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References

1. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, *et al*.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. *JAMA* 2015;314: 1039–1051.
2. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease: bronchopulmonary dysplasia. *N Engl J Med* 1967;276:357–368.
3. Manuck TA, Levy PT, Gyamfi-Bannerman C, Jobe AH, Blaisdell CJ. Prenatal and perinatal determinants of lung health and disease in early life: a National Heart, Lung, and Blood Institute workshop report. *JAMA Pediatr* 2016;170:e154577.
4. Keller RL, Feng R, DeMauro SB, Ferkol T, Hardie W, Rogers EE, *et al*.; Prematurity and Respiratory Outcomes Program. Bronchopulmonary dysplasia and perinatal characteristics predict 1-year respiratory outcomes in newborns born at extremely low gestational age: a prospective cohort study. *J Pediatr* 2017;187:89–97.e3.
5. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. *Pediatrics* 1988; 82:527–532.
6. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–1729.
7. Gage S, Kan P, Oehlert J, Gould JB, Stevenson DK, Shaw GM, *et al*. Determinants of chronic lung disease severity in the first year of life: a population based study. *Pediatr Pulmonol* 2015;50: 878–888.
8. Poindexter BB, Feng R, Schmidt B, Aschner JL, Ballard RA, Hamvas A, *et al*.; Prematurity and Respiratory Outcomes Program. Comparisons and limitations of current definitions of bronchopulmonary dysplasia for the prematurity and respiratory outcomes program. *Ann Am Thorac Soc* 2015;12:1822–1830.
9. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, *et al*. Bronchopulmonary dysplasia: executive summary of a workshop. *J Pediatr* 2018;197:300–308.
10. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, *et al*. The diagnosis of bronchopulmonary dysplasia in very preterm infants: an evidence-based approach. *Am J Respir Crit Care Med* 2019;200:751–759.
11. Hysinger EB, Friedman NL, Padula MA, Shinohara RT, Zhang H, Panitch HB, *et al*.; Children's Hospitals Neonatal Consortium. Tracheobronchomalacia is associated with increased morbidity in bronchopulmonary dysplasia. *Ann Am Thorac Soc* 2017;14: 1428–1435.
12. Shepherd EG, Clouse BJ, Hasenstab KA, Sitaram S, Malleske DT, Nelin LD, *et al*. Infant pulmonary function testing and phenotypes in severe bronchopulmonary dysplasia. *Pediatrics* 2018;141: e20173350.
13. Mourani PM, Sontag MK, Younoszai A, Miller JI, Kinsella JP, Baker CD, *et al*. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2015;191: 87–95.
14. Wu KY, Jensen EA, White AM, Wang Y, Biko DM, Nilan K, *et al*. Characterization of disease phenotype in very preterm infants with severe bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2020;201:1398–1406.

Deconstructing the Melting Pot in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a disease that is typically fatal within 5–7 years of diagnosis for most subjects and occurs in all ancestral populations (1). Since the initial discovery of BMPR2 (bone morphogenetic protein receptor type 2) mutation as a cause of PAH, countless publications have further expanded the genetics of PAH, including discoveries of other causative genes and the role of common gene variant associations (2–4). Yet, few studies have comprehensively explored how ancestry, race, or ethnicity plays a role in PAH development and response to therapy. The lack of such studies is striking given the intense focus on providing personalized care to patients with PAH. Of course, studies of discrete populations, such as minority groups, are challenging to perform in rare diseases given the small numbers of subjects.

Nearly a decade ago, Gabler and colleagues conducted a pooled analysis of data from placebo-controlled trials of the use of endothelin receptor antagonists in >1,000 participants with PAH, and uncovered variations in response to endothelin receptor antagonists related to sex and self-reported race (5). Race-based comparisons focused on black versus white individuals showed a difference in placebo-adjusted beneficial treatment response, favoring white individuals by considerable effect sizes. However, this difference did not meet statistical significance. Although other racial groups were not explored, the study was an important reminder that variations in treatment response may occur among individuals of different racial and ethnic groups. A few subsequent studies reported the impact of self-reported African ancestry; overall, there appears to be a higher degree of severity and perhaps a reduced treatment response among those who self-report as black (6–10).

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The self-reported data suggesting that black individuals have poorer outcomes are troubling and raise more questions than answers. More broadly, this also highlights our inadequate understanding, even to this date, of the role of racial, ethnic, and ancestral factors in PAH and pulmonary hypertension. As a reminder, in biomedical research, the term "race" refers to an individual's appearance. In contrast, "ethnicity" suggests a communal participation in a group (or groups) of individuals who share specific cultural traits, including traditions, language, social practices, and even geopolitical factors (11). Unfortunately, these categorizations typically rely on an individual participant's self-report or assignment by investigators, both of which are highly prone to error, especially when compared with DNA-based determination (12). Errors may arise from an individual's lack of knowledge about his or her actual background and alignment with an ethnic group that has a genetically admixed background (11). As a result, recent studies found that self-reported race is likely to be incorrect and/or have a higher degree of admixture than would be assumed (13, 14). Self-identified Hispanics in New York City, for example, were shown to be 29% European, 26% African, and 45% Native American by ancestry-informative markers (15).

In this issue of the *Journal*, Karnes and colleagues (pp. 1407–1415) explore the role of race and ethnicity in PAH (16). They determined ancestry in patients with PAH using genetic markers by incorporating information contained in several large U.S. datasets. Self-reported race and ethnicity were combined to form selected groups of non-Hispanic white (NHW), non-Hispanic African American (NHAA), and Hispanic subjects. Reasonably consistent with prior studies, NHWs were 97% European, NHAAs were 82% African (16% European), and Hispanics were 85% European, 36% Native American, and 7% African by genetically determined ancestry. Although the groups were similar by most standard PAH-relevant comparisons, Hispanics were younger, with a higher mean pulmonary artery pressure and pulmonary vascular resistance but lower concurrent use of prostacyclin analogs. Intriguingly, in survival analyses, self-reported Hispanic status in both the PAH Biobank and Allegheny Health Network cohorts was associated with a statistically significantly improved transplant-free survival. It does not appear that survival was modified by genetic ancestry according to the *a priori* level of statistical significance.

To strengthen their study, the authors evaluated a distinct database of patients with PAH in self-reported or hospital-assigned categories. This analysis included data for 8,829 NHWs, 2,628 NHAAs, 1,524 Hispanics, 403 Asians, and 185 Native Americans from the U.S. National Inpatient Sample database. Regression analyses of these data showed that both Hispanic status and Native American status were protective of inpatient mortality versus NHW status. In contrast, NHAA status conferred increased mortality compared with NHW status, consistent with prior concerns about poorer outcomes for African Americans with PAH (5–9).

This study has multiple strengths, including the number of subjects studied, the integration of self-report and genetic identification, and the additional value of an extensive inpatient database. Given the importance of distinguishing race, ethnicity, and ancestry, the ability to assess ancestry-informative markers added a layer of depth and supported the authors' conclusion that Native American ancestry may contribute to Hispanics' protection against deleterious outcomes. The large sample size allowed the authors to examine minority groups that are typically excluded or insufficiently studied in large registries of PAH.

However, this work identifies several possible future lines of investigation that could further clarify these data. The inclusion of several consented PAH cohorts increased the sample size, which was needed, but also introduced phenotypic heterogeneity. For example, the PAH Biobank only included idiopathic and heritable PAH, whereas the Allegheny Health Network, Arizona, and Stanford cohorts included all forms of PAH. The years in which the studies were conducted, the duration of follow-up, the relationship between diagnosis and enrollment, and other factors varied among the cohorts. Furthermore, researchers establishing cohorts derived from tertiary clinical care centers may inadvertently select a certain type of subject (for example, those who are particularly ill), excluding subjects from a given category. It is hoped that a large cohort study that can provide more phenotypic homogeneity, as well as a more in-depth degree of functional (e.g., imaging studies of right ventricular function and changes over time) and multi-"omic" assessments, will emerge to explore race, ethnicity, and ancestry in more detail. Also, although the National Inpatient Sample database is a useful addition to such research, it has significant limitations, including a lack of biospecimens, reliance on accurate identification of PAH from *International Classification of Diseases, Ninth Revision, Clinical Modification* and *International Classification of Diseases, Tenth Revision, Clinical Modification* data, and lack of outpatient data. Finally, identification of differences according to race/ethnicity may reflect lifestyle, options for subspecialty care, or other choices that are irrelevant to genetic susceptibility (17).

Regardless, the current study highlights the need to carefully assess differences between and among groups stratified by self-reporting as well as according to genetic markers in PAH. If the findings are replicated, the next steps would involve careful determinations of why differences in clinical outcomes exist and how they may be corrected. The solutions may be complicated and vary depending on the cause—ethnic and ancestral differences have very different underlying causes and thus would require different approaches for alteration. However, understanding subpopulation and, ultimately, individual genetic compositions will be crucial for the next generation of cohort studies, clinical trials, and therapies for PAH. ■

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References

1. Hoeper MM, Simon R Gibbs J. The changing landscape of pulmonary arterial hypertension and implications for patient care. *Eur Respir Rev* 2014;23:450–457.
2. Deng Z, Morse JH, Slager SL, Cuervo N, Moore KJ, Venetos G, *et al*. Familial primary pulmonary hypertension (gene PPH1) is caused by

mutations in the bone morphogenetic protein receptor-II gene. *Am J Hum Genet* 2000;67:737–744.
3. Lane KB, Machado RD, Pauciulo MW, Thomson JR, Phillips JA III, Loyd JE, *et al*.; International PPH Consortium. Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. *Nat Genet* 2000;26:81–84.
4. Morrell NW, Aldred MA, Chung WK, Elliott CG, Nichols WC, Soubrier F, *et al*. Genetics and genomics of pulmonary arterial hypertension. *Eur Respir J* 2019;53:1801899.
5. Gabler NB, French B, Strom BL, Liu Z, Palevsky HI, Taichman DB, *et al*. Race and sex differences in response to endothelin receptor antagonists for pulmonary arterial hypertension. *Chest* 2012;141:20–26.
6. Frost AE, Badesch DB, Barst RJ, Benza RL, Elliott CG, Farber HW, *et al*. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US contemporary registries. *Chest* 2011;139:128–137.
7. George MG, Schieb LJ, Ayala C, Talwalkar A, Levant S. Pulmonary hypertension surveillance: United States, 2001 to 2010. *Chest* 2014; 146:476–495.
8. Blanco I, Mathai S, Shafiq M, Boyce D, Kolb TM, Chami H, *et al*. Severity of systemic sclerosis-associated pulmonary arterial hypertension in African Americans. *Medicine (Baltimore)* 2014;93:177–185.
9. Parikh KS, Stackhouse KA, Hart SA, Bashore TM, Krasuski RA. Health insurance and racial disparities in pulmonary hypertension outcomes. *Am J Manag Care* 2017;23:474–480.
10. Farha S, Hu B, Comhair S, Zein J, Dweik R, Erzurum SC, *et al*. Mitochondrial haplogroups and risk of pulmonary arterial hypertension. *PLoS One* 2016;11:e0156042.
11. Mersha TB, Abebe T. Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities. *Hum Genomics* 2015;9:1.
12. Bustamante CD, Burchard EG, De la Vega FM. Genomics for the world. *Nature* 2011;475:163–165.
13. Salas A, Carracedo A, Richards M, Macaulay V. Charting the ancestry of African Americans. *Am J Hum Genet* 2005;77:676–680.
14. Shriver MD, Parra EJ, Dios S, Bonilla C, Norton H, Jovel C, *et al*. Skin pigmentation, biogeographical ancestry and admixture mapping. *Hum Genet* 2003;112:387–399.
15. Lee YL, Teitelbaum S, Wolff MS, Wetmur JG, Chen J. Comparing genetic ancestry and self-reported race/ethnicity in a multiethnic population in New York City. *J Genet* 2010;89:417–423.
16. Karnes JH, Wiener HW, Schwantes-An T-H, Natarajan B, Sweatt AJ, Chaturvedi A, *et al*. Genetic admixture and survival in diverse populations with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2020;201:1407–1415.
17. Race, Ethnicity, and Genetics Working Group. The use of racial, ethnic, and ancestral categories in human genetics research. *Am J Hum Genet* 2005;77:519–532.

Clarity with INHindsight: High-Dose Isoniazid for Drug-Resistant Tuberculosis with *inhA* Mutations

Isoniazid has been a cornerstone of tuberculosis treatment and prevention since clinical introduction in the early 1950s and remains a key drug in the standard, first-line regimen. Its utility is threatened by expansion of drug-resistant tuberculosis; isoniazid monoresistance, estimated at 10% globally (although in some regions of the world as many as 27% of *Mycobacterium tuberculosis* strains have isoniazid resistance [1]), is associated with substantially worse treatment outcomes even with rifamycin-containing regimens (2). Multidrug resistance (MDR; resistance to at least isoniazid plus rifampin) requires longer and less-effective therapy, threatening the prospects of the global goal to end tuberculosis in the next decade (3). Although new and repurposed agents have shifted the treatment landscape for drug-resistant tuberculosis, none rival the potent early bactericidal activity (EBA) of isoniazid. The possibility of leveraging isoniazid, a safe and widely accessible antituberculosis drug with few pharmacokinetic interactions, is therefore appealing.

After activation by KatG (catalase-peroxidase), isoniazid-derived radicals bind InhA, a fatty acid synthase, potently inhibiting the ability of *M. tuberculosis* to synthesize mycolic acids (4). This results in rapid killing of replicating bacilli at drug concentrations achieved with standard isoniazid dosing at 4 to 6 mg/kg, even for individuals with "fast acetylator" genotypes (5). Mutations in the *inhA* active site or promoter region, causing reduced target affinity or overexpression, respectively, lead to moderate minimum inhibitory concentration (MIC) elevations (0.25–2 μg/ml) (6) and are responsible for approximately 7% of isoniazid resistance globally (1). Because isoniazid displays dose-dependent EBA (7), higher doses may result in exposures that overcome *inhA*-mediated resistance and translate into efficacy.

This is the postulated mechanism for observed clinical benefit of high-dose isoniazid added to conventional agents in MDR-tuberculosis (8, 9). A randomized controlled trial conducted in India (9) and a retrospective cohort study in Haiti (8) both reported reduced time to culture conversion and improved outcomes with inclusion of isoniazid 16 to 18 mg/kg in MDR-tuberculosis regimens, despite most measured isoniazid MICs exceeding the critical concentration of 0.2 μg/ml. High-dose isoniazid has also been studied as part of successful treatment-shortening regimens for MDR-tuberculosis (10, 11), leading to endorsement for this indication as part of a seven-drug combination regimen by the World Health Organization (12, 13). However, there is major uncertainty about the independent effect of isoniazid on *M. tuberculosis* killing and optimal dosing in the context of INH-resistance mutations, leading the World Health Organization to call for more research in this area (12, 13).

In this issue of the *Journal*, Dooley and colleagues (pp. 1416–1424) report findings from the INHindsight study, a phase IIA dose-ranging trial of isoniazid for patients with pulmonary MDR-tuberculosis and *inhA* mutations (14). Participants were recruited at a single site in South Africa and randomized to receive isoniazid at standard (5 mg/kg) or higher (10 or 15 mg/kg) doses. Another group of participants with drug-susceptible tuberculosis was provided isoniazid

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