The Use of Race in Medicine as a Proxy for Genetic Differences

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Race is a prominent category in medicine. Epidemiologists describe how rates of morbidity and mortality vary with race, and doctors consider the race of their patients when deciding whether to test them for sickle-cell anemia or what drug to use to treat their hypertension. At the same time, critics of racial classification say that race is not real but only an illusion or that race is scientifically meaningless. In this paper, I explain how race is used in medicine as a proxy for genes that encode drug metabolizing enzymes and how a proper understanding of race calls into doubt the practice of treating race as a marker of any medically relevant genetic trait.

1. Introduction. Race is a prominent category in medicine. Epidemiologists describe how rates of morbidity and mortality vary with race, and doctors consider the race of their patients when deciding whether to test them for sickle-cell anemia or what drug to use to treat their hypertension. At the same time, critics of racial classification say that race is not real but only an illusion or that race is scientifically meaningless. In this paper, I explain how race is used in medicine as a proxy for genes that encode drug metabolizing enzymes and how a proper understanding of race calls into doubt the practice of treating race as a marker of any medically relevant genetic trait.

2. Race as a Category in Epidemiology. Most health statistics in the U.S. are stratified by race. Data on morbidity and morality are routinely collected by race; epidemiologists routinely use race as a control variable in their search for risk factors and typically find that race is a good indicator of the risks of death and disease in the United States (Jones et al. 1991). The rates of many diseases, including major infectious diseases, many cancers,

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diabetes, asthma and strokes are different between the races (Fein 1995). Heart failure is more common among blacks than whites and symptoms of heart disease develop at an earlier age and progress more rapidly among blacks (American Heart Association 2001). Blacks in the U.S. are seven times more likely to die of tuberculosis than whites and three times more likely to die of HIV/AIDS (Cooper 1993). In short, with a few exceptions, people classified as "black" have a poorer health profile than those classified as "white." So, race, in the view of most epidemiologists, is an important category (Cooper and Cooper 1986).

For many years, race was taken to be biological race. People believed that there are biological races and that blacks and whites were divided by genes much as males and females are divided by a Y chromosome. The biological conception that prevailed until recently included the following three tenets: (A) a conjunction of physical characteristics divide the races, (B) these characteristics are heritable and express genetic differences between the races, and (C) the genetic differences are concordant and result from differences in descent—that, at some point, the races were reproductively isolated, differences developed, and the differences have been inherited.

Today, most biologists oppose all three tenets. They allow that biological differences between populations customarily sorted as separate races are at best statistical; the populations, if biologically different at all, are differentiated only by average frequencies of a few polymorphic genes (Cavalli-Sforza et al. 1994). In addition, the differences are not concordant; the differences between populations with respect to one gene vary independently of any differences in another, and, as a result, there is no cluster of genes possessed by all and only individuals customarily sorted at some site as members of the same racial group.

Biological race assumes that our customary races—the people we customarily classify as black or white—are divided by genes or heritable traits, but most biologists now understand that no cluster of genes or heritable traits divide them. Though there are heritable differences between us, they do not cluster and do not pick out the classes we call "races." So, for example, we differ in skin color, and these differences are heritable, but skin color is inherited independently of other traits like blood type or eye color. Moreover, differences in color are continuous rather than sharp and vary as much within as between racial groups, and differences in skin color divide us into subgroups that cut across rather than match the groups we call races (Jones 1981).

The fact that there are no biological races is contingent, for the mechanisms of inheritance and selection could have divided our species into biologically significant varieties or subspecies. Had our natural histories between different, we might have been more different than we are. Nature

has a recipe for making races but ignored it. The recipe is this: First, isolate a breeding population. Second, wait for some distinctive heritable characteristics to appear. Third, give their conjunction a selective advantage. And fourth, let selection operate for a very long time, but be sure to keep the population isolated. However, human evolution did not proceed according to such a recipe. Human populations, according to our best evidence, have not been geographically isolated for long enough periods of time; during all of natural history, there has been too much breeding between populations to give us biological races.

What are we to conclude from the fact that there are no biological races? Some people conclude that there are no races, that race is a myth or an illusion. But racial divisions can be biologically salient even if they are not themselves based in biology. Marital status and occupation are not illusions, but there is nothing in human biology that places an individual in any of these categories either. Genes do not make us married or single, but the generalization that, in the U.S. today, single men are more likely to die of heart disease than married men is not only meaningful but true.

Race is like marital status; no one would be married or single had we not invented matrimony; however, given that we did, we now divide ourselves along discernible boundaries, into categories like "husband" and "wife" or "single" and "divorced" and treat each other differently depending on which of these categories we belong to. So too with race; we assign each other a race and treat each other differently depending on that race. As a result, epidemiologists can discover that the rates of mortality or morbidity are different for one race than another even though race is not biological just as they can discover that health risks vary with marital status even though marital status is not in our genes. In other words, race can be a biologically salient category even though there are no biological races, and race can mark the risk of a biological condition like diabetes or heart disease even though race is not itself a biological condition but a social status.

3. Race as a Proxy. While epidemiologists use race as a population variable in their studies of differences in morbidity and mortality, doctors sometimes use race as an individual variable, as a way to classify an individual patient. Doctors use race as an individual variable, for example, when they use race as a proxy for an individual patient's response to a medical treatment or as a proxy for a gene.

One variable X is used as a proxy for another Y when X is used in the place of Y to make a particular decision about an individual. Let Y be a variable that is material to an interest I but that cannot be directly measured, and X a variable that can be directly measured but is not material to I but correlates with Y. In that case, X is a proxy for Y if X is

used instead of Y in making a decision about the individual in order to further I.

SAT scores, for example, are used as a proxy for first-semester college grades when admissions officers choose between applicants based on the scores; race is used as proxy for performance when employers practice what economists call "statistical discrimination" and use race to choose between applicants when deciding who to hire for a job, and race is used as a proxy in law enforcement when police officers base a traffic stop on the race of a motorist. To use race as a proxy, in any of these circumstances, is to engage in what has come to be called "racial profiling."

When doctors use race as a proxy for a medical trait, they engage in racial profiling too, but there is an important difference between the medical and law enforcement use of race, for, in medicine, there is good evidence that race correlates with a disease, while, in law enforcement, the evidence that race correlates with crime is poor. As a result, many doctors believe that racial profiling in medicine is reasonable and fair, even if racial profiling in law enforcement is not. They reason that if it is legitimate for an epidemiologist to stratify a population by race when explaining differences in disease rates within the population, then it should be legitimate for doctors to divide their patients by race as well when deciding how best to treat them.

There is, however, an important difference between using race as an individual and using race as a population variable. The use of race to screen individuals for sickle-cell anemia illustrates the difference. Sickle-cell anemia is a recessive genetic disease and is much more common in blacks than whites or Asians in the United States; so common among blacks and rare among whites that for many years sickle-cell anemia has been called a black disease.[1] During most of the nineteenth and much of the twentieth century many physicians were so convinced that sickling is a black disease and the sickle-cell gene a black gene that they refused to diagnose the disease in white patients or reasoned that apparently white patients with the disease are black (Tapper 1999).

But the doctors were mistaken, and whites with origins in the malarial regions of Europe are more likely to carry the gene than blacks from re-

1. Sickling is an inherited hemoglobin disorder and the result of a single recessive gene; individuals who are heterozygous for the gene have the trait, while only individuals who are homozygous have the disease. The frequencies of the allele for the trait are high in central Africa as well as southern India and Italy, since exposure to malaria is high in these regions and the sickle trait confers resistance to the malarial parasite. A larger proportion of blacks than whites or Asians in the United States have the sickle-cell trait due to the larger proportion of American blacks from central Africa than the proportion of American whites from southern Italy or American Asians from southern India.

gions of Africa in which the risk of malaria is slight. Since the proportion of blacks in the United States from a malarial region of Africa is larger than the proportion of whites from a malarial region of Europe, the incidence of sickle-cell anemia is greater among blacks than whites here in the United States.

Though both blacks and whites carry the sickle-cell gene, when tests developed to identify carriers of the gene, many states in the United States targeted blacks for screening because health officials continued to treat the sickle gene as a black gene and used race as a proxy for the disease. In 1972, Kentucky, for example, enacted a statute requiring blacks applying for a marriage license to undergo a blood test to determine whether they were carriers of the gene, but no such test was required of whites even though, by the 1970s, sickle-cell disease was understood to occur in both blacks and whites; screeners, in other words, continued to target blacks, while whites, no matter what their origins, were typically ignored.

Though race is still used in the United States as a proxy for sickle-cell anemia, there are good reasons not to. First, race over-predicts the sickle-cell trait in blacks and under-predicts the trait in whites, since the intra-racial differences in the frequency of the allele are high. That is, many blacks who are not carriers will be marked as carriers, if race is used as a proxy, and many whites who are carriers will not be marked.

Second, to use race as a proxy for a genetic trait encourages the belief that race is a genetic category, for many people assume that if a disease is genetic and its incidence is much higher in one race than another, then race must be a genetic. As a result, using race as a proxy for the sickle-cell trait or disease helps to sustain the assumption that people of different races differ in their genetic makeup and that there are more genetic differences between than among blacks and whites in the U.S.

Third, to use race as a proxy for a genetic trait distributes the risk of genetic discrimination unequally between blacks and whites. Firms unable to practice racial discrimination, because of the civil rights laws, are able to use the results of the sickle-cell test to deny blacks employment. If blacks are targeted for testing and individuals who test positive are denied jobs, then blacks are at greater risks than whites of suffering genetic discrimination. In other words, race-conscious screening has a disparate impact on blacks in employment, whenever an employer has access to genetic information about job applicants.

4. Racial Profiling in the Clinic. Race has been used by doctors as a proxy for diseases but also as a proxy for a patient's response to treatment, for blacks and whites respond differently to a number of drugs widely used to treat a number of common illnesses. According to some recent studies, while blacks and whites with congestive heart disease respond the same to

beta blockers they respond differently to angiotensin-converting-enzyme (ACE) inhibitors (Exner et al. 2001).[2]

Doctors use race as a proxy for a response to these drugs when they target their black patients for beta-blockers and reserve ACE inhibitors for their white ones. Response to the heart drug is the material trait and race the proxy. Doctors do not know how an individual patient will respond to each of the different heart drugs, but they know or think they know a patient's race, and given the correlation between drug response and race, they predict that the black patient will respond better to the one drug than the other.

However, to use a patient's race to predict his response to a medical treatment is problematic for the same reasons that the use of race as a proxy of sickle disease is problematic. First, to target blacks for one drug ignores the intraracial differences in drug response, and adversely affects black patients for whom the "white" drug would be a more effective treatment. That is, even if, as the studies seem to show, blacks respond better to one drug than another, a significant number of blacks respond equally well to both or better to the "white drug." Thus, treating all black patients the same, offering them all the "black drug" denies some blacks a better or equally effective treatment.[3]

Second, targeting blacks assumes that race is a better predictor than any environmental factor or a better predictor than a patient's family history of a response to either of the drugs, but the assumption is not reasonable since the rate at which a drug is metabolized varies as a result of many factors, age, environment and lifestyle as well as genes. The studies that showed a racial difference in the response did not control for differences between the black and white patients in SES or other factors that are known to influence drug metabolism.[4] As a result, they offered no good evidence that the differences in response are due to race rather than to a third factor that varies with drug response and race. If differences in SES or lifestyle explain most of the variances between the black and white patients in response to a heart

2. Data on race in the study was obtained from an eligibility form in which participants identified themselves as American Indian, Asian, black, white, Hispanic or "other." Participants who identified themselves as black or white where the comparison groups for the analysis.

3. According to the Exner study (Exner et al. 2001), 14 percent of black patients benefited from the ACE inhibitor compared with 49 percent of white patients. Thus, denying the drug to all black patients denies 14 percent of these patients a drug that is likely to be an effective treatment for their disease.

4. Black and white patients in the Exner study were matched according to certain prognostic variables, e.g., sex, age, and left ventricular ejection fraction, but not according to SES, or measures of lifestyle.

drug, it would be more reasonable for a doctor to use these as a proxy for the response than race.

Third, even if the difference in drug response was due to a genetic difference between the two populations, there is no reason to treat race as an independent variable that explains the difference, since the genes controlling drug response vary independently of race. Were the populations identified by sex rather than race, on the other hand, there could be a reason to treat sex as a variable that explains the genetic difference in drug response between the populations, since the gene that controls the response could be located on a sex chromosome. That is, while there are no race genes, there are sex genes, and, as a result, sex is a legitimate explanatory variable when explaining genetic differences between populations, while race is not.

Fourth, the inference from an individual's race to his response to a treatment substitutes race for ancestry (for whether the individual has family in a region in which the incidence of the allele is high). The use of race as a proxy is based on a population-genetic approach to differences in response. The population approach identifies populations whose gene frequencies are to be compared and uses genetic technologies to discover whether the incidence of the alleles is different between the populations. Race enters in when the populations are identified by race.

However, because there is so much genetic variation within any one racial group, race is a poor way to identify populations for genetic comparison. The human groups that are called different races are not distinct lineages. Genetic differences do exist between human populations in drug response, but the existing racial categories do not capture these differences very well. Ancestry captures the differences better, since there is less genetic variation within groups identified by common genetic ancestry than groups identified by race.

Fifth, there is no reason to believe that when a doctor assigns a race to her patients, her assignments match the assignments of race on which the studies of drug response relied. Those studies relied on self reports; the subjects were assigned the race that they assigned themselves when asked. But there is considerable evidence that self-identification is not a reliable indicator of race; for how individuals report their race varies with who is asking and the choices a person is given (Harris 2000). Individuals with mixed parents, for example, are likely to describe themselves as mixed race or multiracial if given the option, but as black or white if they are not. The subjects in the drug study were not given a mixed-race option, and had they been, the results of the study might have been different. In addition, there is evidence that the assignments of race to patients by doctors is not reliable, for different doctors often assign a different race to the same patient or assign her a race different from the race she assigns herself. As a

result, there is reason to doubt that a doctor does know her patient's race better than she knows the patient's response to a heart drug.

When doctors use a patient's race as a proxy for her response to a drug, they employ a particular form of statistical inference and reason as follows: (1) a high percentage of blacks with heart disease do not respond as well to ACE inhibitors as they do to beta-blockers; (2) this patient is black and has heart disease; thus, (3) this patient is likely to respond better to a beta-blocker than to an ACE inhibitor.

The inference is reasonable only if (1) and (2) include the best available evidence relevant to whether the patient will respond better to the one drug than the other. That is, (3) should be judged on an evidential base that includes the best available evidence, for the credence which it is rational to give a statement at a time is determined by the degree of confirmation that the statement possesses on the best evidence available at the time (Hempel 1965).

The issue is not whether a patient's race should be the only trait by which to decide between alternative treatments, but whether race should be used at all. Most doctors take a patient's age, environment, and lifestyle, as well as his race into account in choosing between heart medications. That is, if they infer (3), they do not rely on (1) and (2) alone. The question is whether a doctor should allow race to enter into the decision at all.

To be fair to a patient, a doctor needs to treat him as an individual rather than as a representative of a racial group, and if the doctor is to treat him as a representative of any group at all, the group should not be identified by race if race masks a population-level variable that bears more directly on the medically relevant trait. When a doctor uses race as a proxy for a treatment response when ancestry is more significant, she is like an admissions officer who uses race as a proxy for college performance when she could use high school rank or SAT scores. In neither case is the use of race fair to the individual.

Proxies are only useful when we lack direct access to the material trait. A college does not need to use SAT scores or high school rank to infer a student's college grades if it has access to the student's college transcript. Doctors, given advances in genetic technology, may soon have access to a patient's genetic transcript. Should she have his transcript, the doctor will not need to infer from his race or even his ancestry whether he is genetically disposed to respond better to a beta-blocker than an ACE inhibitor.

However, even when the technology is available, doctors will have access to some but not all patients' genetic profiles, for patients will not have equal access to this technology anymore than they do to present-day healthcare. For patients who are not able to afford or who refuse the genetic tests, proxies will continue to have a use in diagnosis and treatment,

but race should not be used as a proxy since genetic ancestry has more predictive power and, unlike race, does not require doctors to draw a color line or decide which of their patients are black and which are white.

5. The Case for Profiling. Supporters of racial profiling in medicine usually offer one of the following two defenses of the practice. First, they remind us that not many years ago we objected to drug research that tested the safety or efficacy of a drug, especially heart drugs, on white males and applied the findings to blacks and females. In response to these objections, doctors began to look for differences in drug response between the races and sexes and, finding differences, began to discriminate between their patients based on their sex or race. As a result, profiling is an enlightened and salutary response to the doctors' past indifference to differences.

This argument overlooks the differences between the categories of race and sex. A gene X that regulates drug metabolism can vary with a gene Y on a sex chromosome, but there is no race chromosome or race gene Y for X to vary with. As a result, doctors have a reason to study sex differences but not racial differences in drug response and a reason to use sex but not race as a proxy for response when deciding how best to treat an individual patient. Sex has more explanatory and predictive power in the clinic because there are genes for sex and good reasons to believe that the genes for sex and some genes for drug metabolism are concordant.

The second argument in support of race as a proxy in the clinic is based on the utility of dividing patients by race. Doctors should choose one treatment T1 over another T2 for a patient p if the expected utility for p of T1 is greater than the expected utility of T2 for p. If T1 can be expected to be a more effective treatment for p than T2 when p is black, then it is reasonable for a doctor to choose T1 over T2 when p is black. In short, given a correlation between race and drug response, for a doctor to ignore a patient's race in choosing between T1 and T2 would be for her to base her expectations of treatment outcomes on less than the best available evidence and to choose a treatment with a lower- over a treatment with a higher-expected utility for the patient.

This argument assumes that the statistics on race and response are the only available or the best available statistics on differences in treatment response, and, as I have argued, statistics on ancestry or family history are better. But what if the better statistics are not available? Doctors in the U.S. study how response varies with race rather than with family history, and as a result, a doctor might know that a beta-blocker is more likely to be effective with a black patient than an ACE inhibitor but not that the ACE inhibitor is more likely to be effective with a patient with family in Senegal than one with family in Burundi. Statistical inferences are reasonable if

based on the best available evidence, and the evidence available to doctor is limited by the variables used in randomized drug trials, and if race is used as a variable and ancestry is not, racial statistics can be the best statistics available to the doctor.

But what counts as available? If there are no statistics on how response varies with ancestry because no one looks beyond race, then the best evidence is not available to doctors to use in deciding how best to treat their patients, but the evidence should be. Doctors who ignore a patient's medical history have less relevant evidence on how he will respond to a treatment than doctors who study his history; but doctors should study the history and make the historical evidence available. The best available evidence should include evidence that would be available had doctors done what they ought to do.

The argument from utility also suffers from a too-narrow notion of utility. Doctors in the clinic, according to many books on medical ethics, should focus on the well-being of the patient and not the well-being of others who might be affected by a choice of treatment. The doctor is to consider the costs to each patient of dividing her patients by race and not the cost to black or whites as a group. But even if the doctor should only consider the cost to an individual patient or only attempt to maximize the patient's expected utility when choosing a treatment and not the expected utility of blacks as a group, the issue of whether race should be used in medicine as a proxy is a question of policy and not what, in the absence of policy, a doctor should decide to do.

When we turn to policy, social utility, rather the cost or benefits for an individual patient, becomes a reasonable or legitimate concern. Even if an individual patient is better off if his doctor is conscious of his race than if she is blind to his race, the practice of race-conscious medicine is likely to leave blacks less well off as a group, for the practice will reinforce current divisions between blacks and whites in healthcare, education, and employment, and the current divisions are to the advantage of whites and to the disadvantage of blacks as a group. In considering healthcare policy what matters is social welfare, and race-conscious has less expected social utility than race-blind medicine in today's racial climate in America.

6. Conclusion. Race, I have argued, should not be used in medical practice as a proxy for a disease or for a response to a medical treatment. To stratify health statistics by race is reasonable, as long as employment, housing, income, education, or healthcare are stratified by race; but to use race as a proxy for a gene is bad science, because race and genes vary independently, and bad policy, because the practice helps to sustain a harmful racial ideology.

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