Emerging Concepts in Precision Medicine and Cardiovascular Diseases in Racial and Ethnic Minority Populations

George A. Mensah, Cashell Jaquish, Pothur Srinivas, George J. Papanicolaou, Gina S. Wei, Nicole Redmond, Megan C. Roberts, Cheryl Nelson, Larissa Aviles-Santa, Mona Puggal, Melissa C. Green Parker, Mollie A. Minear, Whitney Barfield, Kathleen N. Fenton, Cheryl Anne Boyce, Michael M. Engelgau, Muin J. Khoury

Abstract: Cardiovascular diseases remain the leading cause of mortality and a major contributor to preventable deaths worldwide. The dominant modifiable risk factors and the social and environmental determinants that increase cardiovascular risk are known, and collectively, are as important in racial and ethnic minority populations as they are in majority populations. Their prevention and treatment remain the foundation for cardiovascular health promotion and disease prevention. Genetic and epigenetic factors are increasingly recognized as important contributors to cardiovascular risk and provide an opportunity for advancing precision cardiovascular medicine. In this review, we explore emerging concepts at the interface of precision medicine and cardiovascular disease in racial and ethnic minority populations. Important among these are the lack of racial and ethnic diversity in genomics studies and biorepositories; the resulting misclassification of benign variants as pathogenic in minorities; and the importance of ensuring ancestry-matched controls in variant interpretation. We address the relevance of epigenetics, pharmacogenomics, genetic testing and counseling, and their social and cultural implications. We also examine the potential impact of precision medicine on racial and ethnic disparities. The National Institutes of Health’s All of Us Research Program and the National Heart, Lung, and Blood Institute’s Trans-Omics for Precision Medicine Initiative are presented as examples of research programs at the forefront of precision medicine and diversity to explore research implications in minorities. We conclude with an overview of implementation research challenges in precision medicine and the ethical implications in minority populations. Successful implementation of precision medicine in cardiovascular disease in minority populations will benefit from strategies that directly address diversity and inclusion in genomics research and go beyond race and ethnicity to explore ancestry-matched controls, as well as geographic, cultural, social, and environmental determinants of health. (Circ Res. 2019;125:7-13. DOI: 10.1161/CIRCRESAHA.119.314970.)

Key Words: ancestry ■ bioethics ■ genetics ■ genomics ■ pharmacogenetics ■ precision medicine

Cardiovascular diseases (CVD), principally ischemic heart disease and stroke, constitute the leading cause of mortality worldwide. In 2017, CVD had an estimated global prevalence of 73 million, causing nearly 18 million deaths. One-third of these deaths occurred in persons younger than 70 years old. In the US alone, CVD caused 793,840 deaths in 2017. The dominant modifiable CVD risk factors include hypertension, dyslipidemia, tobacco use, physical inactivity, obesity, and poor nutrition. Together with the social and environmental determinants of health, these risk factors account for over 90% of the population-attributable risk of a first myocardial infarction. Collectively, CVD risk factors are as important in racial and ethnic minority populations as they are in majority populations. Thus, risk factor prevention, treatment, and control remain the foundation for cardiovascular health promotion and disease prevention worldwide.

Increasingly, however, the role of genetics, epigenetics, and heredity in the pathogenesis of CVD is being recognized. This provides an opportunity for advancing precision medicine (prevention and treatment strategies that take individual variability into account) for all populations. This review explores the emerging concepts at the interface of precision medicine and CVD in racial and ethnic minority populations, beginning with the conceptualization of race, ethnicity, and ancestry in precision medicine, and concluding with the social, cultural, and ethical implications for biomedical research.
Race, Ethnicity, and Ancestry
Categories of race and ethnicity are social, political, and cultural constructs that are invaluable in clinical and public health research. However, they are flawed as biological constructs for genomics and precision medicine. Whether self-reported or assigned, racial and ethnic categories are imprecise, and their definitions change over time. Although self-reported race/ethnicity can help group individuals from geographically distant regions, it is less successful in distinguishing persons who have mixed origins. Self-reported race/ethnicity is less reliable for the Hispanic-American population when compared with ancestry-informative genetic markers (Figure 1). Additional evidence of the fine-scale differences in ancestry within and across the United States is provided by Bryc et al (Figures 2 and 3).

A second important concept is that racial/ethnic categories are heavily confounded by socioeconomic status, income, education, neighborhood characteristics, perceived racism, environmental exposures, access to healthcare, and other social determinants of health. Progress in precision medicine will be accelerated when population subgrouping goes beyond racial/ethnic categories to include these factors as well as ancestry information. For example, it is far more informative to describe a person as a 50-year-old, college-educated woman of West-African ancestry employed as a school teacher in New York City than it is to describe her as simply a 50-year-old non-Hispanic black woman.

Diversity and Inclusion in Genomics
Although the importance of diversity in genomics and precision medicine is well recognized, the majority of published studies are from European ancestry populations. As of 2009, 96% of participants in genome-wide association studies were of European ancestry. By 2016, this figure had declined to 80%, primarily because of an increase in the study of East Asian populations. The number of genome-wide association studies involving participants of African or Amerindian ancestry and Hispanic or Latino ethnicity had not substantially increased. This is now changing with the introduction of large-scale genomics studies such as the Trans-Omics for Precision Medicine (TOPMed) program, the Human Health and Heredity in Africa, and Population Architecture using Genomics and Epidemiology.

Cases where benign variants are misclassified as pathogenic because of lack of diversity in control data sets highlight the crucial need for diverse genomic data and biospecimen resources. For example, Manrai et al showed that common, benign variants in black Americans had previously been misclassified in patients undergoing genetic testing for hypertrophic cardiomyopathy. Differences in allele frequencies between groups may lead to misdiagnosis and contribute to health disparities because of the lack of racial and ethnic diversity in control populations.

Genetics, Epigenetics, and Pharmacogenetics
Recent genome-based advances now offer the opportunity to measure individual variability in genes, environment, and lifestyle that constitute an important basis for precision medicine. Next-generation sequencing approaches also allow us to look for genetic patterns or variants, gene expression, and regulatory networks in subpopulations that correlate with disease phenotypes. For example, a recent study shows a greater risk for CVD in blacks harboring certain variants of the LPA gene. Deep coverage whole genome sequencing in 8932 individuals of European and African Ancestry revealed similar heritability and shared variants in SORT1 and KIV2 CNV modifier loci, despite interethnic differences in circulating Lp(a). However, LPA2 intronic variants were identified that had significant but opposing effects in each ancestry group. Additionally, LPA locus variants that were largely private to blacks conferred greater absolute effect on Lp(a) levels when compared with the shared variants. This discovery emphasizes the importance of rarer variants found primarily in specific ancestry groups for the prediction of risk in those groups. It also provides further context for the localization of epistatic effects that could be missed in single ancestry studies or those where minority population inclusion was minimal.

Important Role of Social and Environmental Determinants
The crucial role of social and environmental determinants of health is summed up in the aphorism that health status may be better determined by one’s zip code than genetic code. For racial and ethnic minority populations, nongenetic factors, including social, economic, cultural, behavioral, lifestyle, community, neighborhood, and shared physical environment have important influences on cardiovascular health and related disparities across the lifespan. Current research suggests that these factors may lead to alterations in DNA methylation, accelerated loss of telomeres, and other epigenetic mechanisms that may provide the causal link between social and environmental determinants of health and the development of CVD. For example, the chronic stress of neighborhood deprivation, lack of social cohesion, joblessness, food insecurity, and racial discrimination adversely impact cardiovascular health and may provide the opportunity for hypothesis-driven research in health disparities.

National Heart, Lung, and Blood Institute has identified social and environmental determinants of health as the first of 6 scientific focus areas for implementing its strategic vision in cardiovascular sciences. Social and environmental determinants of health are also prime for hypothesis-driven studies, especially within the context of our cohort studies (Table), the National Institutes of Health’s All of Us Research program, and National Heart, Lung, and Blood Institute’s TOPMed program. For example, if the environmental and behavioral exposures in racial and ethnic minority communities are well characterized, could they be examined in interaction with genomic data to better understand the variation in the epigenome, transcriptome, proteome, and metabolome? What are the biological pathways...
through which these factors interact in different ancestry populations to influence DNA methylation patterns and gene expression, perhaps with a focus on glucose and insulin homeostasis to impact cardiometabolic risk? How does exposure to ambient air pollution interact with genomic variation to influence other epigenetic mechanisms to cause CVD and related disparities?

**All of Us Research Program**

The *All of Us* Research Program is a component of the national Precision Medicine Initiative launched in 2016 with the goal of understanding how genetics, environment, and lifestyle influence the best approaches for preserving health and preventing disease. It will recruit and follow over 1 million volunteers with an emphasis on diversity of people (age,

---

**Figure 1.** Comparison between self-reported ancestry and ancestry proportion estimates (among European, Chinese, African, and Hispanic). Reprinted from Divers et al. Copyright ©2011 (see: http://creativecommons.org/licenses/by/2.0).

**Figure 2.** The distribution of ancestry of self-reported blacks across the United States. Differences, by state, in levels of (A) African ancestry in blacks (blue); (B) Native American ancestry in blacks (orange); and (C) European ancestry of blacks (red). States with fewer than 10 individuals are excluded in gray; (D) The geographic distribution of self-reported blacks with Native American ancestry. The proportion of blacks in each state who have 2% or more Native American ancestry is shown by a shade of green. States with fewer than 20 individuals are excluded in gray. Reprinted from Bryc et al. Copyright ©2015 (see: http://creativecommons.org/licenses/by-nc-nd/3.0/).
race/ethnicity, sexual orientation, and socioeconomic status), geography, health statuses, and data types captured. Importantly, All of Us Research Program’s myriad data types collected on large numbers of participants who are underrepresented in biomedical research offers exciting opportunities to advance precision medicine and mitigate health disparities.

**TOPMed Program**

TOPMed was established by National Heart, Lung, and Blood Institute to characterize the genetic architecture and phenotypic variation of heart, lung, blood, and sleep disorders, with the ultimate aim of improving disease prevention, diagnosis, and treatment. A founding principle was to generate a diverse resource with genomics in multiple non-European ancestry participants. The nearly 145,000 mainly US participants include 40% European, 32% African, 16% Hispanic/Latino, 10% Asian, and 2% in other category. This level of participant diversity will provide much needed molecular biological information for these often under-represented and underserved populations.

**Implementation Research Challenges**

Major contributors to healthcare disparities include unequal access to care, unequal treatment, and often suboptimal quality care delivery. Precision medicine will neither cure these problems nor be immune to their adverse impact on care delivery. However, designing strategies to enable precision medicine interventions to have broad reach, affordability, sustainability, and especially, social and cultural acceptability, and ensure respect in racial and ethnic populations and tribal communities will be crucial. Carefully designed community-engaged implementation research within the complex settings of racial, ethnic, and tribal communities will be invaluable. Additionally, the use of evidence-based tools to guide genetic testing can be useful in fostering precision medicine interventions that are proven effective and ready for the individual- and population-level implementation.

**Cardiovascular Disparities in the Era of Precision Medicine**

Despite remarkable declines in cardiovascular mortality in the United States over the last half-century, racial and ethnic disparities in CVD have remained pervasive. These disparities have been well-documented, and their contributing factors have also been extensively reviewed. As National Institutes of Health leadership recently emphasized, “it is not enough to identify factors that contribute to health disparities: intervention science must be applied in full force to seek solutions.” The question often asked is whether precision medicine will be part of the solution or does it have the potential to exacerbate these disparities?

The emerging consensus suggests that precision medicine may exacerbate disparities unless concerted efforts are made to prioritize diversity in genome-wide association studies and other large-scale genomics data sets and biorepositories. Additionally, differential access to the benefits of precision medicine could exacerbate racial and ethnic disparities in cardiovascular health. The myriad, complex, multilevel factors that contribute to unequal treatment are all plausible in the era of precision medicine and could also contribute to cardiovascular disparities. The challenge is to...
embrace these complexities and develop and test interventions that lead to equitable access to the benefits of precision medicine.32

The good news is that lessons from TOPMed, population architecture using genomics and epidemiology, and Human Health and Heredity in Africa suggest that diversity and inclusion in genomics studies are feasible. When appropriately informed, racial and ethnic minority populations are willing to participate in genetic studies.33 Studies with large numbers of racial and ethnic minority populations have already yielded important information to advance precision medicine. Examples include findings in sickle cell trait,34 APOL1,35 and lipid mutations.36 These findings provide new information for a more personalized evaluation and prevention of chronic renal and atherosclerotic CVD in persons who carry the related trait, risk alleles, or mutations, as part of the effort to advance precision medicine.

Other important considerations include recognition that racial and ethnic populations are not monolithic. Strategies to enrich participant diversity must be mindful of the cultural, linguistic, geographic, and genetic diversity, especially in Asian American and Hispanic populations. Gaining ethnic, tribal, or community trust is also crucial for full and active participation in genetic studies as well as in the acceptance of precision medicine interventions.

**Ethical Implications**

Rapidly emerging areas of biomedical research always pose a variety of ethical issues, but particularly when research involves vulnerable populations, including underserved racial and ethnic minorities. The historical legacy of the Tuskegee study of untreated syphilis and other unethical human experimentation have generated mistrust.37 Other important considerations include issues of cultural disrespect, discrimination, and stigmatization. For example, to make treatment more precise, the use of genetic and epigenetic data requires stratification of patients into groups and subgroups.38 Inherent in this division is the risk of stigmatization and discrimination at individual, community, and population levels.39 Meanwhile, identification of a genetic reason for poor health in a given population could create a disincentive to address social and economic factors that contribute (sometimes substantially) to disease. Before widespread implementation of genetic testing beyond the research setting, careful analysis is needed to assure that this is the best use of resources to improve population health40 and that appropriate, culturally tailored genetic counseling will be available, affordable, and acceptable to inform action.41 Finally, we cannot ignore the potential adverse social and psychological effects of challenging underlying beliefs about self-identity. These ethical issues should not be seen as obstacles that prevent doing research, but rather as questions that help ensure that the use of precision medicine is implemented in a way that benefits all concerned.

**Conclusions**

Increasingly, the genetic contributions to health and disease are being leveraged to advance clinical management of CVD as part of the precision medicine endeavor. It is unclear whether these advances will ameliorate or exacerbate current CVD disparities. The emerging consensus suggests that the lack of diversity in genomics studies risk exacerbating disparities. Strategies that directly address diversity and inclusion and go beyond just race and ethnicity to explore ancestry-matched
controls, as well as cultural, social, and environmental determinants, are crucially needed. Early successes of TOPMed and the National Institutes of Health’s All of Us Research Program are reassuring. There is also an emerging consensus that precision medicine will not be immune to the challenges of unequal healthcare access and care delivery challenges. Designing interventions for a broad reach, affordability, sustainability, and cultural acceptability in racial and ethnic minority populations and tribal communities will also be crucial.

Acknowledgments

We thank our colleagues, Dr David Goff, Jr and Dr Nakela Cook, who provided constructive comments on an earlier version of the article. The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the United States Department of Health and Human Services.

Disclosures

None.

References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392:1736–1788. doi: 10.1016/S0140-6736(18)32203-7
2. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392:1789–1858. doi: 10.1016/S0140-6736(18)32279-7
3. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2015. NCHS Data Brief. 2018;328:1–8.
4. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937–952. doi: 10.1016/S0140-6736(04)67640-2
5. Lloyd-Jones DM, Hong Y, Labarthe D, et al; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association’s strategic Impact Goal through 2020 and beyond. Circulation. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
6. Kathiresan S, Srivastava D. Genetics of human cardiovascular disease. Cell. 2012;148:1242–1257. doi: 10.1016/j.cell.2012.03.001
7. Collins FS, Varma H. A new initiative on precision medicine. N Engl J Med. 2015;372:793–795. doi: 10.1056/NEJMp1500523
8. Burchard EG, Ziv E, Coyle N, Gomez SL, Tang H, Karter AJ, Mountain JL, LaVeist TA. Disentangling race and socioeconomic status: a key to understanding health inequalities. J Urban Health. 2005;82:i226–i34. doi: 10.1093/jurban/jjt091
9. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature. 2016;538:161–164. doi: 10.1038/sreach1616
10. National Heart, Lung, and Blood Institute. Trans-Omics for Precision Medicine (TOPMed) Program. NHLBI. 2016. https://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed. Accessed May 31, 2019.
11. Human Heredity and health in Africa. H3Africa Vision. https://h3africa.org/index.php/about/vision/. Accessed December 8, 2018.
12. Matis C, Ambie JL, Byuses S, et al; PAGE Study. The Next PAGE in understanding complex traits: design for the analysis of Population Architecture Using Genetics and Epidemiology (PAGE) Study. Am J Epidemiol. 2011;174:849–859. doi: 10.1093/aje/kwr160
13. Williams DR. Race/ethnicity and socioeconomic status: measurement and methodological issues. Int J Health Serv. 1996;26:483–505. doi: 10.2190/UQFT-7B7Y-HQ15-JT14
14. 10.1038/sreach1616
15. 10.1161/CIRCRESAHA.114.302347
36. Crosby J, Peloso GM, Auer PL, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014;371:22–31.

37. White RM. Misinformation and misbeliefs in the Tuskegee Study of Untreated Syphilis fuel mistrust in the healthcare system. *J Natl Med Assoc*. 2005;97:1566–1573.

38. Batten JN. How stratification unites ethical issues in precision health. *AMA J Ethics*. 2018;20:E798–E803.

39. Clayton EW. Ethical, legal, and social implications of genomic medicine. *N Engl J Med*. 2003;349:562–569. doi: 10.1056/NEJMra012577

40. Chowkwanyun M, Bayer R, Galea S. “Precision” public health - between novelty and hype. *N Engl J Med*. 2018;379:1398–1400. doi: 10.1056/NEJMp1806634

41. Halbert CH, Harrison BW. Genetic counseling among minority populations in the era of precision medicine. *Am J Med Genet C Semin Med Genet*. 2018;178:68–74. doi: 10.1002/ajmg.c.31604