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Equity in Genomics: A Brief Report on Cardiovascular Health Disparities in African American Adults

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Abstract

Background: African Americans are more likely to die from cardiovascular disease (CVD) than all other populations in the U.S. Although technological advances have supported rapid growth in applying genetics/genomics to address CVD, most research has been conducted among European Americans. The lack of African American representation in genomic samples has limited progress in equitably applying precision medicine tools, which will widen CVD disparities if not remedied.

Purpose: This report summarizes the genetic/genomic advances that inform precision health and the implications for CV disparities in African American adults. We provide nurse scientists recommendations for becoming leaders in developing precision health tools that promote population health equity.

Conclusions: Genomics will continue to drive advances in CVD prevention and management, and equitable progress is imperative. Nursing should leverage the public's trust and its widespread presence in clinical and community settings to prevent the worsening of CVD disparities among African-Americans.

Cardiovascular disease (CVD) is the leading cause of death in the United States (U.S.) and African American adults are disproportionately affected.[1] The overall prevalence of hypertension in the U.S. is 29%, but the prevalence is 44% in African-American women and 42% in African-American men, respectively.[1] Mortality rates from sudden cardiac death in Black men are twice that of their White counterparts (175 per 100,000, vs. 84 per 100,000,

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respectively).[1] Further, the Black–White racial gap in CVD mortality, including sudden cardiac death, hypertension, and ischemic heart disease, is estimated to be responsible for over 5 million years of life lost between 1999 and 2010.[2] Although the sentinel report "Unequal Treatment" moved racial and ethnic health disparities to the forefront of the nation's clinical, research, and policy agendas, pervasive disparities persist in the CV health of people of African descent living in the U. S.[1,2]

While genomics/genetics have the potential to improve the prevention and management of CVD, the bulk of this research has occurred in people of European descent. Since completion of the mapping of the human genome in 2003, researchers have applied genetics/genomics knowledge to CVD prevention by identifying how changes in the genome or the expression of the genome may attenuate or increase CV risk.[3–6] Increasingly genetics and genomics are being used to anticipate response to medications (e.g., antihypertensives and anticoagulants)[7,8] and to explore how behaviors and social experiences interact with biological factors to influence health.[9–12] The rapid advancements in genomics research have been one of several areas of precision medicine or personalized health, which consider differences in people's genes, environments, and lifestyles to develop treatment and prevention strategies based on the unique constellation of these factors in different individuals. However, because most genetics and genomics research has been conducted in homogenous groups of European descent, much of this knowledge is not applicable to African Americans. Consequently, the "promise" of precision health cannot be realized universally, and may in fact perpetuate already critical health inequities in CV health for African Americans.

In this report, we present a concise, narrative description of genetic/genomic advances that are informing precision health, and the implications for addressing CV disparities in African Americans. We provide important contextual background by reviewing the pertinent history, accomplishments, and challenges in CV genetics/genomics on reducing CV health disparities in African-Americans. We also present examples of how results of genomic analyses may differ by ancestry and the research opportunities that could have an impact on reducing inequities and informing future nursing practice.

"Race" in genetics.

Genetics/genomics in CVD disparities must be understood within the social construct of race. Despite having no biological basis, hierarchical categories based on skin color have been used to define "race,"[13,14] and historically the construct of race has been employed to understand population differences in health outcomes. Thus, there are concerns that genetics/genomics research may be misunderstood as legitimizing race, may risk the idea of "genetic determinism," and/or may exacerbate stereotypes of people of color. Science demonstrates, however, that between any two humans there is more shared genomic material than different genetic material,[13] yet small differences in the genome can have significant implications for health and wellness. Population stratification, or the presence of systematic differences in the genome due to *ancestry*, is a common reason for differences in the genome.[8] Ancestry refers to the geographical origin of one's ancestors, and is an entirely different concept than the social construct of race.[13,14]

Genomics and CV health inequities: Past

An historical perspective provides context for how inequities in CVD and genomics research have emerged and enhances understanding of why representation of individuals from different ancestries in genomics research is equally important to social justice and scientific advancement. A brief recounting of CV discovery over the last two decades provides concrete examples of how advances in genomics may inadvertently exacerbate CV health inequities. In the mid 2000s, genome wide association studies (GWAS) using innovative technology that rapidly scanned entire genomes accelerated the pace of genetic/genomic discovery for complex diseases like CVD.[5,6] In 2007, the first genome risk variants associated with coronary artery disease were identified on chromosome 9p21region by two independent teams of investigators, both using research samples of European ancestry.[3,4] The risk variants are associated with increased atherosclerotic burden in individuals of European ancestry, but are not associated with atherosclerosis in people of African ancestry.[15,16] In 2014, Ni and Zhang[17] hypothesized that the reduced frequency of the risk allele in people of African descent has not been established, because it would require larger sample sizes than currently available to detect a potential relationship. The association with CVD could be a type 2 error, because of inadequate representation of racial and ethnic diversity in genomics research, or conversely, could be due to population stratification.

Research on the genetic architecture of coronary artery disease suggests that changes in a nucleotide base pair, called a single nucleotide polymorphism (SNP), that are associated with CVD are population-specific. Genetic variants at any single locus may have different effects on disease outcomes based on ancestry. With the significant disparity in hypertension prevalence in African-Americans, and the cadre of diseases associated with blood pressure, significant research has focused on unraveling the genetics of blood pressure. One of the first GWAS in a sample of African-Americans aimed to replicate the findings from the first ever GWAS of blood pressure completed in 2007.[18] Investigators tested the six SNPs that were closest to statistical significance in the original study in a multi-ethnic sample of 11,000 U.S. residents.[18] Of the six polymorphisms tested, only one SNP, rs1937506, was significantly associated with blood pressure. However, the effect of the single base pair switch differed in three ethnic groups. In individuals of European descent, this change resulted in an almost 25mm Hg *decrease* in blood pressure. In individuals of Hispanic heritage, the same change *elevated* blood pressure by almost 25mm Hg. There was *no effect* on blood pressure in participants of African ancestry.[18] Similar findings were reported from a recent meta-analysis of subclinical CVD from eight studies, with a total sample size of 5,800 African-Americans.[19] None of the 67 SNPs previously shown to be associated with outcomes in people of European descent met genome wide significance for coronary artery calcium (calcified plaque). Further, two of the three SNPs (in *SOX9* and *PRKCA)* trended toward significance, but with the opposite effect of what was seen in a European American sample.[19] The authors noted that small effects could possibly be detected in a larger sample, however at the time, they had already included every available data point for coronary artery calcium. These studies clearly demonstrate how the lack of diversity in existing genomics samples may impede progress in risk identification, tailored interventions, and pharmaceutical therapies, all of which are components of current and future precision health.

Genomics and health inequities: Misconceptions

CVDs are complex, with factors like health behaviors, social influences, and genetic risk all contributing individually and cumulatively. Genetic variation is one of many factors that contribute to multifactorial diseases like CVD. Thus, changes in the genome are not deterministic, but rather, gene expression is modified by the environment, health behaviors, and other biological factors. For example, the adverse social experience of discrimination can interact with genetic risk variants to raise blood pressure through various pathways such as reducing typical nighttime reductions in blood pressure.[9,10] Tobacco use is a health behavior that raises CVD risk and may interact with genetic risk variants. In a sample of almost 1100 African American females, Taylor and colleagues identified two SNPs on chromosomes 14 and 17 that did not have a direct effect on blood pressure, but interacted with cigarette use to raise systolic blood pressure.[11] Likewise, lifestyle factors like physical activity can attenuate harm from genetic risk.[12] Integrating multifactorial contributors to CV health is important to: (1) understand how CVD inequities have unfolded; (2) determine future research needs; and (3) establish best practices for applying genomics/genetics information to prevention and treatment strategies in the context of other social influences on health.

Genomics and health inequities: Representation matters

The geographic representation in genomics research has increased since 2007, but representation from people of African and Latin American ancestry lags.[8,20] In 2009, the proportion of people in GWAS of European descent was 96%. While that percentage is now approximately 80%, much of the increase in diversity is due to the increased inclusion of Asian populations, up to 11% (Figure 1), with participants of African ancestry making up less than 3% of GWAS.[8] Because of poor representation, African-Americans are more likely to be given false results from genetic tests[20] or to not benefit from genomics-enhanced risk assessment and prescribing algorithms.[8] As such, they do not receive the highest quality or technologically advanced care available, and this exacerbates already established disparities in CVD outcomes.

Genomics and CV health disparities: Nursing implications

Distributive justice.—Advocating for equitable access to the benefits of advances in genomics research is a principle of distributive justice.[21] One way that nursing can contribute to distributive justice is through patient education. As a community-facing profession, nursing can leverage the nation's established trust in nurses to engage African American participants in genomics/genetics research, including providing information about the risks, benefits, capabilities, and limitations of genetics/genomics research. Studies show that racial and ethnic minority populations are concerned about the health of their communities and are more willing to participate in genetic studies when they are well informed, preferably in close collaboration with the research team.[22] Successful participation of minoritized populations, like African Americans, in genetics research requires multiple methods of recruitment that are thoughtful, intentional, and tailored.[23] Taylor, a nurse scientist, employed innovative recruitment methods using historically Black sororities, participant resource pools, and churches to successfully recruit 42

African American generational triads (grandmothers, mothers, and granddaughters) into a hypertension genetics study.[23] The challenges of recruiting underrepresented minorities into genetics/genomics research must be overcome, because ultimately, oversampling of these population subgroups will be needed to move toward distributive justice.[21]

In 2018 the leadership committee of the American Heart Association Council on CV and Stroke Nursing identified precision CV nursing care as a priority area for future research.[24] The council's leaders encouraged nurse researchers to incorporate genomics and epigenomic measures into their research as a way to personalize interventions for disease prevention and health care delivery for different populations. More research is needed to examine how genetic variation interacts with health behaviors, and the social and physical environment to contribute to susceptibility to CVD. Also, nurse researchers can investigate innovative, ethical approaches for recruiting and consenting African American individuals and other minoritized ethnic groups in the U.S. into genomics studies. The mistrust of racial and ethnic minority communities towards researchers stems from a history of structural and governmental practices that have disregarded the best interest and autonomy of the individual.[25,26,27] A recent study of African-American nurses discussing challenges related to seeking and utilizing genomics information identified opt-out consent forms, which assume consent unless participants actively decline, as a potential trust degrading practice.[25] Other research suggests that racial and ethnic minorities prefer opt-in consent,[26] although this is not a consistent finding.[27] While opt-out may yield more participants, there may be longer term ethical costs and repercussions. There is an opportunity for nurse ethicists and researchers to investigate best practices for consenting African-American adults for CV health studies involving genomics and the potential to develop innovative trust-building practices.

Nursing informatics.—Embracing communication technology is another strategy that nursing can use to promote genomic health equity. Clinical nurses can partner with nurse informaticians to design tools for the electronic health record to promote timely and equitable translation of genomics knowledge into practice. Recent policy recommendations from the American Academy of Nursing advocate for improving the health information technology infrastructure to advance equitable precision health implementation.[28,29] One suggestion is to include a three-generation family history in the electronic record, which could be used to identify individuals who may be at risk for a genetically linked disease.[28] For example, long QT syndrome is an example of an inherited cardiac disease responsible for sudden cardiac death, and it has a genetic cause in at least 75% of individuals.[30] Having nurses who are trained to conduct a thorough, comprehensive family history,[28] and implementing clinical decision support to trigger when a referral is indicated could identify patients at risk who might otherwise be missed.

Incorporating nurse navigators that assist with care coordination of genetic counseling referrals, respond to patient's concerns and misconceptions about genetics testing, facilitate discussions about genomics and precision health clinical trials, and identify potential barriers related to mistrust is an important area of future CV research.[31] Nursing leaders participating in a recent roundtable on genomics and precision health identified that using nurse navigators have successfully addressed some health disparities in oncology.[29] Once

patients receive a genetic counseling referral, having culturally sensitive nurse navigators who can assist in brokering the process from referral generated to appointment completed could yield similar successes for CVD. Nurse researchers should investigate clinical outcomes, best practices, and cost-effectiveness of such interventions, as well as training specific needs for precision health nurse navigators. Nurse scientists and DNP prepared colleagues could partner together on many of these research initiatives such as study design, implementation in the clinical setting, and translation of key findings into nursing practice.

Telehealth.—Telenursing has been used to extend care to communities that may be missed, such as rural locations, and as communications technology advances, it can be leveraged to advance equitable dissemination of genomic-based healthcare. Advanced practice nurses are already providing genetic evaluation and counseling using telehealth technology.[32] While this technology has been most widely used in oncology and obstetric care, there are potential applications for CV health care. Registered and advanced practice nurses could use telehealth technology to provide genetics-informed guidance on titration of medications (e.g. Warfarin), health education, and initiation of anti-hypertensive treatment. Removing barriers to care by bringing genomics-based healthcare to patients in the community could help level the playing field.

Telehealth has been accelerated to the forefront of primary and specialty care with COVID-19, and, while the infrastructure and pay systems need further refining, telehealth is likely to become a permanent feature in healthcare. Nursing researchers can prioritize intervention research that leverages telehealth to bring genomics informed CV care, health education, and medication management into reach for African Americans who may have limited healthcare access. To achieve this goal, the negative effects of structural racism on health care and health outcomes will need to be investigated in this context. Critical areas for research will be identifying and addressing manifestations of implicit bias in video and phone appointments, as well as establishing strategies for increasing patient trust in a provider they have not previously met in person.

Genomics and CV Health Disparities: Looking ahead

Some efforts at improving representation of diversity in genetic research are underway. Recognizing the need for larger sample sizes to detect significant associations, both private and public research consortia have formed to pool data from multi-ethnic research studies to propel CV genomics research forward. The *All of Us* research program was launched as part of the Precision Medicine Initiative and aims to enroll a million participants who are representative of the broad ancestral backgrounds of people living in the U.S. Enrollment commenced in May of 2018, and as of July 2019, 175,000 individuals had been enrolled with more than 75% coming from historically underrepresented communities.[33] Nurse scientists are also increasing the representation of diverse ancestries in genetics/genomics research. In the Intergenerational Impact of Genetic and Psychological Factors on Blood Pressure (InterGEN) Study, researchers are exploring the transgenerational transmission of changes in genome expression related to environmental experiences and patterns of behavior through study designs focused on African American families versus only individuals.[34] The 2011 NHGRI strategic plan included a broad focus on increasing the diversity in research

cohorts, workforce, and education in community settings, and the pending release of the next NHGRI strategic plan in 2020 will hopefully continue this focus. With so many rapid advances in technologies, like next-generation sequencing, it is an exciting, albeit precarious, time in genomics science, as precision health goals are becoming reality for many, but not all.

The profession of nursing is uniquely positioned to be influential in incorporating genomics and genetics due to nursing's presence across the care continuum. Nurses have earned the most respected profession year after year,[35] because we are the ones who sit with patients and decipher complex diagnoses, clinical data, and test results into digestible chunks of information. To maintain that trust and earned respect and to continue to lead as researchers, practitioners and educators in the genomic era, nurse researchers will need to invest in studying how nursing can integrate genomics into its research profile, and be empowered to lead innovative application of precision health tools to improve CVD disparities among African Americans. Additionally, nurses have the responsibility to ensure that other healthcare leaders know they have this expertise so that it is appropriately leveraged within their institutions. Nurses are key in translating discoveries from genomics research into improvements in human and population health. Disseminating results to multiple stakeholders, including research participants and the communities they represent, is critical to ensuring that research data are used ethically and equitably and promote trust and transparency in the genomics/genetics research enterprise.

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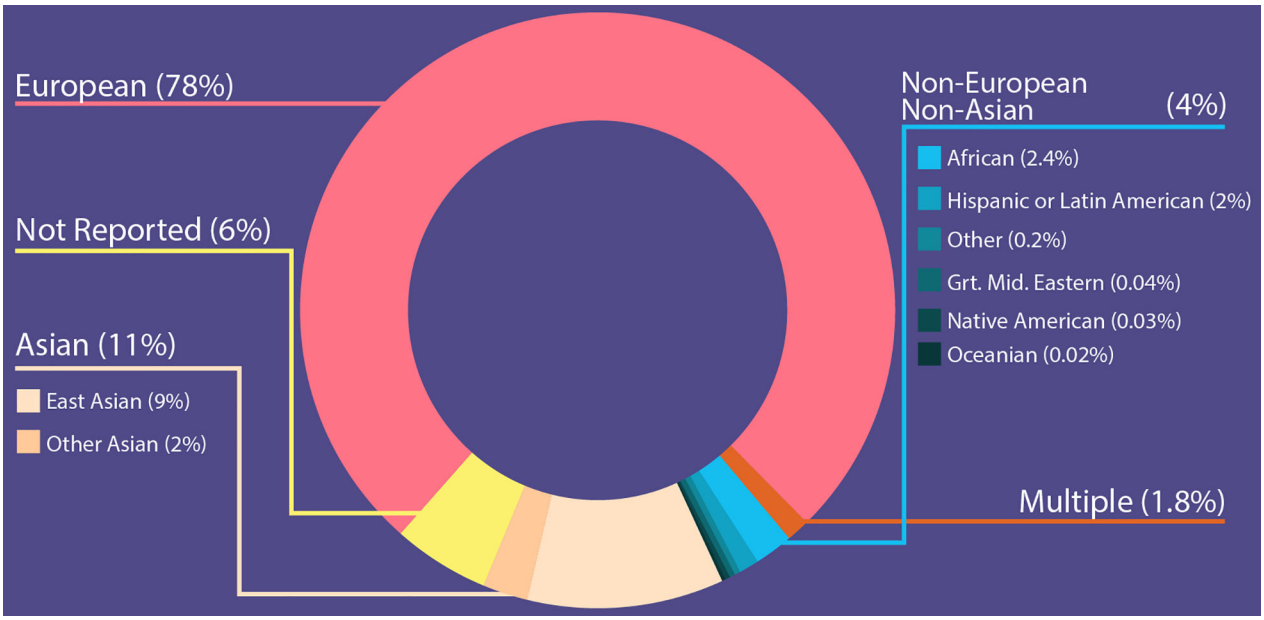

Figure 1.

Racial and ethnic diversity of individuals in the NHGRI GWAS catalog.

N=110, 291,046, Ancestry labels listed as provided by the GWAS catalog

NHGRI = National Human Genome Research Institute, GWAS = Genome Wide Association Study; Data available at: https://www.ebi.ac.uk/gwas/ancestry, Last accessed 9/28/2019.