2021 FFG ESSAY CONTEST WINNERS

Essay Question: There are long standing racial disparities in health care in the United States; how do you see these relating to the fields of genetics and genomics and what is a possible solution to address these issues?

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1ST PLACE ESSAY - Aseel Rawashdeh, Texas

As Todd climbs out of bed one morning, a throbbing pain takes over his inflamed ankles. After several weeks of experiencing this recurrent pain, Todd decides it's time to pay the doctor a visit. A short time after he arrives, he discovers that he may have bursitis. Without a second thought, the doctor sends samples of Todd's joint tissue to a lab for a biopsy and genetic testing. Less than an hour later, Todd is informed that his results qualify him for a new and specific therapeutic. Just three days later, his pain and inflammation are cured.

But what if you are not a white American like Todd? Chances are, because the genomes of people like you haven't been sequenced and studied extensively, no particular treatments are available that target your specific genetic profile. Instead, you're prescribed standard painkillers: the same ones that make you nauseous and give you constipation. Worst of all, your ankles still hurt.

Although this future scenario is hypothetical, it reveals both the promise and challenges of precision medicine. This novel medical model, as opposed to the current one 'size-fits' all model, involves the personalization of healthcare by integrating patient genetics into diagnostic and treatment practices [1]. While researchers are developing innovative technology to meet these demands, there is still an alarming lack of diversity in current genetic databases. As of 2019, almost 80% of the data in genome-wide association studies (GWAS) comes from individuals with European ancestry, despite this group only making up 16% of the global population [2, 3]. The remaining 20% is composed primarily (>14%) of data from individuals of Asian Ancestry. This imbalance of available data is already leading to immense health disparities while also hampering progress for everyone in the field of genomics.

Before discussing the implications of genetic underrepresentation, it's necessary to examine the factors that perpetuate this inequality. Since the Human Genome Project's conclusion in 2003, sequencing technology has become faster and cheaper, leading to an enormous increase in available genomic data. But, the vast majority of this data is from people with European ancestry. This is particularly problematic when we examine the 'reference genome' or the standard genomic sequence that is 'representative of the human species' [4]. A 2018 study conducted by researchers at Johns Hopkins revealed that over 10% of

the DNA of individuals of African descent is not represented in the reference human genome [5]. This has led to the ‘preferred cohort’ effect, where the genomic data of European ancestry cohorts is the most well-characterized, so they’re repeatedly utilized in various research projects [6]. This snowball-like effect magnifies genetic disparities in medical research.

Missing information about the genomes of people of color is already proving to have adverse effects on their health. Researchers are discovering that the etiology of some diseases can be linked to population-specific mutations. For example, the underdiagnosis of cystic fibrosis (CF) in African-descent individuals is due to distinct pathogenesis compared to individuals of European descent. The most frequent CF-causative allele in European-ancestry is a deletion mutation called deltaF508 on the CFTR gene, accounting for CF in greater than 70% of patients [7]. However, deltaF508 causes less than one-third of CF cases in people with African ancestry [7]. This is because a different mutation called 3120+1G->A (a splicing mutation) contributes to almost 65% of CF cases in people with South African ancestry [8]. In another instance, patients of African ancestry were incorrectly diagnosed with a high risk of hypertrophic cardiomyopathy based on pathogenic genetic markers exclusively identified and studied in white populations [9]. Despite these variants' benign nature in some African Americans, the misdiagnosed patients were advised to implement intrusive lifestyle modifications (i.e., stopping sports) and suffered economic costs from preventative treatments (i.e., implantation of a cardioverter-defibrillator). Researchers agree that including diverse cohorts in genetic studies would have likely prevented this. Cases like these demonstrate how understanding and testing for specific pathogenic variants in underrepresented populations is crucial for adequate diagnoses and prophylactic clinical interventions.

The exclusion of ethnically diverse populations in genetic research also impedes crucial discoveries that can benefit everyone. For instance, studying nonsense mutations in a gene called PCSK9 in people of African descent has led to the important discovery of the gene’s role in regulating LDL levels [10]. This knowledge has translated into the development of a new drug that targets loss-of-function mutations in PCSK9, which lowers LDL cholesterol in the blood and subsequently decreases the risk of heart disease, obesity, and stroke [11]. Analyzing these genetic variations responsible for the resilience inherent to certain populations or geographical regions can help advance the knowledge of important diseases.

Despite clear patterns indicating that including genetic diversity in research has far-reaching advantages, a majority of studies still occur in populations of European descent and therefore have limited utility across other racial and ethnic groups. To challenge this bias, reform needs to start from the top. In other words, the current underrepresentation of scientists from a multiplicity of ethnic backgrounds prevents the integration of diverse perspectives, hypotheses, and priorities integral to designing more representative protocols. Researchers of color may also help overcome barriers associated with participant recruitment, namely, the justified lack of trust from communities of color when it comes to medical research due to repeated ethics violations. Giving researchers of color authority over important decisions can aid in the development of culturally sensitive recruitment strategies specific to each community. Additionally, another problem with current approaches is that they often are limited to US residents, which excludes individuals from other regions. This is significant because varied environments select significant genetic variations. The governments of non-western countries should be encouraged and provided aid to establish the local infrastructure and expertise necessary to collect population-specific genomic data to establish a reference genome more relevant to those populations. In the end, tackling the genetics diversity problem will require patience, dedication, and international collaboration, but it’s necessary if precision medicine is going to revolutionize healthcare for everyone.

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2ND PLACE ESSAY - Raeva Hina Pandey, California

Genomics and genetics play a major role in understanding the root causes of diseases stemming from a single gene or multiple genes, leading to early and correct diagnoses as well as targeted treatments (1). However, 80% of all genomic studies have been carried out on individuals with European ancestry. Given the genetic diversity of humans, there are major hurdles in using this knowledge base to help people of non-European origins (2).

Racial disparities are not only prevalent in genomic and genetic research but also overall in a broader front, such as in the public health sector of the United States. The onset of the COVID-19 pandemic has brought the discussion about racial disparities in healthcare to the forefront, especially since this pandemic has disproportionately harmed Black, Asian, and Minority Ethnic communities (3). Racial disparities can only be addressed with deliberate efforts to support diversity and equity in the fields of genetics and genomics.

A predominant focus on individuals of European descent in research indicates that health care and disease disparities may increase rather than decrease. Such Euro-centric research risks missing crucial, racial population-specific genetic variants uncommon or not found in European populations. Minority populations in the United States face a higher chronic disease burden. Unfortunately, though, the lack of genetic and genomic representation for these disproportionately suffering minority populations means that they have less access to health care serving their genetic needs (4). Clearly, research centered on individuals mainly of European descent offers an incomplete picture of genomic and genetic findings. In many cases, such research may not serve the health care needs of other racial groups.

Racial disparities are also pervasive in the American health care system. In clinical decision-making, health care providers' use of race is one problem tied to treatment disparities. For example, providers use race as a proxy for disease risk and genetic variation assessment. From a clinical perspective, some argue that race is potentially a good proxy for disease risk and biogeographic ancestry assessment, particularly when thinking about recommendations for disease treatment or screening. Moreover, using race as a proxy in health care addresses race-specific disparities. However, even as genomics, genetics, and precision (personalized) medicine offer potential solutions to use race as a proxy, there are notable concerns surrounding this method. First, all members of a racial population do not share the same genetic ancestral markers and alleles. Second, race involves self-perception and identity, which do not always accurately reflect one's course of illness, disease risk, or true genetic background. Finally, others argue that using race as a proxy could bring about stereotyping and bias, which in turn could increase misdiagnoses (5). In essence, racial disparities currently have nuanced implications within the American health care system.

One solution to improving the health of all racial groups while benefiting genetic and genomic research is including more diverse population representations in genetic and genomic studies. Specifically, racially diverse population representations in genetic and genomic research would likely strengthen the field of pharmacogenomics, which examines the genetic underpinnings of variation responding to pharmacologic exposures. In turn, these findings impact the field of precision medicine by offering clinical decision-making information, based on the genetic information of a patient, regarding drug dosages and pharmaceutical selection. If genomic and genetic studies represent racially diverse populations, precision medicine can improve disease diagnosis, prevention, and treatment for all individuals (2). Undoubtedly, studying racially diverse populations holds vast promise to improve all individuals' health.

Another solution to improving the health outcomes of different individuals is continuing to study the use and role of race within precision medicine. In other words, understanding how much health care providers know about genetic variation as well as how they use and consider race in clinical decision-making is vital in health professional education. Although health care providers still use race as a proxy, they may also hold beliefs and follow practices that limit genomics' and genetics' potential to advance precision medicine. Hence, growing genomic and genetic knowledge should help health care providers to use race beneficially in clinical decision-making (5). In all, studying health care professionals' views on race is essential in making the American health care system racially equitable.

There are extensive racial disparities in genomic and genetic health care and research. Possible solutions to address racial gaps should include selecting a more diverse population representation in research. Such efforts should also involve health care providers acknowledging unconscious racial bias and using race-specific data to treat their patients. Ultimately, addressing racial disparities in genetics and genomics necessitates deliberate measures to support equity and diversity.

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3RD PLACE ESSAY - Sachi Badola, Massachusetts

Within the United States healthcare system, existing racial disparities cannot go unaddressed or unsolved. The root of racial disparities is racism, which constructs unequal access to healthcare for specific communities. The unprecedented coronavirus pandemic proves the urgency of the matter, as historically marginalized groups and lower socioeconomic status groups are disproportionately burdened by the health and social impacts of disease(16). Studies from the National Academy of Medicine emphasize that for almost all therapeutic interventions, including diagnostic and treatment interventions, African Americans and other minority groups receive a lower quality of healthcare than white communities(17). This discrepancy applies to precision medicine: if genomics fails to incorporate minority population's genetic data, advancements in genetics may disproportionately impact ethnic minority groups. Recent advances in genomic assay technologies allow us to identify a range of diseases and disorders, including Mendelian, chromosomal, and multifactorial. However, scientists rely on available genetic and healthcare data to interpret this information and draw conclusions. People with well-represented lineages are more likely to get a correct diagnosis and a better treatment regimen based on their genomic markers. Currently, the dominantly European genomic dataset limits the accuracy of gene validity and variant interpretation, hindering our use of genomic medicine for worldwide populations. Without greater diversity in this genomic data, healthcare system disparities may be further heightened. By including diverse populations in research through initiatives like the All of Us Research Program and engaging with other countries and ethnicities to generate genomic data, precision medicine holds the potential to eradicate racial disparities in healthcare.

Evidence-Based Variant Classification with Predominantly European Data

Scientists interpret genetic findings by comparing them to the prevalence of specific variants in the population through genetic studies, including genome-wide association studies (GWAS) and other experimental evidence. A majority of genomic data comes from research participants and patients of European ancestry;about 78% of GWAS participants and 54% of disease associations come from European descent(2). Although primarily beneficial to populations with European ancestry, these genetic findings have been useful overall: 3,000 genes have been reported in association with at least one Mendelian disease(12). The ClinVar database classified 55.8% of observations from the clinically relevant variants among European ancestral populations as pathogenic or likely pathogenic(11). However, in an ExAC database of 61,486 individuals, only seven individuals of South Asian origin were identified with a mutation in MUTYH. This variant was classified as a variant of unknown significance due to the predominantly European-descent dataset. Without the South Asian population genomic data, it is unclear if the variant is a pathogenic founder mutation for this specific population(14). Patients who belong to underrepresented groups in genomic data face ambiguous genetic test results and interpretation, including many variants of unknown significance(12).

Benefits of Increasing Diversity in Genomic Data

Increasing diversity in genomic data holds the potential to benefit future genetic research on many levels, from more accurate disease-gene associations to more equitable preventive healthcare. Misinterpreting gene validity in the absence of curated health data results in clinical consequences for non-European patients. One example of this is the association of PCSK9 loss of function mutations with lower cholesterol levels and low coronary heart disease risk in African Americans. In contrast, data from individuals of mainly European descent classified the same mutations as highly pathogenic for hypertrophic cardiomyopathy, a clinically actionable disease. This data suggests that limiting studies to a single ancestry group restricts the utility of findings for non-European populations(1). Furthermore, it

restricts the identification of new disease-variant associations, which are often dependent on allele frequencies in specific populations, as seen with the association of variants in the gene KCNQ1 and Type 2 Diabetes Mellitus (T2DM) in a South East Asian population. The identified pathogenic variants(rs2237897 and rs2237892) have a higher minor allele frequency(0.39 and 0.38) in comparison to European populations(0.04 and 0.06). Researchers would need a larger cohort to identify the association based on the minor allele frequency of European populations for this gene-disease association(2). Additionally, asthma-related deaths are around five times higher in individuals with African, Puerto Rican, and Mexican ancestry. By studying genetic variants in these populations, scientists found that these individuals had a decreased sensitivity to a common inhaler drug called albuterol(6). Considering this, genomic research must include more diverse populations, as studying and including their data results in more equitable clinical care, identification of novel drug targets, and better prediction of disease risks in populations.

Limitations and Implications

While genetics and genomics offer possible solutions to limit racial health disparities, further efforts outside of genomics must be made to reform the healthcare system. By teaching medical students about health equity and population health, future physicians will be better equipped to care for specific communities and ethnicities and provide equitable care for all. Furthermore, hospitals and clinics across the nation should implement training programs and workshops that discuss ways to eliminate implicit bias among healthcare providers.

Call to Action

While genetics and genomics offer many benefits for population health and precision medicine, a lack of significant efforts to eliminate racial health disparities will put minority groups at a further disadvantage. The genetics and genomics fields have a responsibility to ensure that the benefits of precision medicine are equitable and significant for all ethnicities within the United States. While there has been ongoing progress in incorporating more diverse data sets in genomics, there is still a significant lack of representation for various populations(15). Researchers across the globe should follow the All of Us Research Program's lead, a NIH program with an ambitious plan to build one of the most diverse databases in history by sequencing one million people in the United States. Learning from this program's participant engagement strategies and building focused consortiums on minority populations can help other groups in the United States.

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