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Challenging the Role of Genetic Ancestry in Explaining Racial/Ethnic Health Disparities

To the Editor:

We read with interest the recent study by Karnes and colleagues (1) that reports a reproducible health advantage of reduced mortality among Hispanic patients with pulmonary arterial hypertension (PAH). They conclude that their findings "reinforce the presence of racial/ethnic disparities in PAH and suggest that these disparities are due in part to genetic differences between race/ethnic groups." More specifically, they claim that Native American (NA) genetic ancestry may provide a potential benefit for PAH survival. However, the authors provide no racially specific genetic data relevant to a PAH pathway. We believe their conclusions overstate the evidence for genetic differences underlying the reported health disparity, as they *1*) rely on inconsistent definitions of race/ethnicity, *2*) use potentially biased estimates of genetic ancestry, and *3*) neglect important confounding factors.

First, we note inconsistencies in definitions of race/ethnicity across analyses and groups. Hispanic ethnicity was defined explicitly as a "combination of genetic, environmental, and sociocultural factors," but only self-identified (or hospital-identified) race/ethnicity was used in all primary analyses. In sensitivity analyses, individuals with genetic admixture also were required to self-identify as Hispanic, a requirement not equally applied to white, NA, or African American patients. A clear and consistent definition of race is key to measuring racial disparities. Using different amounts of rigor for defining groups undermines any conclusions they draw about the disparity and what is driving it.

Second, a primary conclusion of the study was that NA ancestry may contribute a PAH survival benefit. However, NA ancestry was not significantly associated with decreased mortality, given the broad confidence intervals around the estimate (hazard ratio, 0.48; confidence interval, 0.23–1.01; $P = 0.053$), even without adjusting for multiple testing. Furthermore, Asian ancestry was problematically assumed to be NA ancestry, as their estimation method did not have sufficient resolution to distinguish the two. In fact, they concluded an NA ancestry effect without a single NA patient in their reference panels. Furthermore, these conclusions were based on very small minority sample sizes, such that 78% of participants were white, which is reflective of the larger problem of underrepresentation of minorities in most existing genomic studies (2).

Third, confounding factors could alternately explain these associations. The Hispanic patients in their study were on average 10–15 years younger than other groups, which alone could explain their survival advantage. In addition, there are racial differences in disease subtypes such that white and African American individuals tend to have worse prognoses, which would give the appearance of Hispanic individuals having a PAH advantage (3). Finally, the researchers included no sociocultural or environmental data in any analyses other than drug use as a rough proxy for access to medical care. Hispanic patients often demonstrate a health advantage associated with psychosocial resources, such as social support and Hispanic cultural values (4). Without taking into account any sociocultural or environmental influences, a genetically based conclusion cannot be drawn.

In sum, this study's concluding suggestion that "these disparities are due in part to genetic differences between racial/ethnic groups" is not supported by the data provided and could alternatively be explained with unmeasured sociocultural/environmental or other confounding factors. Concluding that genetic differences drive racial health disparities without sufficient data is not a problem unique to this study but reflects a historical legacy of assumptions about the essential nature of biologically distinct "races" dating back to the origins of medicine in the United States (5). A genetic advantage associated with NA ancestry would require evidence of an NA-specific genetic marker located in a PAH-relevant pathway. Karnes and colleagues' conclusion runs the risk of diverting attention from sociocultural or environmental influences that may contribute significantly to mortality rates in PAH. ■

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Reply to Non and Chang

From the Authors:

We read the letter from Drs. Non and Chang with interest and recognize the critical need for discussions around race/ethnicity and ancestry in pulmonary arterial hypertension (PAH), especially because these terms are often conflated in studies of genetic association. Because of the rare nature of the disease, a paucity of PAH studies incorporate sufficient representation of diverse populations. The issue was directly recognized by the *Journal* (1) calling for more research efforts to address health disparities in PAH. In response to these challenges, we assembled five multiinstitutional cohorts, all including Hispanic patients, and attempted to address part of this gap (2). To our knowledge, our primary finding was the first to evaluate and report a reproducible survival benefit in Hispanic patients across clinical settings using *self-reported* race/ethnicity. Drs. Non and Chang primarily raise concerns related to sensitivity analyses within the supplement and accounting for the roles of environmental factors and socioeconomic status (SES). We agree that these factors are critical to consider when studying effects of race/ethnicity, as demonstrated by prior reports from our team (3). However, we maintain that our methods/conclusions already address many of their concerns.

First, the survival advantage in Hispanic patients remained significant after rigorously adjusted analyses, including accounting for age and prostacyclin use. These adjusted findings suggest that the survival benefit is not solely based on younger age. They also directly address published data on prostacyclin that report both its influence on survival (4) as well as its reduced use in Hispanic patients (5). We acknowledged that our findings support the broadly observed Hispanic paradox, recognizing possible roles of SES and genetic factors. In addition, the prevalence of PAH subtypes is different across races/ethnicities (5), which could influence survival outcomes. However, we observed a consistent survival advantage in patients with idiopathic PAH from the PAH Biobank and across broader group 1 PAH populations in our meta-analysis.

Second, we acknowledged that although genetic variability specific to Native American (NA) populations *may* provide a survival advantage to Hispanic patients, our observations *may also* reflect the various SES factors captured by self-report of Hispanic ethnicity. However, registries in PAH, like many diseases, not only lack adequate representation of people of color but also all variables (clinical, genetic, and SES) that can influence survival. Despite this limitation, we respectfully disagree with the claim that genetically based conclusions cannot be derived without accounting for any SES and/or environmental influences. Rather, we believe that the survival advantage in Hispanic patients demands further study of this disparity and its contributing factors, including both genetics and sociocultural factors. Genetic analyses can be especially valuable when presented in synchrony with results related to self-reported race and in the context of possible SES influences.

Third, for consistency in definitions of race/ethnicity, our primary analyses *only* used self-identified race/ethnicity. We acknowledged that although self-reported race/ethnicity may introduce misclassification from a genetic standpoint, it has the potential to capture a host of SES and/or environmental information such as diet, lifestyle choices, and healthcare practices. Our ancillary analyses involved identifying race/ethnicity based on genetics and were performed to assess the robustness of our primary results with self-reported race/ethnicity, observing consistent findings using both approaches. Using only genetically derived ancestry to define Hispanic patients in these supplementary analyses would have been insufficient and unreliable. The mosaic-like ancestry (admixed with genomes of European, African, and NA ancestors) (6), combined with unique SES factors, limits ancestry-based definitions of discrete race/ethnic groups in Hispanic individuals. This limitation was a major driver for our

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