COMMENT

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ED KASHI/VII/CORBIS

Common asthma drugs can work less well for children of some ethnicities.

Missing patients

Effective clinical studies must consider all ethnicities — exclusion can endanger populations, says **Esteban G. Burchard**.

In 1997, when I was a resident at Harvard Medical School in Boston, Massachusetts, an African American teenager was found dead just blocks away from the teaching hospitals. He had died of an asthma attack while clutching his inhaler.

It is widely known that racial and ethnic minorities in the United States have higher rates of diseases such as asthma[1] and cancer[2], and receive worse care[3]. Compared with white people with similar conditions, minority individuals get fewer heart bypasses and influenza vaccinations.

Less well known is the fact that many drugs work better in people of European origin than in others. One class of asthma drug (long-acting β2-agonists) is even associated with higher mortality in African Americans[4].

Populations of non-European descent are harmed because they are not studied as intensely, and clues that could reveal new aspects of disease biology are missed. Including diverse populations in clinical and biomedical research is a must, ethically and scientifically. Research infrastructure needs to be retooled accordingly.

My mother was Mexican, an overworked single parent who learned English and put herself through university. I spent much of my time growing up with a Chinese surrogate family. My wrestling coach, an African American and member of the 1984 US Olympic team, became my mentor and father figure. Later, in medical school, I lived in housing that was set up by Jewish students. These experiences have prompted me to consider health disparities across racial and ethnic populations, which I discuss here using the terms and criteria established by the US Centers for Disease Control and Prevention (CDC; see go.nature.com/a2euvo).

The year that the young man in Boston died, my colleagues and I identified a variant associated with asthma in the gene for interleukin 4, a cell-signalling protein that coordinates immune and inflammatory responses. In our study[5] of 772 individuals, the variant was associated with lower levels of lung function, leading to more ▶

severe disease in white people. Although black children are more likely than white children to be diagnosed with and die from asthma (see 'Asthma inequalities'), few black patients were included in the study, so we had insufficient statistical power to establish the genetic association in black people. However, our analysis found that the variant was 40% more common in black people. This led me to wonder whether some health disparities might result from genetic differences, as well as social and environmental factors.

That same year, the CDC published data showing that the occurrence of and deaths from asthma were threefold higher in Hispanic communities in the northeastern United States than in those on the west coast. I immediately thought that the observation could result from genetic differences between Puerto Ricans (concentrated in the east of the country) and Mexicans (concentrated in the west). This realization spurred the Genetics of Asthma in Latino Americans (GALA) study, which started in 1998 in Boston, New York and San Francisco, California. For one analysis, children with asthma were asked to breathe into a measuring apparatus after receiving standard treatments. The research[6] showed that the biggest predictor of drug response was ethnicity — stronger than age, sex or disease severity. Commonly prescribed asthma medications worked less well for Puerto Ricans than for Mexicans and African Americans.

"Grant applications should be regarded more favourably, not less, for analysing minority populations."

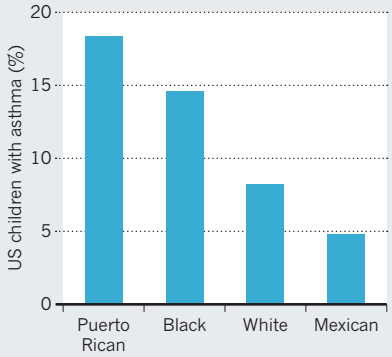
Such disparities occur across other ethnicities and conditions. Heart disease and stroke are the two leading causes of death worldwide, and the blood thinner clopidogrel is widely prescribed to people who have had a heart attack or a stroke. In March, officials in Hawaii sued the drug's manufacturer for failing to disclose that it is frequently ineffective in the state's largely east Asian and Pacific Islander population, placing them at higher risk of recurrent heart attacks.

VICIOUS CYCLE

Many barriers keep studies that could characterize such disparities from being proposed, funded, carried out and published. The hospital where I work runs dozens of clinical trials, but it serves mainly people of European and Asian descent. To recruit enough subjects for the GALA study we sent staff to other parts of the San Francisco Bay Area, to Mexico and to Puerto Rico. We established a network of physicians with experience serving diverse communities, used bilingual clinical coordinators and engaged community clinics, religious leaders and community activists. That I am a bilingual physician–scientist from an ethnic minority was invaluable for brokering these connections.

ASTHMA INEQUALITIES

Genetic variants contribute to disparities in asthma incidence and treatment efficacy.



SOURCE: REF.1

Once participants were recruited, we measured genetic ancestry using reference data from the 1000 Genomes Project and the Human Genome Diversity Project. This was not easy — fewer than 4% of genetic association studies have been conducted in people of non-European descent. We had to create our own human genetic reference panels by teaming up with another investigator who had collected samples from Native Americans.

Our work paid off. We were able to show that considering genetic ancestry can improve the accuracy of diagnosis of lung disease in African American and Mexican populations. We have also identified genetic variants that might explain why asthma drugs work less well for Puerto Rican and African American children. Clinical trials are now under way to assess the efficacy of asthma medications in different ethnic populations, based on genetic variants.

Such work, focused on minority populations, faces a vicious cycle. As a reviewer for the US National Institutes of Health (NIH), which is funded by US taxpayers, I witnessed how grant applications that propose genetic analyses in minority populations in the United States are criticized because reviewers considered these populations more difficult to analyse than more-genetically-homogenous European populations. Sadly, I believe that many NIH reviewers see rich genetic ancestry largely as a potential confounder. They do not appreciate that it can be leveraged to reveal new risk factors.

Publishing such results is also difficult. Most high-impact journals require that an association be found in samples from two independently recruited studies. This demand is straightforward in European populations, because many banked samples exist. It is much harder to meet for other groups.

Disparities are self-perpetuating. Minority scientists are often best placed to gain community 'buy in' and trust in minority populations, but these scientists are at a disadvantage in other ways. According to one analysis, black scientists in the United States were 13% less likely to get NIH funding than white researchers[7]. In short, investigators who want to focus on minorities face extra challenges.

COUNT EVERYONE IN

The NIH Revitalization Act of 1993 mandated that NIH-funded research must include minorities. Twenty-one years later, diversity-focused clinical research is still the exception, not the rule. Although black people and other minorities in the United States have greater rates of and mortality from cancer than white people[2], they are generally less likely to be enrolled in clinical trials. Of the 10,000 clinical trials funded by the National Cancer Institute since 1993, only around 150 studies focused on racial or ethnic minorities[8].

Such gaps and their effect on health care must be assessed. Funding agencies should do more to collect evidence on what research is needed, promote research training, and provide venues for discussion of disparities in biomedical research. At a minimum, the race and ethnicity of study participants should reflect the population with the disease being investigated. Grant applications should be regarded more favourably, not less, for analysing minority populations. Journals should require appropriate representation and analyses before publishing clinical studies.

Investigators must also form partnerships with physicians and residents in under-represented communities — they too have a vested interest in improving studies. Finally, there must be increased recruitment of minority physicians and scientists and mechanisms to enhance their training and retention.

At every stage of the scientific discovery and review process, investigators should keep in mind that ancestry can contribute to differences in disease and drug response. To do otherwise is to ensure worse health for us all. ■

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