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Science & Society

Equity in Health: Consideration of Race and Ethnicity in Precision Medicine

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The causes for disparities in implementation of precision medicine are complex, due in part to differences in clinical care and a lack of engagement and recruitment of under-represented populations in studies. New tools and large genetic cohorts can change these circumstances and build access to personalized medicine for disadvantaged populations.

Health Disparities, Ancestry, and a Changing US Population

In 2020 'more than half of the nation's children are expected to be part of a minority race or ethnic group,' according to US Census Bureau [1]. Evidence of this changing demographic is seen in the genetic composition of the US population, where multiple studies have shown an increase in ancestral variation since the mid-1960s when social and legislative barriers to inter-racial marriage were struck down [2]. Further support that this is a recent change are US Census data showing that, in 2018, 53% of the US population aged 0–21 years identified as being more than one racial/ethnic group compared to only 10% of those aged 54–72 years [2,3].

Unfortunately, there is currently limited representation of minorities and disadvantaged populations in scientific research, despite increasing diversity in the US. This situation increases the risk of perpetuating and exacerbating health disparities. Increased knowledge of disease risks and patterns across diverse populations is important to mitigate impacts of disease, and without this knowledge the benefits of research will be unequally realized. Health disparities are present across a wide variety of diseases and health conditions. Differences in socioeconomic status, access to care, stress, lifestyle, and genetics have been proposed for these disparities.

Genetic factors likely contribute to many disease disparities, but limited progress has been made in understanding genetic determinants of disparity and their interactions with environmental, behavioral, and social determinants of health. Most large-scale genetic studies (>70%) have focused on European ancestry populations [4], despite an acknowledged need to increase the intensity of research in minority groups [5]. This is problematic because genetic predictors of disease in European ancestry populations do not consistently maintain predictive power in other populations and use of poorly calibrated models could exacerbate disparities [4].

Causes of Health Inequity

Health inequity is a long-standing issue in the US healthcare system. Social determinants of health, including poverty, lack of access to quality education, lack of access to quality healthcare, unfavorable work and neighborhood conditions, and the clustering of disadvantaged groups of people, are often cited as leading causes of these disparities [6]. Additionally, studies indicate that although minority and disadvantaged populations are most directly impacted by health disparities, rural populations, regardless of age, race, sex, or sexual orientation are also affected [6].

Those who are economically disadvantaged, whether due to living in a rural area or being a member of an economically disadvantaged community face several common factors that contribute to health disparities. These include gaining entry to the healthcare system, accessing a location where services are available, and maintaining services with a trusted provider. Chronic disease treatment requires multiple clinical encounters, access to medication, and updating treatment plans to provide adequate care, making unequal access an important cause of disparities. Uninsured people face barriers to entry for healthcare services, and this group is more likely to die prematurely, have illnesses, and be diagnosed later than insured people [7]. A review of 25 studies additionally demonstrated that between 10% and 51% of patients reported access to care was inhibited by transportation [8]. People with consistent access to care with a primary care physician have lower mortality from all causes [9]. A holistic approach to the precise application of medical resources to reduce disease burdens would address these issues as well as underlying biological differences between people.

In addition to environmental conditions such as nutrition, pathogens, climate, economic, social, and cultural factors that influence health disparities, evolutionary adaptations to historical environmental stresses can also contribute. Examples of this include high rates of diabetes in the Native American Pima tribe after exposure to a western diet [10], and adaptation at the *APOL1* gene locus to resist the trypanosomiasis parasite that causes African sleeping sickness, but also leads to kidney disease [11]. The alleles that contribute to these disparities were swept to high frequency by natural selection but also confer increased risk of disease, and so whether they are in general beneficial or deleterious depends on the context the population that carries them lives in. Other traits with geographic variation in humans, such as skin pigmentation, lactase persistence, dietary adaptations, and altitude tolerance have also been influenced by natural selection. The observation of a geographic disparity

does not always imply underlying differences in genetic risk factors between populations, which is well discussed by Rosenberg *et al.* [12]. When genetic differences are accurately detected, they may reflect biological factors that would be ideal targets for precision medicine development.

Disparity in the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Pandemic

The SARS-CoV-2 pandemic is an example of current health disparities and health inequity. The Centers for Disease Control and Prevention reported that 89.3% of a representative subset of those who tested positive for coronavirus disease 2019 (COVID-19), as of 30 March 2020, had one or more comorbidities [13]. Furthermore, these comorbidities that are at higher rates among minorities, including hypertension, obesity, diabetes mellitus, and cardiovascular disease, have been identified as potential biological vulnerabilities for more severe COVID-19 outcomes. These findings are evident in the mortality rate for COVID-19 in Chicago and New York City.[i] The age-adjusted COVID-19 mortality rate is greatest among African-American/black individuals (133.5 per 100 000) compared with Latino (93.6 per 100 000) and European ancestry/white (49.4 per 100 000) individuals.[i] In New York City, the age-adjusted COVID-19 mortality rates are similar among Latino (240.41 per 100 000) and African-American (224.88 per 100 000) individuals, while both are higher than among European ancestry (111.78 per 100 000) residents.[ii] The causes for these differences are not yet fully understood, but the documented inequity in healthcare access has both contributed to the extent and severity of the ongoing disparity in the pandemic in the US.

Precision Medicine and Disparities

The development of precision medicine approaches to improve accuracy of diagnoses, understand biological and environmental elements of disease risk, and improve safety and efficacy of treatments has been relatively slow within minority and disadvantaged populations. The pursuit of personalized medicine is a high priority at large academic medical research centers where incorporating genetic information into clinical records has become more common. However, these approaches are often inaccessible to economically disadvantaged populations and those who live in more rural areas.

Precision medicine has been successful historically. Early examples of precision medicine come from the diagnosis and characterization of inborn errors of metabolism such as phenylketonuria [14]. These disorders are individually rare, but collectively common and can often be mitigated or cured by restoring homeostasis to the disrupted metabolic pathway, in some cases through genotyping. More recent examples have improved drug safety by characterizing dosing responses to drug treatments such as with the anticoagulant coumadin (warfarin), which avoids drug titration protocols. There is use of different treatment strategies for hypertension in African compared with European ancestry populations, where antirenin drugs are more effective in European ancestry, while volume-lowering treatments with diuretics and calcium channel blockers show better outcomes in African-ancestry patients. Other examples include cancer diagnoses such as breast cancer (*BRCA*) and pregnancy and prenatal screenings using Rh testing and fetal genetic testing [15,16].

The reasons minorities and economically disadvantaged populations have had limited access to personalized medicine are complex and directly tied to the causes of health disparities. These causes are described earlier, and also include distrust of researchers combined with a lack of consistent long-term community engagement and other strategies to increase diversity in recruitment from under-represented populations for clinical studies.

As genome-wide association study platforms were developed to accommodate diverse populations, collections of biological samples linked to electronic health records as well as health and lifestyle surveys also started to become more common. Early biobanks were often assembled from clinical populations with sampling biases relative to cohort studies, but were also able to recruit relatively large numbers of minority participants. National and university-level biobank programs have since been established in the UK, Japan, Finland, Iceland, Estonia, China, and the US, and offer researchers unprecedented opportunities to ask research questions and study genetic causes for health disparities in diverse samples of 10^6 participants. Additionally, research resources developed by direct-to-consumer genetic testing companies include substantial numbers of minority participants with diverse ancestries. Recently, the chief executive officer for the company 23andMe issued a statement that acknowledged the genotyping platform used by the company should be improved to better evaluate non-European genetic backgrounds, with Ancestry.com making a similar statement, shortly afterward.

Health disparities exist in the US within the context of historical and current racial discrimination along with social and economic inequity. Comprehensively addressing these disparities requires changes in systems beyond the fields of medicine and medical research. However, researchers have a critical role in identifying novel treatments and strategies to mitigate disparities. The continued development of technology, population resources, and sustained engagement with minority communities are critical to this endeavor. The National Institutes of Health has made improving the health of minorities and reducing health disparities part of their

primary mission, with targeted research funding and development of research tools focused on community engagement. Recognition of the additional burdens on health of minorities, the weaknesses of existing research resources, research opportunities, and the challenges of finding substantive solutions to these issues, is an end to the beginning of the work to provide equitable access to healthcare resources.

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Resources

[i]https://www.chicago.gov/city/en/sites/covid-19/home/latest-data.html

[ii]https://www.statnews.com/2020/06/10/23andme-ancestry-racial-inequity-genetics/

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Spotlight

Editing the Mitochondrial Genome: No CRISPR Required

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Precise gene editing of mitochondrial DNA (mtDNA) is essential for the generation of model systems to study rare mitochondrial diseases but was long deemed impossible – until now. A recent publication by Mok *et al.* describes a gene editing tool capable of installing point mutations in mtDNA, and it does not involve CRISPR.

Mitochondria are considered the cell's powerhouse that produce the vast majority of ATP, the main cellular power source. Interestingly, they are the only organelle besides the nucleus that contains genetic information stored in the form of DNA. Each cell contains dozens of mitochondria, with each mitochondrion containing dozens of copies of mtDNA. Unlike the 3.3 billion DNA bases found in nuclear DNA, which is linear and constitutes the vast majority of our genome, mtDNA is circular and relatively small, with a little over 16 000 base pairs harbouring only 37 genes that encode 13 proteins, 22 tRNAs, and two rRNAs. Although it is small in size, mutations in mtDNA can lead to several severe neurodegenerative and muscular diseases, such as Leber's hereditary optic neuropathy (causing blindness) or mitochondrial diabetes (causing deafness and type I or II diabetes), and it is estimated that approximately one in 5000 individuals carry disease-causing mtDNA mutations [1]. However, the study of mitochondrial diseases has been hampered by the fact that mtDNA is passed down maternally and because each cell contains hundreds to thousands of copies of mtDNA, so animal models are difficult to generate using conventional gene editing techniques. In recent years, designer nucleases such as mitochondrially targeted zinc-finger nucleases (mtZFNs) [2] and TAL effector nucleases (mitoTALENs) [3] have been used effectively to specifically generate double-stranded DNA (dsDNA) breaks in mitochondria as a tool to eradicate disease-causing genes. So far, however, these tools have not been able to correct disease-causing mtDNA mutations due to the fact that mitochondria are incapable of repairing dsDNA breaks [4] or performing homologous recombination [5], effectively resulting in loss of the modified mtDNA on mtZFN- or mitoTALEN-mediated cleavage. To faithfully install desired mutations in the mitochondrial genome while leaving them intact, a gene editing tool that does not introduce dsDNA breaks is therefore required.

In 2016, David Liu's group introduced a variety of such tools called 'base editors', which implemented the latest generation of