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REVIEW ARTICLE

Advancing Precision Medicine Beyond 'Asian' Race

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Advances in precision medicine afford a unique opportunity to develop personalized disease prevention, treatment, and interventions. However, the use of race and ethnicity persists as a measure of innate biological differences for individuals of Asian descent in clinical decision-making, with race-specific body mass index cutoffs as the most well-known example. We posit that precision medicine must move beyond using 'Asian' race as the sole motivating risk factor for intervention while acknowledging the socio-political construction and impact of Asian race and ethnicity on health outcomes. We recommend the continued development of holistic health data to comprehensively encompass the genetic, environmental, and social variables that Asian race and ethnicity have been used to proxy.

Key Words: Asian American ▪ Asian health ▪ precision medicine ▪ race-based medicine

Precision medicine seeks to optimize disease prediction, prevention, management, and treatment to an individual's unique genomic profile and is achieved through emerging high-throughput 'omics' technologies such as genomics, proteomics, metabolomics, exposomics, etc.[1] This paradigm has evolved to encompass not only genetics but also the significant role that one's lifestyle and environment have in shaping their health outcomes.[2] Despite these advancements, race and ethnicity continue to be conflated with population-level genetic differences and are often used to justify clinical decision-making.[3] Race and ethnicity are social constructs that have and will continue to semantically evolve. In general, race has historically encompassed broad groupings of people stratified by ancestral origin and physical characteristics while ethnicity refers to a person's cultural identity.[4] Authors have cautioned against the use of race and ethnicity as a measure of population-level genetic differences because it can lead to unequal treatment and inaccurate diagnosis among racial and ethnic minority groups.[5,6] For example, one study found that a race-specific pooled cohort equation generated different estimates of 10-year cardiovascular risk for Black vs. White participants despite presenting with identical cardiovascular risk factors (i.e. smoking, blood pressure, age, etc.).[7] Using such equations may contribute to over-treatment of statins and the associated financial sequelae of unnecessary medications.[7,8] This concern is exacerbated when epidemiological studies and clinical decisions adjust for race and ethnicity a priori, leading to broad generalizations of race-based physiological differences that are not tailored toward individual differences in genes, environments, and lifestyles.

We recommend a data-informed approach to screening that would be equitably sensitive and specific among all racial and ethnic groups while minimizing the need for inappropriate clinical procedures. Some clinical algorithms, such as the American Gastroenterological Association guidelines for gastric cancer surveillance, continue to use race and ethnicity as a risk factor.[9] Although it is important to acknowledge that there are racial disparities in gastric cancer, it is equally important to consider (1) the underlying limitations of data used to create these algorithms and (2) identify mutable social and behavioral risk factors that may lead to racial disparities. Addressing these issues will help to curb invasive and costly procedures such as endoscopies based on minority race and ethnicity as a primary risk factor.

Scientific critique of data and the use of existing clinical algorithms, such as those for estimating glomerular

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POPULAR SCIENTIFIC SUMMARY

- The emerging field of precision medicine will provide opportunities to improve treatment and prevention of disease. While understanding genetic and biological differences to disease is important for precision medicine, we argue that doctors and researchers should be careful about how they use 'race' in precision medicine. We encourage doctors and researchers to be mindful of the environmental, and social factors that can contribute to differences in health among Asian people.

filtration rate and predicting vaginal birth after cesarean delivery, have led to recalibrated equations without race and ethnicity.[10,11] These new equations are equally accurate models for clinical risk stratification. In November 2023, the American Heart Association announced the PREVENT equation for predicting cardiovascular disease risk which does not include race as a variable.[12] One of the stated rationales for removing race as a variable in this equation is that including race in risk calculations implies that health differences by race and ethnicity are not modifiable and perpetuates the idea that race is a biological construct.[13] Additionally, the PREVENT equation incorporates social determinants of health (SDOH) through neighborhood measures of disadvantage, which help to assess the upstream, structural determinants of racial and ethnic health disparities. In this paper, we focus on Asian American populations. We argue that using the 'Asian' racial category as a generalized proxy for race-based differences in physiology perpetuates outdated notions of racial essentialism that limit the personalized promise of precision medicine.

The 'Asian' racial designation, according to the United States (US) Census, refers to individuals with origins from any of the 48 countries or three territories that comprise the Asian continent,[14] such as India, Pakistan, China, Cambodia, Japan, Korea, Vietnam, the Philippines, etc. Each of these countries and territories is composed of numerous ethnicities, each with its distinct culture, language, and history. Today, there are approximately 23 million people of Asian descent living in the United States with the population projected to double by 2060.[14,15] Defining who is considered 'Asian' has been a challenge for the US Census Bureau since the Census began enumerating immigrants from China in the mid-1880s,[16] evidenced by the fact that the number of recognized nationalities considered 'Asian' has fluctuated over the past two centuries.[17] For example, Asian Indian individuals, 'were counted as 'Hindus' in censuses from 1920 to 1940, as 'White' from 1950 to 1970, and as 'Asians or Pacific Islanders' in 1980 and 1990'.[18]

Given these complexities, the application of race-based clinical algorithms, while attempting to better account for population-level health disparities, poses a potential stigma for patients. For instance, the World Health Organization and American Diabetes Association have recommended the use of an Asian-specific body mass index (BMI) cutoff for overweight at BMI ≥ 23.0 kg/m^2 compared to the standard 25.0 kg/m^2 for patients of other racial backgrounds.[19,20] This recommendation is based on evidence that there is a greater prevalence of metabolic syndrome at lower BMI levels among individuals who identify as Asian.[21,22] The underlying theory for this observation is that Asian-identifying patients exhibit a 'skinny fat' phenotype (higher tendency to accumulate visceral fat over subcutaneous fat than patients of other racial groups at similar BMI levels) and are therefore at an elevated risk of insulin resistance.[23] However, a study comparing Asian ethnic groups in the Singapore Adults Metabolism Study found that differences in body fat partitioning across compartments did not explain ethnic differences in insulin insensitivity.[24] Another study noted that among Chinese Asian, American White, and American Black people, incident hypertension and diabetes rates in the upper end of healthy BMI (e.g. 23.0– < 25.0 kg/m^2) group were consistently higher than those in the lower end of healthy BMI (e.g. 18.5– < 23.0 kg/m^2 group.)[25] The authors did observe that Chinese Asian people had a greater cumulative incidence of hypertension and diabetes at lower BMI levels compared to American White people.[25] Prior arguments against lower BMI cutoffs [26] for Asian American individuals have cited that the same logic could be applied to African American women, where the utility of a race-specific BMI cutoff depended on the outcome studied and the measure of association used.[27] Instead of simply moving the cutoff for what is classified as 'overweight' among Asian people, more focus is needed to address the usefulness of BMI as an accurate indicator of cardiometabolic disease. Previous reviews have noted issues with using BMI as a measure of adiposity.[28] BMI may not accurately measure adipose tissue, which creates the molecular intermediates that ultimately lead to cardiometabolic disease. Instead, others have advocated for newer measures that better account for biomarkers that are more correlated with adiposity, such as the visceral adiposity index.[29]

The issue with an Asian-specific BMI cutoff is it can become the sole reason for screening Asian patients without considering other risk factors or their social and environmental context. Consequently, this situation might result in Asian patients experiencing stigma from medical providers and thus contribute to increasing medical distrust.[30,31] Rather than relying on race as a risk factor, healthcare professionals should instead focus on screening patients for diabetes mellitus with lower BMIs based on signs of elevated body fat (i.e. body roundness, body fat percentage)[31,32] or with anthropometric tools that may be more accurate and readily available at estimating adiposity (i.e. visceral adiposity index,[29] waist circumference,[33] waist-

to-hip ratio,[34] waist-to-height ratio).[35] Furthermore, a recent study utilizing the 2021 US Preventive Services Task Force (USPSTF) diabetes screening guidelines to all non-symptomatic adults ≥ 35 years of age, regardless of BMI, showed the most equitable performance in terms of sensitivity and specificity across all racial and ethnic groups.[36] This study emphasizes the importance of adopting inclusive screening strategies that prioritize accuracy and equity in healthcare practices.

Advances in our understanding of the genetic causes of differences in metabolic syndrome among Asian populations have been informed by recently published genome-wide association studies (GWAS). For example, a GWAS conducted among a Kinh Vietnamese population identified candidate single nucleotide polymorphisms associated with an increased risk of developing type 2 diabetes mellitus and metabolic syndrome.[37] Multiple candidate genes have also been discovered among individuals of South Asian descent for diabetes risk factors (insulin resistance, pancreatic B-cell function, etc.).[38] These studies, while focused on specific racial groups, attempt to elucidate the underlying genetic mechanisms behind disease. However, identification of such genetic markers within specific racial groups is not what leads individuals to their racial classification. Instead, we reiterate that these genetic markers are correlated with increased disease prevalence among these groups, but not the sole cause of increased disease prevalence by race.

Future studies are warranted to identify genetic, environmental, and social explanations for differences in clinical management as opposed to Asian race-adjusted clinical algorithms, such as the fracture risk assessment tool (FRAX), pulmonary-function tests, eltrombopag dosing, etc.[31,39–41] The FRAX calculator reports 10 year risk of major osteoporotic fracture for Asian women at about half that for White women which could potentially delay intervention with osteoporosis therapy.[3] For pulmonary-function tests, spirometers apply correction factors of 4–6% for Asian people, which could result in inaccurate estimates of lung function and thus misclassification of disease severity for Asian people.[42] Eltrombopag has a lower recommended starting dose for East Asian patients based on small, limited pharmacokinetic studies. This may result in inappropriate dosing and treatments for East Asian patients.[31] Therefore, it is imperative to move beyond generalized race-based algorithms to prevent the repercussions of medical misdiagnosis and dosage errors. Research is needed to gather more comprehensive data to create precise algorithms that ensure safe, effective medical care.

We acknowledge the success of targeted, country-specific population health interventions in Asian countries. For example, the Korean National Cancer Screening Program for gastric cancer played a key role in increasing the number of curable cancers by early detection and improving overall survival.[43] While epidemiological insights have identified populations most at risk, advances in population health data collection and quality allow for a targeted approach on the specific factors contributing to increased disease morbidity and mortality. While Korea has the highest age-standardized incidence rates of gastric cancer worldwide,[43] there are appreciable geographic disparities by region in Korea, evidencing that more precision is needed to address this health disparity beyond Korean racial identification.[44] Moreover, a review of the epidemiology literature has identified multiple contributing environmental and lifestyle factors to gastric cancer among Koreans, such as *Helicobacter pylori* infection, cigarette smoking, alcohol intake, obesity, and high sodium intake, with the estimated population attributable fraction of *H. pylori*-related gastric cancer as high as 76% among the Korean population.[44] It is thus important to use precision medicine as a framework to consider the influence and interaction between genes, environment, and lifestyle in developing targeted interventions on modifiable risk factors.

To fully embrace the promise of precision medicine, the medical community must shift its focus from using broad racial categories to understanding and identifying the intricate genetic, environmental, and social factors that contribute to an individual's health outcome. Studies have looked at how SDOHs such as citizenship, socioeconomic status, insurance status, health literacy, and racism impact the risk of health outcomes among Asian Americans.[45–48] Future research examining the joint, multifactorial impact of SDOHs on health outcomes by Asian subgroups is necessary to create tailored interventions and policies. Moreover, given the 276% increase from 2010 to 2020 in individuals who identify as multiracial in the US,[49] there is an urgent need to step away from using Asian race as a measure of shared genetic disposition and exposure and overly relying on algorithms to assign race to individuals.[50] Despite the Asian American population being the most diverse and fastest-growing racial and ethnic group in the US,[15] this population faces underrepresentation across various dimensions of clinical research. This is exhibited in minimal funding – such as how only 0.17% of clinical research funded by the National Institutes of Health was focused on Asian Americans, Native Hawaiians, and Pacific Islanders between 1992 and 2018[51] – and consistently low enrollment rates both historically and more contemporarily, as exemplified in COVID-19 prevention trials with a 3.8% representation compared to an expected 5.9% relative to the US population.[52] The lack of progress in representation is also evident in research papers, with only 24.4% of high-impact medical research studies in North America identifying Asians as a distinct race/ethnicity between 2015 and 2016.[53] In the genomics field, there are also concerns about the dominance of Europeans and the underrepresentation of diverse racial and ethnic groups, including Asians.[54,55] For example, the bias of representation may exacerbate existing disease and healthcare disparities – as critical

genetic variants are absent from the data, as important and large effect size associations are missed, and as study findings may not accurately extrapolate to non-European and understudied populations.[56,57] Notably, compared to other racial and ethnic groups, Asian Americans were the least interested in participating in research studies[58] and the least likely to participate in health research.[59] In specific contexts, such as infertility clinics, Asian patients were less likely than their non-Hispanic White counterparts to express interest in research participation.[60] Furthermore, intra-population disparities exist across subgroups, with foreign-born Asians being less likely to opt to donate excess embryos for research purposes, in contrast to Europeans and US-born Asians.[61] Reasons for low participation may include mistrust of institutions and negative experiences, feeling intimidated by English, and insufficient translated materials.[62] This collective evidence underscores that community-informed approaches are needed to increase the representation of Asian Americans in clinical trials.[63] While initiatives such as the National Institutes of Health's All of Us research program underscore the importance of capturing this diversity and facilitating more accurate precision medicine approaches,[64] more work is needed to improve poor-quality data infrastructure (e.g. missing or misclassified data for Asian Americans and data aggregation of Asian American subgroups) and to reduce biases on the part of researchers and healthcare providers.[65] More work is also needed to lower the barriers to public availability of disaggregated racial information in US federal health datasets, such as by decreasing data processing times and exorbitant fees.[66] Nationally representative health surveys can also be linked to electronic health records to increase data quality and allow for a more comprehensive understanding of health determinants.[67]

We contend that healthcare providers apply a race-conscious approach to healthcare to dismantle preconceived notions of intrinsic, biological differences tied to race.[31] In other words, we assert that healthcare providers should understand the nuances of the use of race and ethnicity in health. In addition to collecting better data on Asian groups, the health field must understand the social and environmental factors surrounding 'why' Asian people experience increased morbidity for certain diseases. We also recommend that precision medicine and public health researchers utilize the most up-to-date race and ethnicity reporting guidelines[4] for Asian health disparities studies, explicitly stating the goal and conceptual justification for Asian ethnic group stratifications. As the public health and healthcare community navigates the evolving opportunities afforded by precision medicine, a critical understanding of race as a sociopolitical construct that affects health through systemic and interpersonal racism is necessary to ensure that every patient receives individualized and quality care.

ARTICLE INFORMATION

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Disclosures

None

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