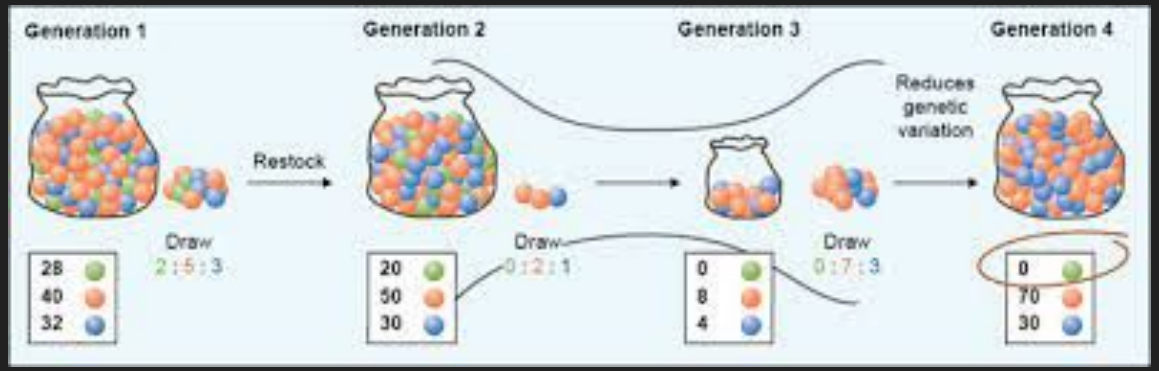
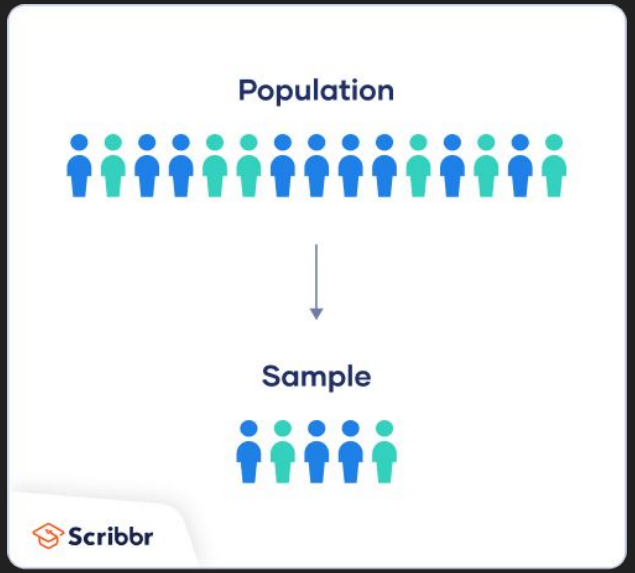
“Population” also hopelessly ambiguous



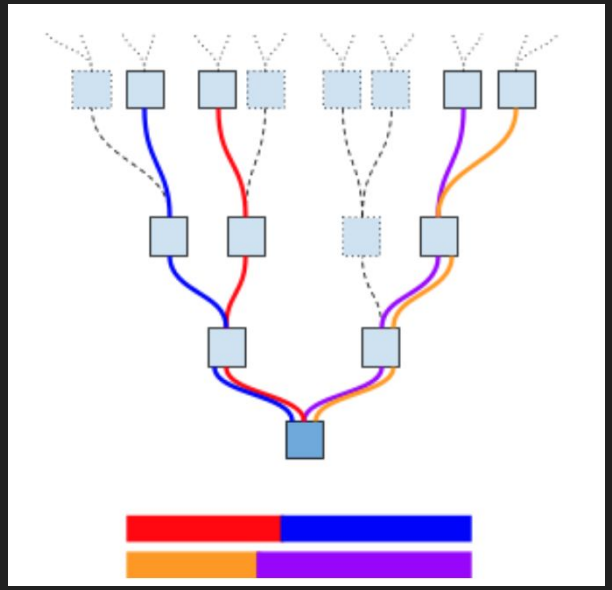


4. “Genetic ancestry” is a precisely defined concept, but seldom the one called for in applications

Genetic ancestry = the Ancestral Recombination Graph

Describes the inheritance of each part of the genome of every individual who ever lived.

An individual's genetic ancestry is the subset of paths through their family tree by which they have inherited DNA from specific ancestors.



Following Mathieson and Scally, *What is Ancestry?*

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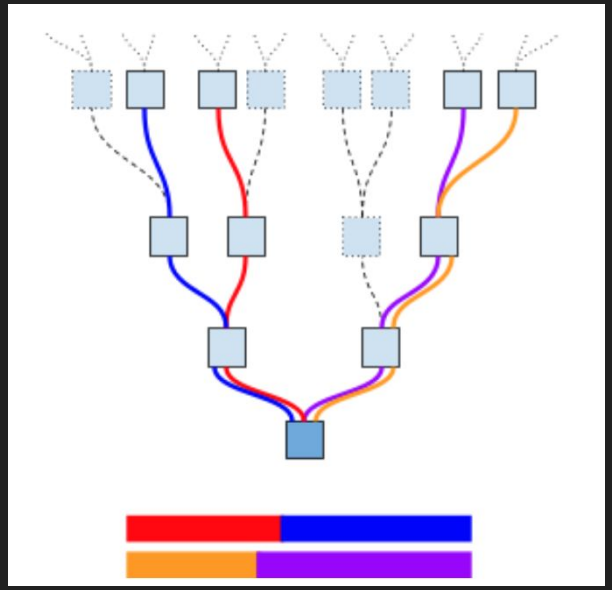

Groups not inherent to the concept
Nor is any contextualization beyond genealogical connections

Genetic similarity

“quantitative measure of the genetic resemblance between individuals that reflects the extent of shared genetic ancestry.”

NASEM report on the use of population descriptors in genetics research, following Graham Coop

Often, when the term “genetic ancestry” is used, “genetic similarity” is actually what is a) being referred to, and b) the appropriate concept

5. Two golden rules

An Ethical Framework for Research Using Genetic Ancestry

Anna C. F. Lewis, Santiago J. Molina, Paul S. Appelbaum, Bege Dauda, Agustin Fuentes, Stephanie M. Fullerton, Nanibaa' A. Garrison, Nayanika Ghosh, Robert C. Green, Evelynn M. Hammonds, Janina M. Jeff, David S. Jones, Eimear E. Kenny, Peter Kraft, Madelyn Mauro, Anil P. S. Ori, Aaron Panofsky, Mashaal Sohail, Benjamin M. Neale,* and Danielle S. Allen*

Perspectives in Biology and Medicine, volume 66, number 2 (spring 2023): 225–248.

1. Get the right concept of difference for a specific use case

- Will always be context dependent
- Often we're interested in developing our mechanic understanding of what is going on, so, what could have a mechanistic role?
    - Use Directed Acyclic Graphs as a tool
- If you're using vague concepts like "Ancestry" or "Population", you're not trying hard enough

2. Appreciate that most use cases involve multiple relevant dimensions of difference

Singling in on one dimension of difference should need special justification

For example, perhaps genetic similarity, language spoken, and geographical location are all mechanistically relevant

AJHG

Volume 109, Issue 12, 1 December 2022, Pages 2110-2125

Review

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ORIGINAL RESEARCH article

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Ancestry: How researchers use it and what they mean by it

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Thank You!

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Perspectives in Biology and Medicine, volume 66, number 2 (spring 2023): 225–248.

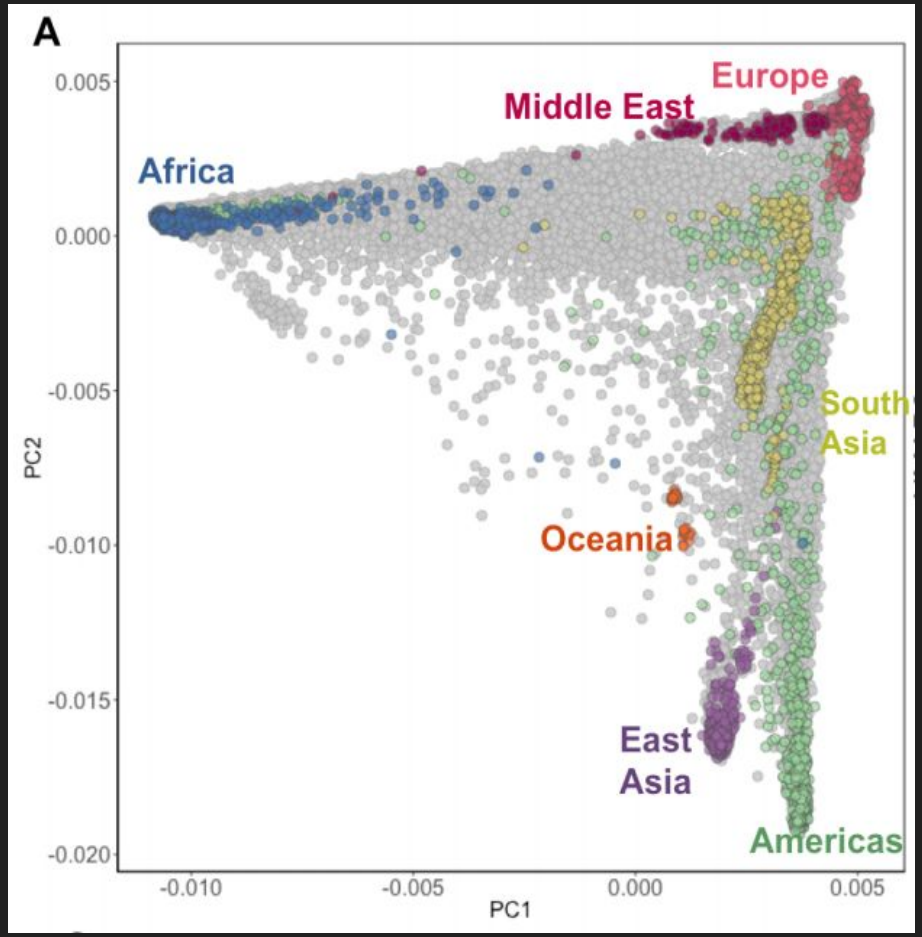
APPENDIX

Theme	N	Sub-themes	n
Awareness of impact on particular communities	75	Investigators should respect study populations.	32
		Awareness of past and present impacts of racism in science and medicine should be encouraged/increased.	28
		Investigators should consult specific communities during the research process.	15
The need for further research and guidelines	57	Guidelines should be developed and regulation tightened for future research involving race, ethnicity, or ancestry.	22
		Further research into important considerations and current pitfalls of research involving race, ethnicity, and/or ancestry should be conducted.	35
The need for transparency	47	Investigators should be transparent about why they are using population categories.	13
		Investigators should be transparent about how any population categories used are defined.	22
		Investigators should make their data and collection methods publicly accessible.	6
		Investigators should fully analyze and explain their findings	6

The use of appropriate statistical methodologies	40	Investigators should not make causal claims based on associations found in their data.	10
		Investigators should adjust how they interpret and report genetic data.	8
		Investigators should be aware of the contribution of factors other than race/ethnicity, such as socioeconomic circumstances or ancestry, to health outcomes.	19
		Investigators should match collected variables to their study question(s).	3
The role of public reactions and public engagement	30	Investigators should be aware of the potential social impact of research involving population categories and sensitively release results of or information about this research to the public.	23
		Investigators and institutions should consult and educate the public.	4
		The scientific community should increase visibility of and education about important considerations for research involving race, ethnicity, and/or ancestry.	3

The need for an appreciation of nuance	27	Those in the scientific or medical field should use and consider race/ethnicity in a more nuanced fashion.	12
		Those in the scientific or medical field should use and consider ancestry/population in a more nuanced fashion.	5
		Those in the scientific or medical field should consider the relationship between race, ethnicity, ancestry, and population in a more nuanced fashion.	10
The need for diverse samples and practitioners	19	Investigators should recruit more diverse cohorts of study participants.	8
		The makeup of and discussions within the medical community should be diversified.	8
		Researchers should ensure that study populations are representative of the investigated population.	3

Appropriate definitions of population categories and contexts for use	83	Certain population categories should not be employed in research.	12
		The scientific/medical community should continue collecting race and/or ethnicity data and investigating race- or ethnicity-based disparities.	9
		Investigators should employ population categories under certain conditions.	32
		Researchers should adopt or avoid certain definitions of population categories.	7
		Investigators should collect ancestry data instead of race or ethnicity.	8
		Race should not be used as a proxy for other variables in research.	9
		Investigators and authors should be sensitive with terminology.	6



Gray: N=31705 participants from BioMe, a diverse biobank in NYC

"BioMe participants can be observed to fall across the spectrum of global diversity, with many participants falling on a cline between various Subcontinental reference panels, suggesting the presence of varying degrees of admixture."

Belbin et al, *Towards a fine-scale population health monitoring system,* BioArxiv

Genetic ancestry is a historical concept, not one of essences