Individual Genomes Instead of Race for Personalized Medicine

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The cost of sequencing and genotyping is aggressively decreasing, enabling pervasive personalized genomic screening for drug reactions. Drug-metabolizing genes have been characterized sufficiently to enable practitioners to go beyond simplistic ethnic characterization and into the precisely targeted world of personal genomics. We examine six drug-metabolizing genes in J. Craig Venter and James Watson, two Caucasian men whose genomes were recently sequenced. Their genetic differences underscore the importance of personalized genomics over a race-based approach to medicine. To attain truly personalized medicine, the scientific community must aim to elucidate the genetic and environmental factors that contribute to drug reactions and not be satisfied with a simple race-based approach.

In the United States, there are more than two million cases of adverse drug reactions (ADRs) per year, and approximately 100,000 of these result in death.¹ Contributing to ADRs is the variation in genes that encode drug transporters and drug-metabolizing enzymes that can determine a drug’s efficacy and toxicity. Warfarin provides an example of ADRs caused by the interaction between drug and gene products. In one case study, a patient with heart problems was prescribed warfarin.² Over the next 5 years, the man visited the hospital at least 20 times to have his blood samples taken as his doctor tried to establish the correct dosage. During this time, besides the inconvenience, the patient was at risk for hemorrhaging. Finally, in year 4, his DNA was genotyped, and he was discovered to be a poor metabolizer based on the sequence of his CYP2C9 gene, which is involved in metabolizing warfarin. Soon thereafter, the patient’s dosage was stabilized.

Genes in the cytochrome P450 (CYP) family mediate more than 75% of the phase I–dependent metabolism of clinically used drugs.³ Furthermore, polymorphisms in the CYP genes have been responsible for a significant number of ADRs.³ Genetic variation in CYP genes and their differing allele frequencies in various ethnic groups have been extensively reviewed⁴ (see Figure 1 for examples). These differences might suggest that ethnicity/race could be considered in prescribing drugs, in what has been called race-based medicine.⁵ However, the CYP genes have been characterized to the extent that practitioners can now go beyond therapy on the basis of ethnicity into the precisely targeted arena of personalized genomics. Moreover, the costs of technological advances in personal genome sequencing are on an aggressive downward curve, enabling pervasive personalized genomic screening, for ADRs.

Given these trends, race/ethnicity should be considered only a makeshift solution for personalized genomics because it is too approximate; known differences may occur within a defined category. One example of such variability is provided by CYP2D6, which is involved in metabolizing codeine, antipsychotics, and antidepressants. The CYP2D6*17 form has moderately lower enzymatic activity than the wild type.⁴ However, different populations within Africa can have different frequencies for a variant. The *17 allele in CYP2D6 is found in 9%, 17%, and 34% of the Ethiopian, Tanzanian, and Zimbabwean populations, respectively.⁴ Clearly, lumping together all of Africa obscures the differences between the populations. The label “African” or “African-American” is therefore insufficient to determine whether an individual comes from a population with a high frequency of the *17 allele. Even if an individual is known to be, for example, Ethiopian rather than Zimbabwean, the ancestry is less relevant than the true genotype, which could be easily resolved with today’s technology.

Even the term “Caucasian” can be deceptive. If a self-identified Caucasian originates from a founder population in which certain disease-specific alleles occur at higher frequencies (e.g., Quebec French Canadians or Ashkenazi Jews), his or her doctor may miss an important aspect of the patient’s medical history. One’s ethnicity/race is, at best, a probabilistic guess at one’s true genetic makeup.

The recent advent of whole-genome genotyping and whole-genome sequencing of humans has opened up the

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possibility of personalized medicine—medicine based on many individual characteristics in addition to ethnicity/race.6 The genome sequences of J. Craig Venter—a coauthor of this Commentary—and James Watson are publicly available7,8 (Figure 2). Using this information, we extracted the sequence data for six CYP genes that play roles in metabolizing many drugs currently in clinical use3,4 (Figure 2). Although both men are self-identified Caucasians, their DNA sequences for these genes differ (Figure 2). For example, Dr. Venter has two fully functional alleles in CYP2D6 and is an extensive metabolizer, whereas Dr. Watson is homozygous for the *10 allele, which has moderately lower activity and is an intermediate metabolizer. This *10 allele is rare in the Caucasian population (3%) but prevalent in East Asian populations (see Table 3 in Xie et al.4). Yet Dr. Watson’s genotype predicts that he is likely to differentially metabolize drugs such as antidepressants, antipsychotics, and the cancer drug tamoxifen.9 This speaks to the value of knowing genomic sequence instead of relying on a patient’s appearance or self-identified ethnicity. It is unlikely that a doctor would guess that optimal drug dosages might differ for Drs. Watson and Venter without knowledge of their genetic data or extensive medical histories.

Because the costs of whole-genome sequencing and whole-genome genotyping are rapidly decreasing, the technology has become increasingly accessible. Companies such as Navigenics, 23andMe, and deCODE will genotype 600,000 to 1,000,000 markers in an effort to offer personalized genomics; several hundred dollars covers the cost of the technology.10 Before the launch of these three companies, more than 1,100 genetic tests were already available clinically, each test usually priced in the hundreds of dollars. A test for drug response, for example, is offered by DNA Direct. But Navigenics, 23andMe, deCODE, and other companies have propelled genetic testing into the spotlight, such that the average consumer has become aware of the promise of genetic testing.11 This will empower consumers to seek their own genotypes and incorporate this knowledge into their daily lives and interactions with their physicians. Just as it is valuable for a doctor to know that a patient’s medical history includes familial breast cancer, thus calling for vigilance for early cancer signs, a patient aware of his genotype could inform his doctor that he may be a poor drug metabolizer, which might guide the doctor in determining drug dosage and foreseeing possible ADRs. Considering that Americans take an average of 14.3 prescriptions per year,12 knowing the genetic makeup of our drug-metabolizing enzymes would be extremely valuable, as it would provide lifetime value in awareness of potentially fatal ADRs.

But will the promise of personalized medicine benefit all consumers in the United States, including those of an ethnic minority? Although it may seem contradictory, even though we find race-based medicine suboptimal, we strongly support recruitment of minorities in pharmacological studies. Because minorities have been under-represented in pharmacogenetic studies,13,14 the genetic variations observed at differing frequencies in minorities and their effects on drug metabolism have been under-studied. An analysis of drug labels mentioning race showed that a third of the studies found racial differences in drug response.13 However, 42% of the studies either did not carry out an assessment of differences between races or had insufficient numbers of subjects to enable such an assessment. Researchers whose studies have volunteers from different racial/ethnic groups are often unable to assess ethnic differences because of the small sample sizes of the ethnic groups represented.14 Therefore, we suggest that drug companies consider enrolling in their clinical trials equal numbers of volunteers from different races/ethnicities. This could ensure sample sizes large enough to assess racial/ethnic differences and would capture the genetic variation that occurs at higher frequencies in minority populations so that interactions between these variants and drugs can be studied. If there are no racial/ethnic differences in response to a particular drug, then the proportion that benefits would be the same for all individuals, regardless of race or ethnicity. If differences exist, then this type of study design would be better at detecting them.

Some studies that have included ethnic minorities have resulted in the development of race-based drugs.5 One such drug is BiDil, which targets African Americans with heart disease. Once a race-based drug has been developed, there is a possibility that a drug company may terminate its research and not pursue follow-up studies into the underlying cause. This could stunt medical care with race-based medicine, rather than personalized medicine.

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Figure 1 Four variants in CYP genes (CYP2C9*2, CYP2C9*3, CYP2C19*2, and CYP2C19*3) that show different allele frequencies among various ethnic groups. For each variant, its frequencies in the African-American (Af), Asian (As)/Chinese (Ch), and Caucasian (Ca) populations are shown. The nomenclature for a CYP variant is the gene name followed by the allele, which is indicated by an asterisk; for example, CYP2C9*2 is the *2 allele in the CYP2C9 gene. The frequencies for these variants and additional variants can be found in the article by Xie et al.4
is voluntarily financing a study to investigate the genetic basis for the response to the drug.\textsuperscript{15} It is unknown, however, whether companies with race-based drugs will typically pursue such follow-up studies. Howard McLeod, director of the UNC Institute for Pharmacogenomics and Individualized Therapy, recommends that the FDA establish regulatory requirements for the subsequent identification of biomarkers for race-based drugs.\textsuperscript{15} Identification of biomarkers would likely “expand the market, as it would remove race requirements for accessing the medicine. This will make the drug available to more people.”\textsuperscript{15} If genetics is the underlying cause of the ethnic differences in drug response, then finding the loci benefits all individuals who have the appropriate genotype, regardless of their race or ethnicity.

This assumes the simplistic case in which a particular genotype clearly benefits from a drug. However, there are also complex cases in which a variant does not act in the expected manner for a particular ethnic group, e.g., CYP2C9*3 (ref. 4). Although these complications may be due to other genetic differences, cultural factors such as diet and environment can also influence drug response. For example, the higher incidence of hypertension in African Americans has been linked to darker skin color, but this may be due instead to socioeconomic status and higher levels of stress rather than to genetics.\textsuperscript{5} Knowing that socioeconomic status is related to hypertension allows us to identify individuals at risk regardless of race. Given the complex nature of drug responses, it would ultimately better serve all to dissect the relevant factors of a drug response instead of categorically stereotyping a culture with a presumed genetic background. A clear picture of the contributions of genetics, medication, diet, exercise, and environment will help society attain truly personalized medicine.

Because the cost of genotyping and sequencing has decreased dramatically in the past few years, we no longer need to guess the genetic makeup of an individual. With current technology we can definitively determine a million genotypes for an individual in a matter of days, and this will only improve as technology advances. Revisiting the patient on warfarin who was a poor metabolizer, we have no idea what color his skin was, and it does not matter—it was his genotype that ultimately mattered.

\section*{CONFLICT OF INTEREST}

The authors declared no conflict of interest.

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9. Ingelman-Sundberg, M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J. 5, 6–13 (2005).

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What’s Needed for Personalized Therapy in Smoking Cessation

RS Epstein

It has long been known that smoking cessation is one of the most cost-effective public health opportunities available. The fact that some 22% of Americans smoke, despite overwhelming evidence of the consequences, reflects in part the addictive aspects of smoking and the generally modest effectiveness of various strategies for quitting. Although one of the US Department of Health and Human Services goals for the year 2010 is universal coverage of smoking-cession agents, only about a third of payers currently cover the cost of such agents. A major disincentive is that the return on investment has been modeled to take at least 5 years to reach the break-even point, given the cost of the individual agents, the high recidivism rates, the timeline for influencing outcomes, and the relative ineffectiveness of studied agents in broad or untargeted populations. The article by Patterson et al. in this issue intriguingly suggests that there might be a way to use smokers’ phenotypes to determine before treatment initiation which smokers will respond to which therapy. This approach could greatly improve the overall effectiveness of smoking-cession agents and generate cost savings that might in turn have the effect of influencing more payers to cover these agents.

The promise of personalized medicine for smoking cessation

As the article by Patterson et al. suggests, patients and clinicians may gain important benefits from a priori testing. If a smoker learns that a particular therapy has a higher probability of leading him or her to success than previously tried methods, that knowledge could provide the impetus to improve compliance and hence the “self-efficacy” of the treatment. In other words, a smoker may comply better with a treatment chosen on the basis of his or her own makeup rather than on generalized statistics on abstinence, recall of previous personal attempts, or hearsay from friends or family. Indeed, many studies in the smoking-cession literature imply that factors driving self-efficacy influence quit rates; certainly when smokers know that a particular drug has a higher probability of success for them personally based on their own genotype, they may benefit even further from the psychological aid provided by that knowledge. Clinicians may likewise embrace the use of these types of tests, in that they want what is best for their patients. Of course, if the person fails to quit smoking despite individualized therapy, it could be de-motivating.

Personalized or more targeted medicine may also improve the return-on-investment equation that payers use to determine whether they will cover smoking-cession agents. Tighter precision of benefit designs is facilitated by therapeutic approaches that can target specific individuals according to their genetic predisposition for response. This would potentially improve the actuarial analyses on which payers base their decisions on whether to cover the cost of smoking-cession agents. However, a benefit program that would cover these agents would also need to cover the cost of the test—in this case the nicotine metabolism ratio (NMR) test—and coverage for specific agents would be tied to the results of the test. By so doing, and following the article by Patterson et al., perhaps then only a quarter of smokers would be eligible for buproprion coverage, whereas others (e.g., those with low NMRs) would potentially become