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The Explication of Race in Rheumatology Disparities

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The Challenge of Race

The appropriate use of race in medical research and clinical care is a topic fraught with confusion and misunderstanding. Jonathan Kahn, in his insightful book Race in a Bottle[1], eloquently observes that "…underlying such confusion is an even deeper set of assumptions about the nature of race and more broadly of social science in relation to the natural sciences. These assumptions are grounded in the acceptance of race as a social category that is aligned with a near-simultaneous marginalization of race as 'merely' social and hence not deserving of the same sort of care of consideration devoted to "real" natural phenomena, such as genetics." Kahn further elaborates on the distinct language of race compared to the specialized language of biomedical experts, who have spent years honing specific skills and expertise that are not accessible to the general public. In contrast, race is a concept that everyone encounters and discusses in daily life, making it appear obvious, intuitive, and seemingly simple to understand and discuss without specialized knowledge. However, this apparent simplicity is deceptive. Kahn argues that "in some contexts, this may be true; but not in the biomedical sciences," where the use of race requires great care and expertise. The challenge lies in using race to address and understand racism and disparities without reinforcing stereotypes or incorrect and unfounded biological assumptions. The intersection of race with various biological, social, and environmental factors makes it a powerful but potentially misleading tool if not handled with the necessary knowledge, reflection, and sensitivity. Thus, professionals in the field must navigate these waters with precision and a deep understanding of both the scientific implications and the social ramifications of their work.

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This complexity arises because while race is a social construct with no genetic or biological basis, it has profound implications for health disparities and outcomes. Racial disparities exist across rheumatologic conditions, much of which has been studied in systemic lupus erythematosus (lupus). The exploration of lupus in the early 1950s showed little attention to race; it was assumed that the distribution of lupus cases was proportionate to the population under care[2], with a focus on susceptibility among females with certain physical traits: light hair, fair skin, and "inability to tan."[3] However, contemporary studies reveal stark disparities: individuals from underrepresented groups with lupus experience higher rates of premature mortality, hospitalizations/readmissions, disease flares, and adverse pregnancy outcomes, among others.[4–7]

Race Has No Genetic Basis and Is Conflated with Genetic Ancestry

In the early 1900s, the pioneering sociologist and civil rights activist W.E.B. Du Bois argued against the biological interpretation of race, pointing out that perceived racial differences were actually social and cultural diversities, decrying the arbitrary division of human beings into "white" and "black" categories.[8] The Essentialist concept of race that was popular at that time held that the human species was divided into several mutually exclusive yet tangentially overlapping groups based largely on physical features, such as skin color and facial features. The term "Caucasian" arose from the observations of the anthropologist and physician Johann Blumenbach in the 18th century from his research on the measurement of craniums, leading to his proposal to divide humankind into five varieties, asserting that Caucasians (from the Southern slope of Mount Caucasus in Georgia) displayed "the most beautiful form of the skull."[9]

The Population concept of race treats race as biologically separate, discrete, and exclusive populations that differ genetically from one another, whereby each group is considered to have substantial genetic similarity. This terminology (e.g., population, race, ethnicity) can have different interpretations in different fields and for the public, lacking the accuracy needed in science. It also conflates social and biological concepts, reinforcing faulty assumptions that racial typologies delineate "pure" groups, and supporting the reification of race as a biological construct. Ancestry testing and admixture mapping have also contributed to this molecular reification of racial categories, as both assume the existence of "pure" populations. In ancestry testing, one is statistically estimating genetic similarity to individuals from current geographic communities, or reference groups, labeled as "ancestries." Admixture mapping is an approach used to identify genomic regions associated with traits in recently admixed populations, defined as populations with fewer than 20 generations of mixture between two or more ancestrally distinct populations. However, discussing genes and ancestry in terms of percentages and combinations may inadvertently suggest that population or racial purity is or was a reality, potentially reinforcing the erroneous notion that social constructs of race have a genetic basis. This contrasting juxtaposition can be found in the Lupus in Minorities: Nature Vs. Nurture (LUMINA) study, where the researchers attempted to minimize the possibility of misclassification of race and ethnic groups by requiring all four grandparents to be in the same ethnoracial group and geographic location as the patient for entry into the study.[10] The examined ancestry informative genetic variants in 492 patients (164 who self-identified as Hispanic,

181 as African American, and 147 as White) showed significant variations in admixture proportions, underscoring the substantial genetic diversity within ethnoracial groups. Large studies have since demonstrated that populations defined by self-reported race and ethnicity and genetically inferred ancestry are not analogous.[11]

The biological and cultural variation that exists between groups of modern humans evolved as a result of migration and admixture of populations. Africans have the highest levels of diversity among any living population as well as extensive population substructure due to ancient and modern migration events across sub-Saharan Africa, as well as extensive admixture in the region. The complex dispersal of modern humans out of Africa left a strong signature on the genetic variation of all non-African populations, including lower levels of diversity.[12] Any two peoples' genomes are, on average, ~99.6% identical and ~0.4% different.[13] Genetic and social scientists began calling for an end to the use of race as a variable in genetic research.[14] In 2020, the American Medical Association (AMA) formally adopted policies that recognized race as a social, not biological, construct and suggested that when race is described as a risk factor, it is more likely to be a proxy for influences like structural racism instead of a proxy for genetics.[15]

The Problems with Race-based Medicine

Vyas et al. wrote, "…despite mounting evidence that race is not a reliable proxy for genetic difference, the belief that it is has become embedded, sometimes insidiously, within medical practice."[16] Examples include the Atherosclerotic Cardiovascular Disease Risk Calculator, Spirometry Calculator, Estimated Glomerular Filtration Rate Calculators, and the Vaginal Birth After Cesarian Section Calculator, some of which have removed race-correction factors. In contrast, others remain optional and in use. Rheumatology has not been immune. The myths that giant cell arteritis is rare in non-White populations, Black patients are less likely to undergo knee replacement surgery due to preference, and HLA-B*5801 screening should only be performed for Asian patients have been debunked.[17] The relative lack of efficacy of cyclophosphamide in Black patients with lupus nephritis was largely based on a study that did not describe how race was collected or take into account other confounders.[18] Data from the Aspreva Lupus Management Study is often referenced to support a lower response rate to cyclophosphamide treatment in Black and Hispanic lupus patients compared with White or Asian patients and a higher response rate to mycophenolate mofetil in Black compared to White patients.[19,20] These conclusions were drawn from analyses where statistical significance was found in the "combined Black and other racial group" compared to White patients. The post hoc analysis of the subgroup of Black patients did not show statistical significance. Although belimumab was found to be effective in phase 2 and 3 clinical trials in the general study population, post hoc analyses of efficacy data in patients identified as being of Black African ancestry (only 4-14% of the study population) showed inconsistent results. Consequently, a cautionary statement regarding belimumab use in this population was added to the product label. To alleviate concerns that belimumab may not be safe and effective for patients of Black African ancestry, the Efficacy and Safety of Belimumab in Black Race Patients with SLE (EMBRACE) study was conducted in a post-marketing commitment to the Food and Drug Administration (FDA).[21] Though its findings led to the removal of the cautionary labeling of belimumab use in patients of Black

African ancestry, confusion and concern persisted in the provider and patient communities.[22] Moreover, there was a lack of discussion about why this biological agent would have differential effects by race in the first place.

Race is Socio-Political

The federal government is the largest funder of biomedical research in the U.S. Therefore, how the government defines racial and ethnic categories and mandates their collection and reporting has a profound impact on research and practice. The influence of the winds of socio-political change on these definitions is nowhere better illustrated than by the U.S. Census.[23] Category names often changed from one decade to the next, in a reflection of current politics, science, and public attitudes, changing 18 times over 24 U.S. censuses. It was only in 2000 that one could identify with two separate races. The standards in the U.S. Office of Management and Budget (OMB) have provided a common language to promote uniformity and comparability for data on race and ethnicity for governmental purposes. They are, in the government's own documents, specifically acknowledged to reflect a social definition of race and not an attempt to define race biologically, anthropologically, or genetically.[24] On March 28, 2024, OMB published its most recent set of revisions to the standards for maintaining, collecting, and presenting federal data on race and ethnicity, the first since 1997, that includes using one combined question for race and ethnicity and adding Middle Eastern or North African as a new minimum category.[25] Similarly, the Food and Drug Administration is formulating its own standardized approach for collecting and reporting race and ethnicity data in submissions, including information collected and reported from clinical studies and trials.[26] These data are important for a variety of reasons, including ensuring equitable opportunities to access these research opportunities. The scientific community must, in turn, be careful not to attribute biological responses to race inappropriately.

Moving Forward

We offer a few points for our scientific and clinical communities to consider as we move forward.

It is important to measure race.

Understanding racial disparities in health outcomes helps to identify socioeconomic factors, systemic inequalities, and social determinants of health that may be amenable to intervention and/or policy development and implementation.[27] Race supports cultural recognition and the provision of community-specific resources. Race is a lived experience, including as a proxy for racism and the way that many people identify.

Consider how race is being collected, used, and analyzed.

Self-reporting is the gold standard for identifying race. Ascribing race by another individual based on appearance or other characteristics is fraught with pitfalls. For example, dichotomizing the diverse spectrum of skin color is arbitrary. It is postulated that darker skin pigmentation in those whose ancestors lived in tropical environments protects

against ultraviolet radiation that destroys folate, allowing for improved fetal development.[28] However, skin color cannot distinguish those from tropical countries or regions. Nor can we forget the tremendous variation in skin color throughout the world.[29] Race is not a covariate for which to be arbitrarily controlled nor an afterthought in a limitation section. The use of race as the only proxy for social determinants of health may be appropriate in some instances. However, more granular data should be utilized when available, and researchers should consider and make every effort to adjust for conceptually relevant measures of socioeconomic status or social class when comparing racial and ethnic groups.

Advances in societies and journals need continued support and work.

The AMA and its journal have been leaders in establishing guidance on reporting race and ethnicity.[30] The National Academies of Science, Engineering, and Medicine declared that race, ethnicity, and geographic origin should not be used as proxies for genetic ancestry groups.[31] The American College of Rheumatology crafted a diversity, equity, and inclusion (DEI) mission statement that has been woven into the fabric of the organization, resulting in the formation of a DEI Committee, the creation of a Director of diversity, equity, and inclusion, and DEI considerations as part of the author guidelines across its journals. These efforts must constantly be upheld, refined, and disseminated across our specialty and beyond.

We must foster cross-disciplinary discussion with humility and patience.

Advances in medical research require the breaking down of silos. Yet, there are few opportunities for basic, clinical, and social scientists to openly learn from each other and discuss challenges as they relate to race within rheumatology. Engaging with representative community members and incorporating the perspectives of diverse communities is paramount for addressing race and racism. As rheumatology seeks to better care for diverse individuals, equitable diversification of the rheumatology workforce is also important. Race may be the “third rail” in certain political discussions. However, in the biomedical sciences, we must be able to openly discuss these issues with humility and patience. Adopting an antiracist posture requires being intentional, being critically introspective, and sitting with discomfort.[32] One of the authors (SL), as Co-Chair of the Continuing Assessment Review Evaluation (CARE) Lupus Module in 2015-2016, approved a question in which the rationale for the answer supported the notion that there was a differential response to mycophenolate mofetil and intravenous cyclophosphamide by race and ethnicity in lupus nephritis, one example among many mistakes in retrospect. To err is human, but to forgive is not reserved only for the divine. We must learn from the past to build a better future together.

Race is complex globally.

Race is imbued by different sociopolitical and historical contexts across regions and countries. For example, the U.S. category of “Hispanic” cannot be applied across Latin America. France, Germany, Hungary, and Japan prohibit or restrict the collection of racial data.

Conclusion

Rheumatology stands at a crossroads where the integration of a scientifically rigorous and socially aware understanding of race and ethnicity is crucial. This approach will improve our scientific understanding and lead to better health outcomes by addressing the broader social and environmental factors that affect health disparities.

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