

Currents in Contemporary Ethics

For Asians Only? The Perils of Ancestry-Based Drug Prescribing

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The term “personalized medicine” increasingly has come to mean the use of genetic testing in prescribing pharmaceutical products.¹ The scientific basis of this approach to medicine is that, because of genetic variations, humans differ in their response to treatments. This observation is the cornerstone of pharmacogenetics and pharmacogenomics.

Ethical problems sometimes arise when this principle is applied on a group basis. For example, if humans could be divided into two genetic groups, a group with genotype A and a group with genotype B, members of each group might respond differently to a particular drug. The group with genotype A might have an adverse reaction to a drug. The group with genotype B might have a therapeutic response to the drug. Personalized medicine focuses on ensuring that individuals likely to respond positively to a drug receive it, and individuals likely to respond negatively are not given the drug. Although often defined as a way of *individually* tailoring treatments, personalized medicine is better characterized as a way of tailoring treatments to groups of people with some shared genetic trait or traits. Hence, personalized medicine may be viewed as “subgroup medicine.”

A key question of subgroup medicine is to ask how should human subgroups be defined. The method of defining subgroups determines who is most likely to be tested for a genetic trait and therefore who receives or does not receive certain treatments. For example, if subgroups are defined based on height, a scientist might determine that people over six feet tall are more likely to have a certain allele, and that this allele determines

the response to a drug for a particular disorder. Thus, people over six feet tall would be more likely to receive a genetic test, and clinicians would use the test result to determine whether they should receive a particular drug. The result would be an increase in the “personalized” care for people over six feet tall. On the other hand, people under six feet tall with the same disease would not receive the genetic test and the opportunity for personalized medicine.

In a world of unlimited resources, everyone who needed a drug with pharmacogenetic information associated with it would receive the appropriate genetic test prior to being prescribed this drug. However, genetic testing of all people who might benefit from a drug raises cost concerns. In addition, recognition of phenotypic homogeneity (such as similar blood pressure measurements) often precedes scientific identification of the genetic basis of disease. Consequently, researchers often attempt to determine which subgroups of people are most likely to have certain known or presumed alleles. In the absence of genotypic information, subgroups may be defined based on a person’s physical or social environment, disease type, symptoms, and so on. The focus of this article is the use of ancestry for defining subgroups. Recently, ancestry has been used to identify a subgroup of people most likely to have a certain allele linked to an adverse drug response, and the FDA’s policy response to this scientific information raises serious concerns.

Overview of Unique Carbamazepine Labeling

On December 12, 2007, an FDA Alert was issued that modified the drug

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labeling for the anti-seizure medication carbamazepine by including genotype and ancestry as factors to consider when prescribing the drug.² The alert stated that potentially fatal skin reactions, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN), can be caused by carbamazepine therapy. SJS/TEN results in blisters that can be permanently disabling or lethal. The FDA Alert indicates that patients with the genetic marker HLA-B*1502 are more likely to have this reaction when taking carbamazepine.³ If the label simply made these statements, phy-

The FDA Alert also indicates that 10-15% of people from China, Thailand, Malaysia, Indonesia, the Phillipines, and Taiwan carry this gene variant, but no supporting research studies are provided.⁶ Also, the FDA Alert indicates that about 2-4% of South Asians and less than 1% of people in Japan in Korea have this allele, but no supporting research studies are provided for these statements either.⁷

The referenced studies used different approaches to determine ancestry (also labeled as “ethnicity” in one study) including: skin color, place of birth, and place of birth of the per-

son. In addition, the referenced studies are referenced. A more thoughtful alert would have recognized the limitations of these studies and stated that the prevalence of the allele in other populations of various ancestral backgrounds has yet to be determined.

The FDA Alert also states that patients with ancestry from areas in which the allele is present (presumably “broad areas of Asia”) should be screened before starting treatment. With these statements the FDA creates a new standard of care for physicians. Given this information, a physician must decide first if a patient needs carbamazepine, then determine if the patient is of Asian ancestry in calculating the risk of an adverse reaction and the need for a genetic test. It is unclear how the physician is to determine whether a patient has ancestry from broad areas of Asia. This problem arises whenever ancestry or other social categories are used in stratifying patients for subgroup medicine.

To date, biomedical researchers and physicians do not have a widely used test to determine if a person is of Asian ancestry or has ancestry from any other region. As a result, both researchers and physicians can only ask a patient and hope that the patient is right. With an increasingly mobile and admixed population, patients’ assumptions about their ancestry might not always be correct. The FDA’s new approach to drug labeling thus increases the responsibilities of patients, and with potentially serious consequences.

The FDA Alert further states that if an individual tests positive for the allele that he or she should not receive carbamazepine unless the “benefit clearly outweighs the risk of serious skin reactions.”⁹ The FDA provides no guidance on how to weigh these risks and benefits. In addition, the alert states that patients who have taken carbamazepine for a few months without having skin reactions are at low risk of these events taking place. Ninety percent of people are thought to react within the first few months, with 10% having reactions at a later point.¹⁰ The alert states that this low risk exists even for individuals who

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sicians prescribing carbamazepine would have to question whether an individual had this particular allele before prescribing the drug. This new information might lead physicians to order genetic testing for all patients prior to prescribing carbamazepine. Alternatively, they might decide to choose a different drug with similar therapeutic properties as carbamazepine without the need for genetic testing. However, the FDA Alert does not end with these statements. Instead, another layer of complexity is added to the algorithm used for prescribing carbamazepine.

The FDA Alert indicates that the genetic variant HLA-B*1502 occurs “almost exclusively” in patients with ancestry across “broad areas of Asia, including South Asian Indians.”⁴ This statement is based on a number of studies performed in patients labeled as Caucasian, French, German, ethnic Han Chinese residing in Taiwan or Hong Kong, and Chinese descendants.⁵ The studies also include three patients born in Vietnam, Cambodia, and Reunion Island, respectively, who were thought to have Asian ancestry.

son’s parents. In two of the studies, no clear method of determining ancestry was discussed. Contrary to the FDA Alert, these individuals were not from broad areas of Asia, but instead, a select group of Asian countries. In some cases, only one individual represented the population of the country, which is clearly insufficient to draw a conclusion about the frequency of the allele in that population. Further, the FDA Alert is not specific about the definition of Asia. In fact, a modern map of Asia includes a much larger region than these studies cover.⁸ A number of countries are not included in these studies, such as Russia, which makes up nearly half of Asia, Mongolia, Turkey, Saudi Arabia, and more. Hence, the statement that people from broad areas of Asia have this allele seems to lack support.

The FDA Alert also indicates that the allele is “largely absent in individuals not of Asian origin.” However, no studies are provided which assess the prevalence of this allele in other populations, except individuals labeled as Caucasian, French, and German. For example, no African popu-

are positive for the genetic marker and for patients of all ethnicities or genotypes, thereby contradicting, to some degree, the focus on people of Asian ancestry. The alert also states that SJS/TEN can occur even in people outside of the high-risk groups, so physicians should watch for symptoms regardless of whether a patient has the HLA-B*1502 allele. This statement seems to acknowledge the confusion caused by the focus on ancestry and provides a way for the FDA to recognize that risks exist for anyone taking the drug. Finally, the alert indicates that all of this information will be included in updated drug labeling for carbamazepine. Overall, the alert provides unacceptably vague and confusing guidance for physicians seeking to utilize this information to improve patient care and informing patients.

government-financed health care, including Medicaid and Medicare, are likely to have greater cost concerns when considering genetic testing for which there is usually no reimbursement. Also, the question could arise as to whether these public programs would be engaging in race or national origin discrimination if they do not pay for genetic testing. Similarly, if private insurers do not pay for this test, they could be viewed as also discriminating against a socially defined group of individuals.

On the other hand, payers might conclude that it is cost-effective to pay for genetic testing for people who are at high risk in order to save money that would be spent treating patients with SJS/TEN. The availability of this test, especially for patients receiving public insurance, would likely be based on whether the prevention

Conclusion

The FDA's use of ancestry in labeling carbamazepine is analogous to the FDA's racially limited approval of the drug BiDil, which was labeled as being for African Americans only.¹¹ The BiDil approval turned out to be scientifically, ethically, and commercially problematic.¹² BiDil and carbamazepine demonstrate the need for a better approach than stratifying people based on self-identified or "researcher identified" ethnicity or ancestry.

The use of ancestry to stratify populations is appealing because it is easier and less costly than genotyping. Yet, such an approach requires two key factors: (1) a scientifically valid way of ascertaining ancestry, and (2) there must be definitive evidence of an association between a particular genotype and a certain ancestry. Over

The use of ancestry in the drug labeling creates potential safety problems for patients, cost concerns for patients and insurers, and potential stigmatization of a drug that has been used for years to treat complex neurological illnesses. Categorizing people for personalized medicine must be done, if at all, in a scientifically valid, sensitive, and ethical manner.

Cost Concerns

Because of the focus on people of Asian ancestry, the cost of care may increase for one subgroup of individuals but not others. Depending on the cost of genetic testing, individuals who are believed to have Asian ancestry will pay more to receive carbamazepine than individuals who do not think they have Asian ancestry. This increased cost for a particular group may lead to a number of problems. The test may be viewed as a method of making these patients pay more for their care, and thereby discriminating against the group. Such cost concerns could lead to disparities in who receives this drug – with people of Asian ancestry less likely to receive the drug in order to avoid the costs. These cost concerns may seem more daunting depending on whether insurers approve payment for the genetic test. In particular, individuals who receive

of harm cost less than dealing with the harm of SJS/TEN. Because SJS/TEN can be fatal, the benefits of prevention may be greater for those individuals most at risk. Thus, insurance companies would need to decide if genetic testing should be approved only for certain subgroups, because of the FDA labeling, or if testing should be approved for all people who need carbamazepine. These problems spring from the lack of a clear indication of the role of ancestry in allele frequency and the lack of a method of determining ancestry. Hence, a more scientific approach of classifying people with particular ancestral backgrounds would be useful for public and private insurers.

time, low-cost genetic testing will obviate the need to use ancestry as a low-cost surrogate for genotype. In the interim, scientifically defensible methods and definitions of ancestry need to be developed.

The inclusion of genetic information in the drug labeling of carbamazepine holds promise for individuals who have the HLA-B*1502 allele, which is linked to adverse reactions to this drug. However, the use of ancestry in the drug labeling creates potential safety problems for patients, cost concerns for patients and insurers, and potential stigmatization of a drug that has been used for years to treat complex neurological illnesses. Categorizing people for personalized medicine must be done, if at all, in a scientifically valid, sensitive, and ethical manner.

Acknowledgements

Dr. Payne has received research support from National Heart Lung and Blood Institute, National Institutes of Health, Grant No. K12HL090020-01

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