crucial and modifiable risk factors driven by systemic racism in medicine. ■

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Reply to D'Couto and Celi: Racial Physiology: A Dangerous Precedent

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From the Authors:

We thank D'Couto and Celi for their interest in our study (1). In our *post hoc* analysis of the NOSARSCOVID (Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19) trial (2), we attempted to examine if the effect of high-dose inhaled nitric oxide on clinical outcomes varied by self-identified race. We recognize that race is predominantly a social construct encompassing several factors, including geographical origins, cultural practices, social determinants of health, and ancestry (3). On the basis of our prior study, self-identified race has been shown to be a suitable surrogate of genetic ancestry in our geographical region (4). In the field of genomics, genetic ancestry can be ascertained using a set of predetermined genetic markers. Therefore, unlike race, genetic ancestry is a biological parameter that may capture biological differences in responsiveness to therapy. In our *post hoc* analysis, self-identified Black patients were recruited mainly from Birmingham, Alabama, and Boston, Massachusetts. To further explore if self-identified race was a good proxy of genetic ancestry among the patients in the NOSARSCOVID trial, we leveraged nationwide data from the All of Us Research Program. Using ZIP codes, we identified self-identified Black All of Us participants from Birmingham and Boston and examined their genetic ancestry. To assign genetic ancestry, the All of Us Research Program uses a random forest classifier that was trained on samples from the 1000 Genomes project and the Human Genome Diversity Project (5). We found that the median probability of African ancestry among self-identified Black participants from Boston and Birmingham was 99% (IQR: 97%, 100%). Thus, self-identified race was an appropriate

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proxy of genetic ancestry among individuals from the abovementioned areas.

Previous research has well documented variations in biological systems across different racial groups (4, 6–11). These variations are believed to stem from genetic ancestry–related differences in the regulation of biological processes. Studies, including ours, have highlighted racial differences in the regulation of the natriuretic peptide system, which plays a crucial role in cardiometabolic health (4, 6, 7). Specifically, self-identified Black individuals tend to have lower natriuretic peptide concentrations compared with their White counterparts from childhood onward, potentially contributing to their higher prevalence of cardiometabolic diseases (4, 6, 7). Moreover, these differences in natriuretic peptide concentrations are also observed when considering genetic ancestry, with concentrations inversely correlating with the standardized percentage increase in African ancestry among self-identified Black individuals (8). These findings underscore the concordance between racial and ancestry-based disparities in natriuretic peptide concentrations, providing compelling evidence for the existence of racial differences in important physiological systems. Similarly, the vasodilatory response of blood vessels to stimuli has been shown to be blunted among Black individuals compared with White individuals (9–11). Even on examining outcomes, acute respiratory distress syndrome (ARDS) mortality rates are higher among Black individuals compared with White individuals (12). Importantly, the racial differences in ARDS mortality persist even after accounting for social determinants of health (13).

Thus, the social construct of race may capture genetic ancestry-based differences in biological systems. Therapeutic modalities designed to target these differences may yield meaningful improvement in clinical outcomes. For example, AA-HeFT (African-American Heart Failure Trial) was a significant milestone in recognizing the racial differences in therapeutic response (14). The trial, conducted exclusively among self-identified Black patients with heart failure, was terminated early because of a significantly lower rate of mortality in patients treated with NO augmentation therapy compared with the placebo group. This landmark trial led to the recommendation to use NO augmentation therapy among self-identified Black individuals. Therefore, D'Couto and Celi's suggestion to shift focus away from examining biological differences by race may impede the development of such precision medicine approaches that may be instrumental in reducing the mortality among Black patients with ARDS.

Although we agree that the small sample size of our study precludes any strong biological conclusions from being drawn, the hypothesis-generating study draws attention to the need for larger studies to examine the NO system and the effect of NO augmentation among Black individuals with hypoxemic respiratory failure. We recognize the potential for race-based inclusion in medical practices, such as estimating renal function, to worsen health disparities, as noted by D'Couto and Celi. Nonetheless, we advocate for targeted therapies to mitigate racial disparities and drive scientific progress through precision medicine approaches, which may pave the pathway to developing individualized approaches to patient care that may improve clinical outcomes. ■

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