VIEWPOINT

Race and Pharmacogenomics—Personalized Medicine or Misguided Practice?

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Viewpoint

The use of race in clinical decision-making is coming under increasing scrutiny, in part because of growing recognition that race-based diagnosis and treatment reflect flawed social, biological, and genetic assumptions. Despite this concern, guidelines, algorithms, and advisory and regulatory bodies (including the US Food and Drug Administration [FDA]) regularly use race in ways that influence clinical decisions. For example, race-based "corrections" have been deemed problematic in algorithms, risk scores, and physiologic calculations used in cardiology, nephrology, urology, and obstetrics.[1,2]

Pharmacogenomics is a field that explores relationships between genes and drug effects, with potential to "personalize" medical therapy. For clinical scenarios in which a genotype is clearly linked to important outcomes, direct genetic testing would appear to obviate the need to use race as a surrogate for genetic predisposition in decision-making. However, pharmacogenomics research often invokes race to stratify genetic risk: The assumption is that racial categories can sufficiently distinguish populations with high or low prevalences of certain genes, allowing clinicians to identify high-prevalence groups for testing. The FDA and authors of clinical guidelines have generally embraced this approach, invoking race and ethnicity in recommendations for genetic screening prior to using certain drugs.[3] However, close inspection of several examples reveals that race-based pharmacogenetic screening is problematic. (In the ensuing discussion, we use "African American" rather than "Black" when a particular guideline or database uses that terminology.)

> Race-based pharmacogenetic screening recommendations may result in considerable practice variation and stereotyping, with unknown clinical consequences and reinforcement of preexisting beliefs about race as a biological construct.

Allopurinol can cause severe cutaneous adverse reactions (SCARs), which are potentially deadly. Researchers in Taiwan were the first to demonstrate the association of the HLA-B*5801 allele with allopurinol-induced SCARs. Subsequent studies confirmed the association and demonstrated wide-ranging HLA-B*5801 frequencies among ethnoracial groups.[3] The American College of Rheumatology (ACR) recently recommended that people of Southeast Asian and African American descent should be tested for the HLA-B*5801 allele before initiation of allopurinol.[4]

However, genetic variation within certain geographic populations or ethnic groups can exceed variation across racial categories. Published HLA-B*5801 allele frequencies demonstrate this intrapopulation genetic diversity and the limitations of the ACR recommendations (**Figure**). Data from Switzerland—available by city, not by race or ethnicity—illustrate the point. Despite Switzerland's relatively small size and comparative racial homogeneity, HLA-B*5801 frequencies vary considerably across the country. Although the average HLA-B*5801 frequency in Switzerland is comparable with the US White population, the city of Basel reportedly has a higher frequency of HLA-B*5801 than the US African American population.[5] Based on cost-effectiveness assumptions in the ACR guideline, a potential theoretical argument is that Swiss residents of Geneva and Basel—but not Lausanne or Bern—should be screened.

The ACR guideline cites Han Chinese, Korean, and Thai as examples of Southeast Asian descent, even though China and Korea are not typically considered Southeast Asian countries. The guideline then states that screening is cost-effective in Asian populations generally. However, Japan is in Asia, but the allele frequency of HLA-B*5801 in Japan is even lower than that of White individuals in the US, who are *not* recommended for screening.[5] In addition, the recommendation to screen all African American patients in the US before prescribing allopurinol belies wide-ranging HLA-B*5801 variation across Africa, where reported HLA-B*5801 frequencies, based on small sample sizes, range from 1% (comparable with White individuals in the US) to 10% (comparable with Thailand).[5] Taken together, these examples indicate that comparing HLA frequencies across racial, ethnic, or geographic groups is complicated by variability in sample size and sampling methods and by inconsistent use of racial and geographic categories.

The FDA issued similarly confusing race-based guidance for genetic screening prior to use of carbamazepine and oxcarbazepine. For example, the drug label for carbamazepine recommends HLA-B*1502 screening in all "at-risk populations" and notes heightened risk "across broad areas of Asia"; however, HLA-B*1502 is nearly absent in South Korea and Japan.[5,6] The label concludes with a note of caution: "In deciding which patients to screen, the rates provided…may

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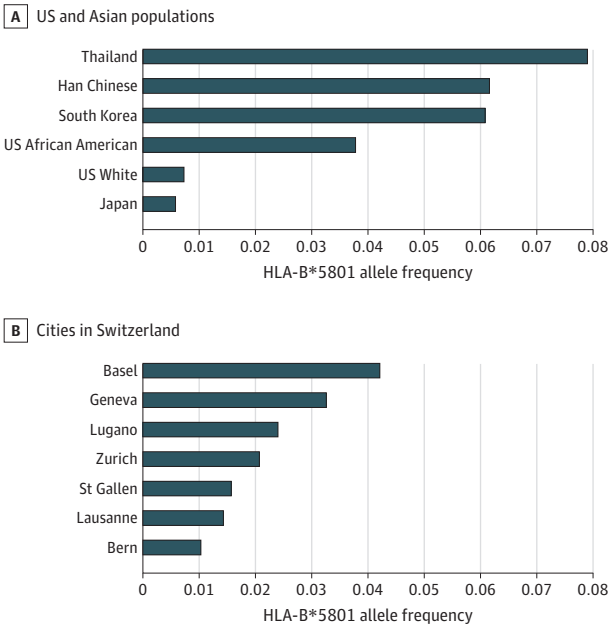
Figure. Example of HLA-B*5801 Allele Frequencies in Selected US, Asian, and Swiss Populations, as Reported in the Allele Frequency Net Database (AFND)[5]



When the AFND reported allele frequencies from more than 1 study within a country, the frequency reported in the largest sample was used. The online searchable database is available at http://www.allelefrequencies.net.

offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry."[6]

The FDA statement acknowledges that clinicians encounter practical issues in applying race-based screening recommendations. Clinical research, and the clinical guidelines derived from it, cannot provide consistent and coherent definitions of racial categories because such categories are fluid, socially constructed concepts.[7] Clinicians are asked to focus on certain races or ethnicities for screening, but definitions (eg, "Southeast Asian descent" in the ACR guideline) vary across authors and over time, and mixed ancestry is rarely addressed and likely increasing in frequency. Given this uncertainty, clinicians are left to rely on their own intuitions. For example, a case study of prescribing guidelines for hypertension in England and Wales based on evaluation of guideline documents and semistructured interviews with 11 experts illustrates confusion and disagreement on identifying and labeling Black people of Caribbean, North African, sub-Saharan African, and mixed descent.[8] Therefore, race-based pharmacogenetic screening recommendations may result in considerable practice variation and stereotyping, with unknown clinical consequences and reinforcement of preexisting beliefs about race as a biological construct.

The race-based screening recommendations for allopurinol, carbamazepine, and oxcarbazepine stand in contrast to the universal screening recommended for abacavir. Approved by the FDA in 1998 for treatment of HIV, abacavir also causes a severe adverse drug reaction associated with an HLA allele, HLA-B*5701. Variations in allele frequency by race have been described, with higher rates among US White individuals (4%) compared with US African American individuals (1%), nearly exactly the inverse of frequencies for HLA-B*5801 in these populations.[5] However, despite the genetic variation, the Infectious Diseases Society of America and the FDA issued guidance that all patients should be screened for HLA-B*5701 prior to use of abacavir.[3]

Pharmacogenomics poses challenges for researchers, policy makers, and clinicians. Universal screening for genetic predisposition to adverse drug reactions would make race-based algorithms unnecessary, but imperatives to use limited resources judiciously may warrant more selective screening, targeted to high-prevalence groups, if such groups can be identified accurately. Although stratifying genetic risk by multigenerational ancestry might seem clinically appealing, race-based or ancestry-based pharmacogenetic decision-making is limited by intrapopulation genetic variation and the fluidity and social construction of racial categories. If nonuniversal, population-based approaches are to succeed, they will require more nuance and clarity than broad racial categories like Black, Asian, and White. Lessons from pharmacogenomics illustrate that race is a poor surrogate for biology, and clinicians would do well to treat it accordingly.

ARTICLE INFORMATION

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