COMMENTARY

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The Attainment of Patient Diversity in Clinical Trials: Race, Ethnicity, Genetics

The overarching purpose of clinical trials is the assessment of the efficacy and safety of investigational products. In order to fully evaluate investigational products, the clinical trial population should reflect the epidemiology of the disease demographics and burden. Is clinical trial patient diversity attainable with regard to race, ethnicity, and genetic variables?

Race is a social construct which pertains to identification with a group based upon phenotypic characteristics. In the United States, the institutionalization of racial categories occurred with the first census in 1790. Race is a primary identifying characteristic reflective of an assigned social position. Ethnicity is a social construct pertaining to a shared culture and language.

The US Food and Drug Administration (FDA) Guidance for Industry and FDA staff on the Collection of Race and Ethnicity Data in Clinical Trials utilizes the US Office of Management and Budget racial categories: White, Black or African American, American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander. The ethnicity categories are: Hispanic or Latino, and not Hispanic or Latino.[1] Racial category ascription may be based on self-identification or assignment by healthcare personnel. Thus, the FDA data standards pertaining to clinical trial participant diversity are based upon the social constructs of 5 racial and 2 ethnicity classifications. What does this data actually inform in the conduct of clinical trials?

Given that race and ethnicity are social constructs, their utility may be with regard to the social determinants of health (SDOH). The SDOH are comprised of those factors which impact upon health and well-being and are influenced by the distribution of money, power, and resources at global, national, and local levels and are subject to policy decisions. Thus, SDOH include education, income, employment, housing security, food security, transportation, social connection or isolation, physical activity, exposure to violence, immigration status, environmental and cultural influences, as well as healthcare (e.g., access, bias, disparate quality, and literacy). Fundamentally, W.E.B. DuBois declared that the concept of race was not a scientific category and that health disparities between blacks and whites were due to social not biological inequality.

The gross historical abuses involving the utilization of indigenous and African American patients in research must be acknowledged to allow for transparency in addressing the resultant subterranean distrust which remains an issue. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was formed subsequent to the Tuskegee Study abuse unveiling, published the Belmont Report in 1979. The Belmont Report has 3 foundational ethical principles: respect for persons, beneficence, and justice. These principles are the basis of the Federal Common Rules oversight of all human subject research and the overarching guidance for Institutional Review Board assessments.

The principle of justice underscores equity in the distribution of the benefits of clinical research. In order to operationalize justice in clinical research, the subject population must be reflective of the patient population. The FDA published the first Drug Trial Snapshot in 2014, which reported the demographics of participants in pivotal trials resulting in approvals of New Molecular Entities or Biologics License Applications from the Center for Drug Evaluation and Research.

To address shortcomings of the FDA Snapshots, which do not include disease prevalence data, the Tufts Center for the Study of Drug Development analyzed participant demographic data of New Drug Applications and Biologics License Applications approved by the FDA between 2007 and 2017 and compiled disease prevalence and census data. A mean disparity percentage was calculated by comparing the actual percentage of demographic subgroup participation by disease, therapeutic area, and year with the expected percentage based upon disease prevalence or upon population distribution census data. The analysis of pivotal trials revealed that the disparity percentage was −65.4% for

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Black participants, −12.4% for Hispanic or Latinx, whereas White and Asian participants were overrepresented at +13.6% and +148.9%, respectively.[2] The authors concluded that the most consistently underrepresented subgroup was that of Black participants.

Approximately 20% of New Molecular Entities in 2015 were associated with differences in exposure, and/or response, across racial or ethnic groups, which resulted in different prescribing recommendations for specific patient populations. Race and ethnicity categories, however, as social constructs are imprecise and are associated with significant genetic admixture within these categories.

The participation of diverse patient populations in clinical research fosters scientific discovery and the development of new therapeutics. In 2010, an FDA boxed warning ("Diminished Effectiveness in Poor Metabolizers") was added to the label of the antiplatelet drug clopidogrel.[3] Efficacy is dependent upon the conversion to the active metabolite by CYP2C19. The identification of CYP2C19 loss of function allele, was noted with higher frequency in Asian subgroups (24% Japanese, 15% Korean, 9% Chinese, compared with 3%-5% Europeans). In contradistinction, 28% of South Asians have genetic polymorphisms which result in increased conversion to the active form and thus an increased bleeding risk.

Given these genetic polymorphisms, although race and ethnicity may convey information pertaining to the presence of specific genetic variants, genetic ancestry is likely to be a better predictor. Genetic ancestry refers to the genetic origin of a given population. Genetic admixture among people of different ancestries is significant for many populations, and there are variations intra- and inter-populations. According to data from the Genes-environments and Admixture in Latino Americans Study,[4] Mexican Americans have a greater percentage of Native American genetic ancestry, compared with Puerto Ricans who have a greater percentage of African and European genetic ancestry.

At present, most genomic research databases, however, are significantly lacking in genetic ancestry diversity comprising of greater than 80% European ancestry. The polygenic risk score for breast cancer has approximately one-third the predictive value in women of African ancestry compared with those of European ancestry. This results in the perpetuation of disparities in equity in access to personalized medicine and clinical outcomes for non-European populations. To address the issue of genomic database diversity, the National Institutes of Health initiated the Precision Medicine Initiative in 2018; presently referred to as the "All of Us" program. The goal is to enroll > 1 million US participants age ≥ 18 years, with a target participation of > 45% ethnic minorities and > 75% underrepresented populations, forecasted enrollment completion in 2024, and subsequent decades long follow-up.

How can clinical researchers strive more purposefully toward attaining the goal of the overarching mandate that the clinical trial population be reflective of the patient population with the disease? Race and ethnicity are undeniably social constructs. In truly equitable societies, these constructs would be nonexistent. Eliminating the utilization of race and ethnicity demographic categories, however, may serve only to exacerbate and not ameliorate inequities in health outcomes. Race and ethnicity data as social constructs may be of most value as predictors of SDOH. Given the significant advances in precision medicine, justice demands that these benefits be accessible to all populations, including those of non-European ancestry. To achieve this, genetic ancestry data, which is a better predictor of the likely presence of certain genetic variants, should also be utilized with concomitant appropriate privacy protections. As such, both race and ethnicity as well as genetic ancestry would serve to better inform clinical research translational applicability to patient care.

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