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# The Use of Race Variables in Genetic Studies of Complex Traits and the Goal of Reducing Health Disparities

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## *A Transdisciplinary Perspective*

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*The use of racial variables in genetic studies has become a matter of intense public debate, with implications for research design and translation into practice. Using research on smoking as a springboard, the authors examine the history of racial categories, current research practices, and arguments for and against using race variables in genetic analyses. The authors argue that the sociopolitical constructs appropriate for monitoring health disparities are not appropriate for use in genetic studies investigating the etiology of complex diseases. More powerful methods for addressing population structure exist, and race variables are unacceptable as gross proxies for numerous social/environmental factors that disproportionately affect minority populations. The authors conclude with recommendations for genetic researchers and policymakers, aimed at facilitating better science and producing new knowledge useful for reducing health disparities.*

**T**he ultimate aim of genetic research is to improve human health and prevent disease. Realizing the fruits of emerging genetic research in the form of concrete health improvements is a worthy goal and a difficult task, particularly with regard to complex traits. Although enormous progress has been made in identifying polymorphisms that appear to be important in the etiology of more than a thousand Mendelian disorders (Botstein & Risch, 2003), progress with respect to complex traits—defined by non-Mendelian inheritance patterns involving multiple gene–gene and gene–environment interactions, higher prevalence, and enormous public health burden—has been far more difficult. In most cases, the total contribution of identified polymorphisms accounts for only a small portion of individual variation in disease known to have a genetic component (e.g., cardiovascular disease, cancer, diabetes). Still, the pace of research is staggering,

and it is critical to proactively identify and address key ethical and policy concerns likely to arise in the process of translating genetic research on complex traits into improved health care.

Perhaps nowhere has the challenge of translating new knowledge into improved health been more evident than in addressing racial disparities in health and health outcomes. Although health services research has exhaustively documented racial and ethnic disparities in quality of care and health outcomes, little progress has been made in identifying the levers necessary to reduce the “disparities gap” (Bach, Hoangmai, Schrag, Tate, & Hargraves, 2004; Ep-

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stein, 2004). Much of this difficulty is due to the imprecise, conflated nature of the race constructs used in biomedical research, wherein administrative categories that have primarily social and political meanings are used unreflectively in the study of human disease and health care. A raging debate continues within the health services research and public health fields about the meaning and significance of race variables in biomedical research. There appears to be significant consensus that such variables stand as proxies for a vast array of social, environmental, and other factors (beyond racism *per se*) that are not measured directly but are often disproportionately distributed across racial and ethnic groups in the United States. Hence, the use of these gross social constructs in health services research and public health has increasingly come under fire. The use of such categories does allow researchers to measure and monitor racial disparities in health status, access, quality of care, and outcomes—the health consequences of systematic disadvantage—but does not provide sufficient nuance to inform efforts to address them. In other contexts, however, the use of self-identified, administrative racial/ethnic categories in biomedical research insidiously conflates the notion of race as a marker of membership in a social group often at risk for receiving inadequate health care or being disproportionately exposed to factors adversely affecting health with the notion that certain races inherently possess excess vulnerability to disease. A critical distinction, often missed, is the distinction between variables appropriate for monitoring the health impact of racial discrimination or systematic disadvantage and those appropriate to studies seeking to determine the underlying causal pathways of disease. As these debates continue, those committed to closing the disparities gap hold fast to documented racial disparities in both access to care and quality of care re-

ceived, as well as health outcomes, using such data in efforts to generate the moral and political traction needed to address such disparities.

This long-standing debate has become only more intense in the context of genetic research on complex traits, as patterns of human variation in the frequency of particular alleles hypothesized to play a role in vulnerability to disease or response to therapy are being identified at an increasing pace, and these differences are being framed predominantly in racial/ethnic terms. Administrative racial and ethnic categories, such as those specified (empirically and periodically modified) by the Office of Management and Budget (OMB; 1997) and used in the U.S. Census, are often imported into genetic studies as gross proxy measures to control for underlying differences in population structure. Not surprisingly, these variables, used in the absence of an adequate array of measures that directly control for the effect of multiple socioeconomic (e.g., stress, experiences of racism, education level, economic resources) and environmental (e.g., quality of housing, exposure to toxins) factors, are often statistically significant. Research results are then reported, framed in terms of significant racial differences in the frequency of certain putative genetic variants. Such research results can easily be misinterpreted to reinforce notions that certain minority groups are somehow constitutively inferior to other groups—typically the dominant “White” group—thus inadvertently engaging a long and problematic history of seeking to document biological superiority or inferiority of certain subpopulations of human beings. In the U.S. context, this obsession with racial comparisons has been expressed primarily in the context of Black–White differences across all disciplines (Institute of Medicine, 2003; Winston, 2004), rooted in historical attempts to justify slavery and the unequal treatment of African Americans in our society, although American Indians have been similarly distinguished from all others in the earliest categorization schemes.

Numerous recent articles and editorials have debated the use of race variables in genetic studies and the implications of such practices for research design, for how genetic research results are interpreted and understood, their meaning for clinical care, their utility for improving health, and their impact on broader societal concerns (Bhopal, 1997; Burchard et al., 2003; “Census, race and science,” 2000; Cooper, 2004; Cooper, Kaufman, & Ward, 2003; “Genes, drugs and race,” 2001; Haga & Venter, 2003; Kaplan & Bennett, 2003; Kaufman & Cooper, 2001; Krieger, Rowley, Herman, Avery, & Phillips, 1993; Lee, Mountain, & Koenig, 2001; Lerman et al., 2000; Osborne & Feit, 1992; Sankar & Cho, 2002; R. S. Schwartz, 2001; Stevens, 2003; Wood, 2001). Some social science critiques (Stevens, 2003) reflect a complete lack of appreciation of the methodological concerns underlying genetic researchers’ use of race variables and advocate for policies we believe most genetic researchers would find inappropriate and unacceptable (e.g., the establishment of an advisory board from whom researchers would need to get permission to publish in any form any “claims about genetics associated with variables of race, ethnicity, nationality, or



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any other category of population”); Stevens, 2003, p. 1075). Arguments forwarded by genetic researchers, on the other hand, sometimes ignore a long social history of destructive uses of racial categories in science and medicine by suggesting that “race” is an acceptable stand-in for geographical ancestry in genetic studies so long as one takes care that there is no “value system attached to any such findings” (Risch, Burchard, Ziv, & Tang, 2002, p. comment2007.11). Social history has definitively shown that any such value-free use of racial categories is an unobtainable fiction. We see a need for constructive interdisciplinary dialogue that both attends to potential social harms stemming from generating genetic research results framed in particular ways and does justice to the methodological concerns and concrete challenges faced by genetic researchers trying to do good science with limited resources.

In this article, we seek to provide a transdisciplinary assessment of these important concerns, using the specific details of emerging genetic research on smoking to ground our analysis. We are a multidisciplinary group of scholars from the fields of genetics, psychiatry, clinical psychology, history of science, anthropology, law, health services research, and health policy, and we are all members of the Georgetown Ethics Research Consortium on Smoking and Genetics. We focus on smoking not only because it is an enormously important public health concern (World Health Organization, 1997) but also because we have come to believe that the complexities of issues involved in the race/genetics debate are virtually impossible to address and resolve in the abstract and are far more likely to be elucidated in the concrete context of a particular line of genetic inquiry. Over the past three years, we have struggled as a group to understand and respond to a set of critically important methodological and social concerns regarding

the intersection of race and genetics from our various disciplinary perspectives. We have sought to identify research strategies that meet genetic researchers’ methodological concerns about potential bias due to ethnic admixture, while minimizing risk of unintended adverse social consequences associated with the racialized framing of genetic research results. It is offered in the spirit of stimulating discussion and debate about best practices in genetic research aimed at understanding the etiology of complex diseases, improving human health, and reducing health disparities.

We begin with a review of the ongoing debates regarding the intersection of genetic research and the social ramifications of racial categories, and we provide a historical context for these debates. Throughout this article, we use the term *African American* rather than *Black* to denote persons of African descent. Although different segments of the African American community have been shown to prefer various labels (Tucker et al., 1996), we use the more pervasive term African American to emphasize those who are descendants of African slaves within the U.S. context. We then turn to the specific case of smoking research, reviewing what is known about smoking in the United States from epidemiological and genetic perspectives, with a particular focus on population differences in smoking phenotypes, and critiquing the use of race variables in extant genetic studies of smoking behavior. We then consider arguments for and against the use of race variables in genetic studies of complex traits more generally. Finally, we offer concrete suggestions aimed at genetic researchers and policymakers as an initial contribution to an ongoing interdisciplinary dialogue.

### **Contested Categories: Ongoing Debates About the Use of Race Variables in Genetic Studies**

Although an important goal of the new genetics is individualized medicine, the nature of research aimed at understanding the role of genetics in disease etiology and treatment response simultaneously places people in new population categories, according to genetic status. These groupings of individuals by genetic status are often overlaid with administrative racial and ethnic categories, thereby reframing genetic epidemiological data in terms of differential frequencies of particular genetic variants across socially defined racial groups. While new advances in genetic research enable researchers to group individuals into new subpopulations according to more finely grained categorizations of sameness/difference at the biological level, the use of self-identified racial categories in genetic research has reinvigorated interdisciplinary debates regarding the definition, meaning, and validity of race as a construct in biomedical research.

In 1999, no less an authority than the Institute of Medicine (IOM; 1999) stated that race could no longer be considered a “biological reality” but was instead a “construct of human variability based on perceived differences in biology, physical appearance, and behavior” (p. 38).



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Although numerous social scientists and humanities scholars welcomed this statement as affirming their long-standing argument about the social construction of race, the real tensions residing in the concept of race could not be so easily dissolved by fiat. Indeed, within a matter of weeks, serious theoretical and methodological debates broke out in related research journals.

Numerous articles in the years following the IOM's statement, in both the scientific and popular press, commented on the continuing tension (Burchard et al., 2003; Cooper et al., 2003; Phimister, 2003; Risch et al., 2002; Sankar & Cho, 2002). A 2000 editorial in *Nature Genetics* ("Census, Race and Science") instituted a new policy requiring that "authors explain why they make use of particular ethnic groups or populations, and how classification was achieved," but nevertheless stated that "race can be a valid variable in scientific studies" since it might serve as a useful "proxy" for other factors such as dietary or environmental differences (p. 98). The *Journal of the American Medical Association* had previously adopted a similar position, stating that "researchers should be conscious of their purpose for collecting racial data," and distinguish between "race as a risk factor and race as a risk marker" (Osborne & Feit, 1992, pp. 275–276). While one commentary in the *New England Journal of Medicine* echoed the IOM's position that "race is a social construct" (R. S. Schwartz, 2001, p. 1392), a companion article stated that

Racial differences in the response to drugs not only have practical importance for the choice and dose of drugs but should also alert physicians to the important underlying genetic determinants of drug response. The logical extension of the studies reported in this issue of the *Journal* will be the identification of the genetic determinants of the reported racial differences, rather than attention to the external phenotypic manifestations of race. (Wood, 2001, p. 1395)

It was within this lack of consensus that Wilson and colleagues (2001) argued in *Nature Genetics* for a "race-neutral approach" to the study of population differences, using genetic markers to "cluster" individuals into populations on the basis of these "neutral" markers rather than into racial groups based on self-identified racial categories. An accompanying editorial provisionally endorsed this "race-neutral approach" as "an attractive alternative" to prevailing practices based on racial categories and went on to state that "the idea of replacing conventional ethnic labels with a defined genetic structure is worth pursuing, in that it moves us closer to the ultimate goal of 'individualized therapy'" ("Genes, drugs and race," 2001, p. 240). Others have argued instead that it is "scientifically appropriate" for researchers to "[identify] genetic differences between races and ethnic groups," with race here understood in terms of "geographical ancestry," not self-identified racial categories, so long as one takes care that there is no "value system attached to any such findings" (Risch et al., 2002, p. comment2007.11). A central problem has been a lack of distinction between self-identified race (i.e., the self-sorting of individuals into groupings according to the OMB racial/ethnic categories) versus racial groupings defined by population geneticists based on continental ancestry. Some have challenged this conflation (Cooper, 2004; Haga & Venter, 2003). Writing in *Science*, Haga and Venter (2003) argued that the "clustering of individuals according to continent of origin based on patterns of allelic frequency is not evidence for the existence of genetically defined races" (p. 466). "Rather than reifying race by perpetuating its use as a variable," Haga and Venter "encourage the practice of individualized medicine by incorporating new knowledge of disease and drug response, genomic and otherwise" (p. 466).

But because individualized medicine is still in the future, there remains what Elizabeth Phimister (2003) described in a recent article in the *New England Journal of Medicine* as the problem of what to do "in the meantime." In the face of incomplete knowledge of the role of genetic factors in common disease and experience of genetic variants associated with monogenic disorders more prevalent in some subpopulations than in others, many have argued that it seems unwise to abandon the practice of recording race at this time (Phimister, 2003). As genetic and biomedical researchers work toward resolution of these methodological and social concerns, it is important to recognize that current debates about the use and meaning of racial categories both reflect and have been shaped by historical practices and controversies within the disciplines of anthropology, biology, and medicine—and cannot be satisfactorily resolved without attending to these historical antecedents.

## **Problematizing Race: Historical Antecedents of the Current Debate**

Debates regarding the conceptualization and meaning of racial categories are not new. The crucial questions—What is race? What are the causes and nature of racial differences



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in disease? To what extent are the current designations used by the OMB adequate, appropriate, or valid to use in analyzing genetic diversity within and between contemporary racially designated groups in the United States? Is race a useful or valid biological variable at the genetic level?—have been answered variously by practitioners in anthropology, genetics, epidemiology, medicine, and other social sciences in the United States since at least the late 19th century. Indeed, many of the current tensions across disciplines are rooted in historical beliefs and practices that differ widely across these same disciplines. We therefore believe that the current debate among genetic, biomedical, and health services researchers cannot be rigorously or successfully addressed without some appreciation of the historical meanings and uses of race. Although a review of the long history of the use of concepts of race in biology, anthropology, and medicine in the United States cannot be addressed in this article, we do suggest that important tensions in current debates can be traced to early 20th century uses of race in these fields.

By 1900, the historian of anthropology George Stocking Jr. noted that there was no generally accepted answer to the question “What is race?” The term *race* was a catchall applied to various human groups, nations, continental regions, language groups, and perceived body traits of peoples whose similar appearance, manner, and speech persisted over time and was therefore self-evidently viewed as hereditary. In the absence of the theory that Mendelism would later provide, all group differences were plausibly, popularly, and scientifically viewed as heritable. In that sense, race was thought of as “accumulated cultural differences carried somehow in the blood” (Stocking, 1994, p. 2).

Historians have argued that physicians were the single most important group involved in biologizing racial cate-

gories. Physicians’ comparisons of disease differences between Whites and African Americans (*Negroes* in their usage) simply assumed that there were innate biological, mental, and physiological causes underlying any such differences. It was widely assumed that the cause of such differences was “racial” and no further exploration or explanation was needed (Haller, 1980). Differences in mortality and morbidity for diverse diseases were seen simply as manifestations of different racial capacities. By 1900, biologists, anthropologists, and physicians viewed race as an “integrated physical, linguistic, and cultural totality” (Stocking, 1994, p. 10).

Anthropologists, led by Franz Boas and his students, began to challenge this view of race beginning in the late 1890s. Eschewing evolutionary typologies in favor of historical and field-based data, Boas and his students distinguished among race, language, and culture, further arguing that any biological meaning ascribed to “race” was nevertheless thoroughly open to social influence (Smedley, 1999). A few decades later, Gunnar Myrdal (1944) would be imported from Sweden to codify this controversial Boasian position, whittling race down to a minimal physical and maximal social size, and labeling the problem *An American Dilemma*. In the postwar shadow of the Holocaust, social scientific acceptance of race as an obvious categorical system was subjected to widespread scrutiny (Keller, 1992), and the majority of anthropologists generally came to see the term as a pejorative legacy from less politically enlightened times (Haraway, 1995; Livingstone, 1964; Washburn, 1964).

Throughout the 20th century, anthropologists increasingly saw race in cultural terms and argued that the biological aspects of race—hair type, skin color, shape of the nose or eyes, and other anatomical differences—were superficial differences far less important than the cultural differences among human groups (Pascoe, 1996). Over the same period, biologists remained convinced that human races existed and that they differed hereditarily in both mental and physical traits (Provine, 1986). Yet biologists and anthropologists could agree that the project of racial classification was fraught with methodological problems, with no agreement on any standard number of racial “groups” or nomenclature to categorize the races of the world (Lewontin, 1995).

### ***The New Biology of Race***

Biologists turned away from the “old classificatory biology of race with its roots in anatomy and morphology, in the post-World War II period, to a new evolutionary biology of man with its roots in genetics, ecology and evolution” (Stepan, 1982, pp. 173–174). As a result, biologists moved from concepts of “race as a type” (a static entity) to “race as a population” (groups constantly changing in their genetic composition because of the evolutionary forces of drift, migration, and selection; Stepan, 1982, p. 176). Yet, this move toward viewing race as a populational concept rather than a typological one also bore the traces of the earlier view. Race was still thought of by many population geneticists as a biological phenomenon and in many cases



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still used as if a population was a type. As a founder of the field of population genetics, Theodosius Dobzhansky, noted in 1968:

The inhabitants of different parts of the world are often visibly different, and the differences are in part genetic. This, in a nutshell, is the essence of race as a biological phenomenon . . . race differences are genetic differences between Mendelian populations, not between persons. And yet races differ in the same traits in which persons also differ. Difficulties arise when a race or any group is given a name, one is likely to assume that the individuals composing the group are all alike or at least very similar. This is typological thinking, [which] befuddles not only the man in the street but some scientists as well. (p. 78)

Although few biologists after 1950 claimed to be typologists in their use of race, the tendency to treat genetic populations in typological terms remained a persistent problem (Gannett, 2001). One cannot glean from the writings of population geneticists in the 1950s and 1960s the antecedents of the view that race was understood to be a social construct or that in biology there are no races (Gannett, 2001). For the most part, race was redefined in this period to mean a specific kind of population, specifically “Mendelian populations which differ in the frequencies of genes for certain morphological and physiological traits” (Gannett, 2001, p. S484). The shift from *race* to *population* thus made the use of the term *race* redundant for many population geneticists, which led to a decline in its use in many but not all human genetic fields. But definitional and methodological problems arose when the populations chosen by genetics researchers were meshed through analysis with groups other researchers still referred to as races. Thus emerged one of the contemporary questions fueling debate today: To what extent are populations as defined by genet-

icists the same as the groups called races in the United States (Feldman, Lewontin, & King, 2003)?

### **Medicine and Public Health**

These emerging tensions within population genetics were fuelled by the dearth of discussion in medicine, epidemiology, and public health regarding the definition and use of race over the same period of time (Cooper & David, 1986; Krieger et al., 1993; Lillie-Blanton & LaVeist, 1996). Medicine’s overwhelming focus continued to be comparisons of disease differences between self-identified White Americans and African Americans, and as such, questions about the definition of race itself were ignored. Researchers such as Jones, LaVeist, and Lillie-Blanton (1991), Williams (1994), and Oppenheimer (2001) confirmed that from the early 1900s until 1990, race had no standard definition in medical, epidemiological, or health services research (Jones et al., 1991; Krieger et al., 1993; Oppenheimer, 2001; Williams, 1994). In epidemiology, race referred to “persons who are relatively homogenous with respect to biologic inheritance” (Jones et al., 1991, p. 1,079). Williams’s (1997) survey of medical and epidemiological dictionaries found that definitions of race in the biomedical sciences and public health continued to view “race as reflecting underlying genetic homogeneity” well into the 1980s (p. 324). The lack of disciplinary clarity or consensus with respect to a central term of analysis was not seen as a major problem for the field and was not a barrier to publication of thousands of articles evaluating racial differences in a host of medical conditions. By 1992, a widely cited commentary in the *Journal of the American Medical Association* acknowledged that although publications about comparative racial research numbered in the thousands, the concept of race “remained, at best, elusive” (Osborne & Feit, 1992, p. 275).

However, the belief that “there are biologically and genetically distinct human races, and that ‘racial’ biologic differences in susceptibility to, manifestations of, or therapeutic responses to specific disease are significant pathophysiological contributors to health disparities in the [United States]” remains prevalent in the medical and public health literature (Institute of Medicine, 2003, p. 217). Indeed, until 2003, medical reports were cataloged in MedLine using outmoded racial categories that infer biological differences including Caucasoid, Mongoloid, Negroid, and Australoid (Institute of Medicine, 2003; Sankar, 2003). Though the categories are now under revision, the National Library of Medicine, which manages the system, acknowledges that the deeper problem “is that even a cursory review of current literature shows studies in which groups are described by implied or explicit racial characteristics continue to be published and to contribute to a deeper understanding of human biology” (Nelson, 2003, p. 120). The continued appearance of these categories has legitimized them as “acceptable descriptive labels for patients and has thus made them seem integral to the proper diagnosis and treatment of disease” (Witzig, 1996, p. 675). Medical textbooks on physical diagnosis compound the problem by not defining race and then instructing students

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to use it in diagnosis (Witzig, 1996). It is by now well known that skin color is not an acceptable proxy for ancestry, yet it continues to be used in everyday practice in clinical reports describing patients. More importantly, these individual patient descriptors are then used uncritically in defining populations for clinical research. Such practices lead to the creation of clinical populations of racially identified individuals, which are then used in studies of biomedical questions, resulting in new knowledge being framed in the same old racial terms.

The point of this brief history is clear: Genetic, anthropological, medical, and epidemiological definitions and uses of race are not analytically congruent in theory or practice. The answer to the question “What is race?” continues to vary across fields. And the questions—What are the causes and nature of racial differences in disease? To what extent are the current designations used by the OMB adequate, appropriate, or valid to use in analyzing genetic diversity within and between contemporary racially designated groups in the United States? Is race a useful or valid biological variable at the genetic level?—can only be answered if disciplinary differences and historical practices with respect to the use of race are assessed. There is no obvious way to dismantle this uneasy legacy, for all efforts at measuring differences in human groups and the potential consequences of such work are mounted in the same or similar linguistic categories that scientists knowingly and unknowingly inherited and sometimes reformed from their intellectual progenitors. Medical researchers continue to borrow aspects of their notions of race from anthropologists, who borrow from geneticists, who are now applying their techniques to analyzing disease. These borrowings carry the unacknowledged and different histories of what race means and how it has been used across disciplines,

giving rise to the tense debates among social scientists, physicians, and genetic researchers today regarding the appropriate uses and proper meaning of racial categories in genetics research. From a practical point of view for the genetic researcher, it is critical to realize that race has a dense and difficult history. The current debates about the appropriate use of race in biomedicine are not novel. Because of its history, the word *race* will always carry multiple and complex shades of meaning. The burdens and benefits of this legacy can only be grasped by focusing on specific, racialized health issues. It is to such a case study that we now turn.

## **The Case of Smoking**

Conflated and conflicting notions of race are present within both epidemiological and genetic research on smoking. We begin with a summary of what is known about group differences in smoking and the role of genetic factors in smoking behavior. We then review and critique the use of race variables in extant genetic studies of smoking and situate this critique within the current debate.

### ***Group Differences in Cigarette Use, Tobacco Dependence, and Related Health Outcomes***

Health disparities in tobacco use and related outcomes are multifaceted and complex. Of note, virtually all extant literatures on racial differences in smoking behavior and related outcomes use self-identified racial/ethnic categories based on the OMB classification scheme. Smoking prevalence among African Americans and Whites overall is similar—25.7% versus 27.4%, respectively (Centers for Disease Control and Prevention, 2004)—yet there are important underlying differences. African Americans are less likely than Hispanics, Whites, or American Indians/Alaska Natives to have smoked cigarettes at some point in their lifetime, as documented in large national studies of adolescents and adults (Kandel, Gebre-Egziabher, Schaffran, & Hu, 2004; Substance Abuse and Mental Health Services Administration, 2001). Among those who do smoke, African Americans smoke fewer cigarettes per day (U.S. Department of Health and Human Services, 1998), start smoking at a later age (Escobedo, Anda, Smith, Remington, & Mast, 1990; Griesler, Kandel, & Davies, 2002), are less likely to progress from occasional to regular smokers (Wortley, Husten, Trosclair, Chrismon, & Pederson, 2003), and when they do, progress at a later age relative to Whites (Trinidad, Gilpin, Lee, & Pierce, 2004).

Yet some evidence suggests that African American smokers have a more difficult time quitting. Approximately 37.0% of African American smokers report successful quit attempts, compared with 40.9% of American Indians/Alaska Natives, 42.9% of Hispanics, 44.7% of Asian Americans, and 51.0% of Whites (Centers for Disease Control and Prevention, 2002). The interaction between race and socioeconomic status (SES) has confounded many studies, with discrepancies in reported quit rates sometimes but not always explained by adjustment for SES (Kiefe et al., 2001; G. King, Polednak, Bendel, Vilsaint, & Nahata,



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2004; McGrady & Pederson, 2002). Measurement issues further cloud quit rate statistics, as quit rates may be much lower among African Americans than reported (G. King et al., 2004).

More persistent smoking among certain groups can have a substantial health impact. African Americans, for example, have higher mortality rates for cancer of the lungs, oral cavity and pharynx, esophagus, stomach, larynx, and pancreas relative to Whites (U.S. Department of Health and Human Services, 1998). There are clearly additional factors, not yet understood, that contribute to excess cancer among African Americans. Controlling for age, education, smoking status, number of cigarettes smoked per day, number of years smoked, and number of years since quitting, African Americans are still two to four times more likely to develop lung cancer than Whites (A. G. Schwartz & Swanson, 1997).

There are several plausible explanations for disparities in smoking behavior, although the relative contribution of individual factors to health disparities remains poorly understood. One important line of research focuses on the convergence of minority identity with lower SES. In the U.S. context, cigarette use is typically higher among lower income, less well-educated subjects (Lantz et al., 2001). Adults with incomes below the poverty level are almost twice as likely as adults in the highest income group to be current smokers (Shoenborn, Vickerie, & Barnes, 2003); 4 in 10 adults with a GED diploma are daily smokers compared with only 8.4% of those who have earned a master's, professional, or doctoral degree (Barbeau, Krieger, & Soobader, 2004; Centers for Disease Control and Prevention, 2002; Krieger, Williams, & Moss, 1997). The overrepresentation of African Americans among lower SES strata thus helps explain why there is similar prevalence between

African American and White smokers, even though African Americans have a lower smoking prevalence relative to Whites within each SES strata (Parmuk, Makuc, Heck, Reuben, & Lochner, 1998). Further, lower SES poses risks with respect to exposure to adverse life events, violence, stress, and anxiety (McLeod & Kessler, 1990; Taylor, Repetti, & Seeman, 1997), all of which may increase liability to nicotine addiction (Diez-Roux et al., 1997; Rakowski, 1988). In particular, stress as a result of discrimination has been associated with poorer well-being, more chronic illness, and increased psychological distress among African Americans (Clark, Anderson, Clark, & Williams, 1999). Several studies have documented associations between self-reported experiences of discrimination and smoking (Guthrie, Young, Williams, Boyd, & Kintner, 2002; Landrine & Klonoff, 2000).

Smoking disparities may also be related to differences in smoking preferences and behaviors or variability in nicotine metabolism (Henningfield et al., 2003; U.S. Department of Health and Human Services, 2003). African Americans are five times more likely to smoke menthol cigarettes than Whites (Henningfield et al., 2003). These preferences have been directly shaped by industry marketing campaigns. Big tobacco companies consciously and aggressively created a menthol market as they extended into "Negro" communities in the 1950s and 60s, where smoking was initially far less prevalent than among Whites (Jain, 2003). Tailored tobacco products and advertising campaigns were targeted to Black smokers (Balbach, Gasior, & Barbeau, 2003; U.S. Department of Health and Human Services, 1998) and low-income communities (Laws, Whitman, Bowser, & Krech, 2002). Wide-spread use of menthol cigarettes among African Americans may help explain why African Americans tend to extract more nicotine per cigarette than Whites (1.41 vs. 1.09 mg per cigarette; Perez-Stable, Herrera, Jacob, & Benowitz, 1998). The higher nicotine intake per cigarette by African Americans likely reflects increased depth of inhalation and is thus hypothesized to be associated with the higher risk of lung cancer (Sellers, 1998). With respect to nicotine metabolism, group comparisons based on study subjects' self-identified race have found African American smokers to have significantly altered rates of nicotine clearance and higher levels of cotinine, the primary metabolite of nicotine, compared with Mexican American or White smokers, which could influence propensity to nicotine dependence (Caraballo, Giovino, & Pechacek, 1998; Perez-Stable et al., 1998). The search for a more nuanced understanding of smoking has led to an increased focus on the role of genetics in smoking behavior and nicotine dependence.

### **Genetic Factors Related to Nicotine Dependence and Response to Treatment**

Genetic research has established that inherited factors play an important role in smoking behavior. Considerable data from twin studies provide evidence for the heritability of smoking initiation and nicotine dependence, with heritability estimates ranging from about 55% to 70% (Sullivan & Kendler, 1999). Individual genetic variants are likely to



account for only a small proportion of the variance attributable to heredity, however (Lerman & Swan, 2002). Results from family and adoption studies are consistent with twin studies. Significant genetic influences have also been documented for age at smoking onset (Heath, Kirk, Meyer, & Martin, 1999) and for smoking persistence (Madden et al., 1999). Although researchers have acknowledged the limitations of association studies (Lerman & Swan, 2002; Sullivan, Eaves, Kendler, & Neale, 2001), these data have provided a rationale for investigating associations of specific candidate genes with tobacco dependence and response to different medications for smoking cessation treatment.

Initial genetic studies of tobacco dependence focused on genes in neurotransmitter pathways implicated in the regulation of mood (e.g., serotonin) and reward processes (e.g., dopamine). Several initial studies reported associations of tobacco use with a dopamine transporter polymorphism (Lerman et al., 1999; Sabol et al., 1999), a dopamine D2 receptor (*DRD2*) polymorphism (Spitz et al., 1998) and a dopamine D4 (*DRD4*) receptor polymorphism (P. G. Shields et al., 1998). However, these findings were not replicated in all cases (Bierut et al., 2000; Jorm et al., 2000). A dopamine beta-hydroxylase gene polymorphism has also been related to cigarette consumption (McKinney et al., 2000) but was not subsequently replicated (David et al., 2002).

There is preliminary evidence that the serotonin transporter gene modifies the effect of anxiety-related traits on smoking behavior (Hu et al., 2000; Lerman et al., 2000). Also, two independent studies have found an association of a tryptophan hydroxylase-1 polymorphism with smoking initiation or earlier age of the onset of smoking (Lerman et al., 2001; Sullivan, Eaves, et al., 2001). For some genetic variants, there is a significantly greater prevalence of the putative risk alleles in self-identified African Americans than in Whites (Lerman et al., 1999), as described in greater detail below.

Genes that influence nicotine metabolism or nicotinic receptors are also thought to influence smoking practices. The *CYP2A6* gene codes for an enzyme that metabolizes nicotine to its inactive form, cotinine. An initial report of an association of *CYP2A6* genotype with tobacco use (Pianezza, Sellers, & Tyndale, 1998) was not replicated in subsequent research (Oscarson et al., 1998) due to incorrect genotyping. However, since amending the genotyping process, several studies have provided evidence that mutations in *CYP2A6* are associated with slower nicotine metabolism and are thus protective for tobacco use (Xu, Goodz, Sellers, & Tyndale, 2002). Genes regulating nicotine receptor function are also prime candidates for smoking risk. While initial studies were negative (Lueders et al., 2002; Silverman et al., 2000), a recent large study showed a protective effect of a haplotype in *CHRNA4*, a neuronal nicotine receptor subunit gene (Feng et al., 2004). Although genetic research on smoking etiology has been limited by the need for more refined phenotypes (outcomes) of tobacco use (Lerman & Swan, 2002) and differences in study methods, and measures and variability in study samples have led to

inconsistent results (Sullivan, Eaves, et al., 2001), studies currently underway have addressed many of these concerns and are likely to advance the science significantly.

An important new area of inquiry in research on genetics and smoking seeks to use information about inherited variation in drug metabolism and drug targets to predict response to pharmacotherapy for tobacco dependence. Pharmacogenetic research may soon provide the scientific base for individualized smoking treatment based on genotype, thereby improving patients' quit rates. Ideally, genetic factors will be one of several individual characteristics considered (e.g., personal preferences, personality, personal history) in developing individualized treatment plans. To date, two pharmacogenetic trials of nicotine replacement therapy have been conducted. In one study in the United Kingdom, including over 700 smokers, a transdermal nicotine patch was found to be significantly more effective than placebo for carriers of the A1 allele of *DRD2* but not those homozygous for the more common A2 allele (Johnstone et al., 2002; Yudkin et al., 2004). In the United States, recent data indicate that a variant in the mu-opioid receptor gene common among Whites is associated with a better therapeutic response to the nicotine patch as well as less abstinence-induced mood disturbance and weight gain (Lerman et al., 2004). Studies also suggest that genetic variation in drug metabolizing enzymes (*CYP2B6*) and dopamine receptors predict response to the antidepressant bupropion, which has become an important first line treatment for smoking cessation (David et al., 2003; Lerman et al., 2002).

### **Racial Differences in Genetic Variants Associated With Smoking**

Many of these earlier studies also report racial differences in the frequency of key alleles hypothesized to increase risk of becoming addicted to nicotine, affect treatment outcomes, or serve a protective function. Virtually all of these studies use self-reported race as the construct to measure human variation, while a very few use self-reported ancestry. Early reports describing associations of smoking with genetic variation in the dopamine D2 receptor and dopamine transporter found that the putative risk alleles for smoking were found at a higher rate among African Americans than among Whites (Lerman et al., 1999). For example, 45% of African Americans and 35% of Whites in this study carried at least one A1 allele of the *DRD2* gene. However, genotypes containing a potential risk allele (short allele) of the serotonin transporter gene were found at a lower rate among African Americans (50%) than Whites (69%; Lerman et al., 1998). Although the sample sizes in these case control studies were moderate (e.g., > 500 subjects), ascertainment was not population based. For example, smokers were ascertained through smoking cessation treatment programs, and as such, the observed racial differences in allele frequencies may not be representative of those in the general population.

The most marked findings for differences by race have been reported for the *CYP2A6* gene, which codes for an enzyme that metabolizes nicotine into its inactive form,

cotinine. There are a variety of low and null activity alleles that have been identified, and evidence suggests that individuals who carry these alleles are at lower risk of developing nicotine dependence (Xu et al., 2002). Such protective alleles for the *CYP2A6* gene (e.g., \*4 allele) are very rare among persons who self-identify as having European or African ancestry (e.g., < 3%) but are found in as many as 24% of persons who self-identify as Japanese or Korean (Schoedel, Hoffmann, Rao, Sellers, & Tyndale, 2004).

## The Use of Self-Identified Race Variables in Extant Genetic Studies of Smoking

What variables have genetic researchers used in assessing racial differences in the frequency of genetic variants associated with smoking behavior? To assess current research practices, we conducted a systematic literature review of all published studies on polymorphisms associated with nicotine dependence or smoking behavior through June 2003. A PubMed search using the search terms *nicotine polymorphism* and *tobacco dependence polymorphism* identified 105 journal articles. After we eliminated studies not primarily focused on smoking or nicotine ( $N = 57$ ) and review articles ( $N = 14$ ), there remained 34 original research articles for review.

These 34 articles are remarkably inarticulate regarding the rationale, definitions, and construction of the race variables used in the analyses presented. Twenty-five of the 34 articles offer no definition of the race variables used. Only six studies explicitly say that race variables were based on subjects' self-reported racial or ethnic background, whereas this practice is assumed to be implicit in the remaining studies (Ahijevych, Tyndale, Dhatt, Weed, & Browning, 2002; Lerman et al., 1999, 2000; Silverman et al., 2000; Uhl, Liu, Walther, Hess, & Naiman, 2001; Vandenberg et al., 2002). Among these six studies, not one indicates whether subjects were offered a range of categories into which they were asked to self-select, and if so, what these categories were. Nor are we told whether subjects were offered the opportunity to select more than one category, as the OMB guidelines currently require. There is a substantial range in the level of refinement of the self-identified racial/ethnic categories implied by study descriptions. Several studies focus on White and African American groups (Ahijevych et al., 2002; Anokhin, Todorov, Madden, Grant, & Heath, 1999; Caporaso et al., 2001; Lerman et al., 2000; Paschke et al., 2001; P.G. Shields et al., 1998). White subjects are differentially defined as Caucasian, of European decent, non-Hispanic Caucasian, and White. Several studies offer a rationale for exclusion criteria (Lerman et al., 2002; Silverman et al., 2000), while in other studies these exclusion criteria are implicit (Lerman et al., 2001; Singleton et al., 1998; Sullivan, Jiang, Neale, Kendler, & Straub, 2001; Sullivan, Neale, et al., 2001).

Only 4 of the 34 original studies (Howard, Ahluwalia, Lin, Sellers, & Tyndale, 2003; Silverman et al., 2000; Uhl et al., 2001; Xu et al., 2002) offered definitions and criteria based on ancestry. Two studies identified Whites on the

basis of self-identified European ancestry (Silverman et al., 2000) or European American ancestry (Uhl et al., 2001). Only 2 of the 34 studies assigned race or ancestry on the basis of ancestry of the subjects' grandparents. Howard et al. (2003) required three of the subjects' grandparents to be identified with a particular ancestral population in order to be classified as such; Xu and colleagues (2002) required all four grandparents to be identified as such. Only 9 of the 34 studies reviewed offered an explicit rationale for the inclusion of race variables in their analysis. Most of these alluded to concerns about population stratification or cited previous research documenting differential frequency of key alleles among groups. Study results and conclusions are mixed. Of the studies examining associations or differences by race related to genetics and smoking, 12 studies concluded that their results were significant enough to warrant further exploration of racial variables in smoking and genetics. Genetic researchers who work on smoking are not unique. The use of self-identified racial variables (not self-reported continental ancestry of subject or grandparents) currently dominates genetic analyses of human variation, with little reflection regarding what dimension of variation these variables are actually capturing in the analysis. Below, we examine valid methodological and social concerns that might encourage the use of race variables in genetic studies and also consider arguments against the use of such constructs.

## Motivations for the Use of Race Variables in Genetic Studies

### Methodological Concerns: The Need to Account for Underlying Population Structure

Are there any valid reasons to use some index of racial background in a genetic study? There are at least two reasons why identifying subpopulations might be important in conducting genetic research. The first applies to all studies of human variation, namely, the need to account for ethnic admixture in a study population in order to ensure that any significant results are indeed related to the variable of interest and are not merely an artifact of underlying population structure of the study population, in which key characteristics are differentially prevalent. The issue here is which index of underlying population structure is appropriate. The second relates to cases in which scientists are seeking to understand the role and function of particular alleles that are rare in most groups but have been found to be relatively more prevalent in a particular population defined by continental origin.

The first context in which one can make an argument that it is important to consider the ancestral background of an individual is in studies that attempt to uncover the genetic basis of a human trait. Thousands of such studies have been conducted, and many have yielded potentially important information about the causes and treatments of human diseases. Two principal study designs are generally used for the genetic dissection of complex traits (Cardon & Bell, 2001). One approach investigates family pedigrees with several affected relatives, and the other compares

cases with a disorder with controls without a disorder. Not considering the ancestral background of the individuals in the study can have important consequences for each type of study. For studies of family pedigrees, the major consequence of ignoring ancestral background is loss of statistical power, although false positive evidence for linkage can also be a problem when there is substantial missing genotype data within the families. For studies of unrelated cases and controls, there is the possibility of a false positive result, due to ethnic admixture, if ancestry is ignored (Kidd, 1993). The risk of false positive results due to population stratification is greater in larger studies (Cardon & Palmer, 2003; Devlin & Roeder, 1999; Freedman et al., 2004). Genetic case-control studies (association studies) are the more commonly applied approach in the literature. Hence, we will consider association studies in more detail.

In an association study, an investigator identifies a group of cases with a complex trait of interest (e.g., Alzheimer's disease, type 1 diabetes mellitus, or nicotine dependence) and a group of matched controls without the trait and then compares the frequencies of some gene variant in the two groups. Perhaps the most famous example of this type of study was in the identification of apolipoprotein  $\epsilon 4$  (APOE) as a risk factor for Alzheimer's disease (Farrer, 2001). For example, suppose cases were three quarters African American and one quarter European American and that the control group had the reverse proportions (one quarter African American and three quarters European American). Despite the notable similarity of humans from all regions of the world, it is not difficult to find a genetic marker that differs considerably by ancestry. For example, one blood group marker is rare in individuals of Northern European and East Asian ancestry and common in individuals of East African ancestry. This genetic marker would be common in the case group and less common in the controls. An incautious investigator might conclude that this marker is causal for the disease rather than merely representing a false positive due to a poorly selected control group.

To avoid this problem, one needs to carefully select the control group: "Individuals selected as controls should not only be free of the study disease, but should also be similar to the cases in regard to past . . . exposure" (Schlesselman, 1982, p. 71). In this context, *exposure* could be both environmental risk and genetic variation in individuals. However, many investigators assume that the environmental influences are minimal. Because of the potential for false-positive results in an association study, many have argued the necessity of assessing race. Much of the debate in the field revolves around arguments about which measures of race or ancestry are valid and appropriate. Sources of information used to construct race variables in genetic studies range from an individual's self-reported race or ethnicity based on the OMB categories, to self-reported ancestry based on a study subject's self-report or reported ancestry of his or her grandparents, to empirical assessment of genetic markers used to categorize subjects into population groups by continent of origin.

There are three general approaches to the problem of false-positive results due to population structure (Sullivan, Eaves, et al., 2001). First, it can be argued that differences in genotype frequency and/or disease frequency must be fairly gross for stratification to produce an artifactually significant result (Wacholder, Rothman, & Caporaso, 2000) and that simply controlling for reported ancestry will greatly reduce the risk. Carefully assessing the ancestry of subjects is critical to this approach (e.g., best practices currently include determining ancestry based on a subject's self-reported ancestry of three or four or his or her grandparents). The second approach is based on study design, with "family-based" association studies being the most widely discussed approach (Sham, 1998). This approach does not require assessment of ancestry but poses challenges with respect to obtaining a sufficient number of families, statistical power, and costs.

The third approach for guarding against the risk of a false-positive result is empirical. These methods require additional genotyping. In one method, cases and controls are genotyped for approximately 20 additional genetic markers as a "diagnostic test" for whether cases and controls are poorly matched (Pritchard & Rosenberg, 1999). If this test is positive, additional genotyping ( $\geq 100$  additional genetic markers per subject) can be used to assign individuals to ancestral subgroups empirically (Pritchard, Stephens, & Donnelly, 2000). This method has been used in a recent pharmacogenetic smoking trial (Lerman et al., 2004). Another approach is to use "genomic control"; with additional genotyping ( $> 60$  genetic markers per subject), the degree of stratification within a sample can be computed and used to adjust the test statistic for a genetic marker (Devlin & Roeder, 1999). For these empirical approaches, direct assessment of ancestry is not required; rather, genetic variation is used to classify individuals into ancestral groups. While it should be remembered that genetic variation among humans from different geographical areas is fundamentally continuous (Serre & Paabo, 2004), the aggregation of human beings into ancestry on the basis of continent of origins has been demonstrated to capture patterns of human variation significant enough to meet methodological needs to adjust for underlying population structure.

Finally, beyond the specific methodological concerns addressed above, investigators might also justify studies within specific populations on the basis of what is currently known about the evolutionary history of those populations and the implications that this may have for genetic research. For example, some investigators have chosen to study populations with unusual histories (e.g., those in Iceland, Finland, the Amish, or the Hutterites), with the justification that populations with more extensive linkage disequilibrium may enable genome-wide association studies to be done with a more limited number of markers. Similarly, once very large numbers of markers in dense maps are available for genome-wide association studies, investigators may justify studies in populations of African descent because of the expectation that such populations will have more limited linkage disequilibrium and therefore

will facilitate more rapid identification of susceptibility genes. Scientific rationale for choice of population is often based on both what is known empirically and what is predicted on the basis of current understanding of population history, both of which are subject to revision. Thus, such studies can have a logical scientific basis, although it is clear even here that it is the history of the population, not race per se, that provides a scientific basis for choosing the population.

### **The Goal of Inclusion and Equal Distribution of the Benefits and Risks of Research**

Aside from methodological concerns, rubrics of race and ethnicity have been critical designations used in service of broader social goals of inclusion and justice. Current practices regarding the use of racial variables in genetic studies are directly shaped by federal policies rooted in historical efforts to ensure inclusion of racial/ethnic minorities and other underrepresented populations (e.g., women, children) in clinical trials. These policies have their origin in the women's health movement. Following the issuance of the report of the Public Health Service Task Force on Women's Health in 1985, the National Institutes of Health (NIH) established a policy, published in 1987, urging inclusion of women in clinical studies (NIH, 1987a). A revised policy later that year for the first time encouraged the inclusion of minorities in clinical research (NIH, 1987b).

Researchers questioned whether research results produced from clinical trials overwhelmingly comprised of White male subjects were equally applicable to other groups. Women in particular questioned whether research results produced from clinical trials comprised of White male subjects were broadly generalizable to members of other groups. The HIV community also advocated for broad inclusion in research protocols, which at that time was the only access point to promising therapies for HIV infection (El-Sadr & Capps, 1992; Levine, 1996; Weijer, 1996). In accord with the thrust of the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978), it was argued that the principle of justice requires that burdens and benefits of research be fairly distributed (McCarthy, 1994). Acknowledging challenges in using "the emerging knowledge about biological differences for the benefit of historically disadvantaged groups" (Dresser, 1992, p. 28), there was concern that women and minorities might react differently or perhaps negatively to prospective therapies that seemed to show promise for White males (Dresser, 1992; Weijer, 1996).

Although the argument for equal inclusion of women in clinical trials has clear biological grounding if sex-linked biology is at issue, the guidelines are notably inarticulate with respect to the argument for inclusion of minorities. The OMB (1997) stance on whether race is a biologically relevant term is somewhat obtuse, stating that

The racial and ethnic categories set forth in the standards should not be interpreted as being primarily biological or genetic in reference. Race and ethnicity may be thought of in terms of social and cultural characteristics as well as ancestry." (p. 36881)

This is not surprising, given that the primary policy objectives of the OMB classification scheme are not health specific but rather to monitor and enforce civil rights laws in a range of areas, including education, employment, housing and mortgage lending, voting rights, as well as health care (OMB, 1997, p. 36879). Challenges and nuances associated with translating the directives into policies guiding biomedical research have not been fully addressed. The extent to which these directives reflect policymakers' beliefs that access to trials effectively means access to treatment (and thus reflects a desire to "do no harm") versus a belief that inclusion of minorities in clinical trials is important because there are significant biological differences between human beings of different racial/ethnic identities remains unclear. The ultimate goal of reducing health disparities, the etiology of which could be differently conceptualized, remained central. Even at that time, however, some worried that the most well-intentioned efforts to improve the health status of minorities might backfire because race was a confusing concept of doubtful biological but overwhelming social significance (P. A. King, 1992a).

Efforts to include women and minorities in clinical trials begun by NIH ultimately led to the passage of the NIH Revitalization Act of 1993, which required NIH to ensure that minorities and women be included in study populations of all NIH-funded research. In 1994, the NIH revised its policies to meet this mandate (U.S. Department of Health and Human Services, 1994). Again, in October 2001, the NIH amended the Policy on Inclusion of Women and Minorities in Clinical Research to clarify the policy in terms of definitions, roles, and responsibilities (NIH, 2001). It is in this revision that the NIH adopted the 1997 OMB revised minimum standards for presenting data on race and ethnicity (NIH, 2001). Researchers are now required to categorize study subjects into the five minimum race categories defined by OMB Directive Number 15 (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, and White) and two ethnicity categories (Hispanic or Latino/not Hispanic or Latino). Researchers must rely on respondents' self-identification to collect data on race and ethnicity, and the respondent must be offered an opportunity to select more than one racial designation, in consonance with the 2000 Census protocol.

Although the federal Food and Drug Administration (FDA) has long requested race and ethnicity data in certain clinical trials, it had not issued explicit guidance on the categories to use in collecting and reporting the data. In January 2003, the FDA issued the draft "Guidance for Industry Collection of Race and Ethnicity Data in Clinical Trials" (U.S. Department of Health and Human Services et al., 2003), which recommended a standardized approach for collecting racial and ethnic data in clinical trials conducted in the United States and abroad for specified FDA products, using the same OMB classification scheme. The FDA guidelines raise the additional problem that categories arguably relevant for populations in the United States might not be as relevant in globally derived study populations.

The initial implementation of NIH inclusion policies was clearly well-intentioned. Without question, ensuring diversity in clinical trials and standardization of data collection are worthwhile goals. In the context of genetic studies, however, these mandatory requirements to recruit and describe human subjects using the OMB categories have inadvertently fostered the use of this same categorization scheme not only in recruitment of subjects but also in the statistical analyses of genetic variation. Although it is theoretically possible for researchers to continue using the OMB classification scheme to characterize study populations (to meet the social goal of monitoring inclusion in clinical trials) and to use more biologically meaningful categorization schemes to account for human variation in genetic studies, the OMB classification scheme remains so deeply entrenched in our cultural vocabulary and in our research practices that self-identified race according to this classification scheme continues to be the predominant construct used to address population admixture in genetic studies to date. The challenge is to make full use of the OMB categories in tracking our nation's progress toward important social goals, as appropriate, including equal access to clinical trials, without encouraging the unreflective use of these same categories in research contexts in which human *biological* variation is the construct being measured.

### **Improving Public Health and Eliminating Health Disparities**

Related to the social goal of equal distribution of the risks and benefits of research is the goal of equal access to health care, and more fundamentally, health and the full range of opportunities shaped by one's health status. The fundamentals of the practice of public health include stratifying segments of the general population by risk in order to target public health interventions toward those communities most likely to benefit from such interventions. Historically, public health data have been stratified by age, sex, and "race," with little systematic assessment of the influence of socioeconomic standing or environmental factors (Krieger et al., 1993). Targeting public health interventions to particular racial/ethnic communities as a strategy to improve public health has certainly met with some success (e.g., screening programs for sickle cell). Increasingly, the social goal of eliminating health disparities has become a central focus of public health policies and programs. Reducing health disparities is one of two overarching goals of the Healthy People 2010, the key document framing much of the work of U.S. public health departments and organizations (U.S. Department of Health and Human Services, 2000), further emphasizing race as a primary category for comparison and monitoring (Burchard et al., 2003; Institute of Medicine, 2003; Kaiser Commission on Medicaid and the Uninsured, 2003; Mayberry, Mill, & Ofilil, 2000; U.S. Department of Health and Human Services, 2000). Significant disparities persist in the prevalence of disease, access to care, quality of care, and health outcomes (Fiscella, Franks, Gold, & Clancy, 2000; Hargraves, Cunningham, & Hughes, 2001; Institute of Medicine, 2003; Kressin & Petersen, 2001;

Saha, Arbelaez, & Cooper, 2003). These disparities fall primarily along racial/ethnic and SES lines, with particular subpopulations (e.g., low-income, uninsured, minority patients) shouldering the most burden (Burchard et al., 2003; Fiscella, Franks, & Doescher, 2002; Institute of Medicine, 2003; Kaiser Commission on Medicaid and the Uninsured, 2003; Mayberry et al., 2000; Schneider, Zaslavsky, & Epstein, 2002).

The OMB race and ethnicity variables have been the primary vehicle for tracking different populations' burden of disease, access to care, quality of health care received, and health outcomes in the United States. Our criticism of their use in genetic studies is in no way meant to undervalue their importance in tracking health disparities—the sequelae of differential access to resources, opportunities, and services expressed in poor quality care, disproportionate disease severity, and adverse outcomes. Recent increased attention to the data collection and monitoring efforts needed to more effectively track health disparities in the U.S. health care system and promote accountability is long overdue and tremendously important (Institute of Medicine, 1999). With respect to nongenetic studies of access to care, the quality of care received, or the health impact of social determinants more broadly, the OMB categories will and should remain potent constructs for addressing inequality in this nation's health care system.

But there is a critical distinction between public health monitoring or surveillance data (and uses of that data to target public health interventions) and etiological research that aims to elucidate the underlying causes and mechanistic pathways to disease (National Committee on Vital and Health Statistics, 2000). Monitoring health disparities is a crucial social responsibility, and this has often been the primary argument posited by genetic researchers who advocate the use of self-identified racial variables in genetic studies. For example, Burchard and colleagues (2003) wrote, "Information about patients' ethnic or racial group is imperative for the identification, tracking and investigation of the reasons for racial and ethnic differences in the prevalence and severity of disease and in response to treatment" and advocate the use of racial differences as "starting points for further research" (p. 1174). But we would join others (Cooper, 2004; Kaufman & Cooper, 2001) in emphasizing that the OMB racial/ethnic categories are not appropriate for use in etiological studies of human disease focused on disentangling complex gene-environment interactions. The use of such scientifically imprecise variables in genetic studies as a stand-in for measurement of genetic heterogeneity or differential exposure to measurable environmental or social exposures (including measures of individual exposure to racism) is methodologically unacceptable, given the availability of more precise measures, and provides little help in elucidating the underlying causes of health disparities. With respect to disease etiology, specific factors such as exposure to environmental toxins, stress, poor quality housing stock, or poor quality diet—all disproportionately visited on minority populations—are probably far more important to measure and monitor if the ultimate goal is improving health (Cooper, 2004; Sankar et

al., 2004). Further, insofar as genetics research considers social and environmental influences and their complex interactions with key genetic variants, the field of genetics may actually have the potential to help biomedical research and public health research break out of the race conundrum and provide valuable information that could actually prove useful in *addressing* racial disparities in health that public monitoring efforts have successfully identified.

## **Arguments Against the Use of Race Variables in Genetic Studies of Smoking**

Despite valid methodological concerns and broader social interests in monitoring health disparities along socially and politically meaningful categories in the contemporary U.S. context, several strong arguments against the use of self-identified race variables in genetic studies of complex traits—reflecting methodological and socioethical concerns—can be made.

### **Methodological Arguments Against the Use of Race Variables in Genetic Studies of Smoking**

Increasingly, the focus of biomedical research and, in particular, genetic approaches, is moving toward personalized or individualized medicine (Collins, Green, Guttmacher, & Guyer, 2003). The broad conceptual goal of this focus is to tailor preventive and therapeutic interventions directly to individuals' personal characteristics rather than to their broad demographic or diagnostic profiles. Accomplishing these ambitious ends requires detailed knowledge of the pathophysiology of a medical disorder, which has led to a tremendous investment in understanding the genetic basis of disease etiology and response to treatment. The continued use of "race" in biomedical research is contrary to the goals of personalized medicine. We see at least four methodological arguments for minimizing the use of race variables in genetic studies.

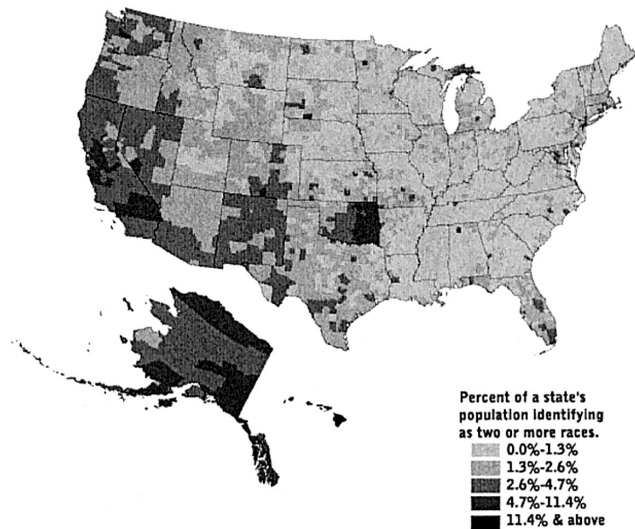
First, the assessment of "race" in a clinical context may be unreliable. Studies have documented poor reliability of racial classifications found in hospital discharge data (Blustein, 1994), emphasizing the variability of medical personnel's subjective appraisal of patients' racial/ethnic identity. Studies comparing data on ethnicity from cancer registries (abstracted from medical records) versus individuals' self-reported race/ethnicity have found similarly poor concordance (Stewart, Swallen, Glaser, Horn-Ross, & West, 1999). In general, most clinical assessments and self-reported personal characteristics have limited reliability (e.g., fewer than 20% of patients reporting allergy to penicillin are truly allergic; Salkind, Cuddy, & Foxworth, 2001). Critically, "race" is highly conflated with other concepts—some individual responses will have more to do with the place of ancestral origin or skin pigmentation and others will reflect cultural identification. Moreover, an individual's self-designated racial identity can change over time (Bentley, Mattingly, Hough, & Bennett, 2003; Hubble, Poyer, & Bentley, 2002).

Second, "race" is likely to lack validity for studies with a genetic focus. Genetic researchers seeking to use race to control for ancestry typically use self-reported race. The degree to which individuals' self-reported race overlaps in any biologically meaningful way with their geographic ancestry is highly variable. Although some studies document as much as 98.0% congruity between self-reported race and administrative data (i.e., death certificates) for African Americans (Sorlie, Rogot, & Johnson, 1992), the consistency of racial information across data sources differs widely across racial groups (e.g., only 57.4% congruence reported for American Indians; H. M. Rosenberg et al., 1999). Several other studies have documented poor agreement between patients' race information across various data sources (Boehmer et al., 2002; Kressin, Bei-Hung, Hendricks, & Kazis, 2003; Moscou, Anderson, Kaplan, & Valencia, 2003). In some instances, the magnitude of dissonance is significant enough to alter clinical research results, depending on which source of race data is used (Boehmer et al., 2002). Individuals have also been found to identify with different racial/ethnic categories, depending on question format or time frame (Bentley et al., 2003; Brener, Kann, & McManus, 2003; Carlson, 2003; Hubble et al., 2002).

The problems with self-identified race are exacerbated in a genetic context, in which racial variables are used as a proxy for underlying biological variation across populations. In a recent comparison of self-reported race versus DNA evidence based on 31 genetic markers, for example, approximately 22% of persons from the Washington, DC area identifying as African American showed a low African genetic contribution but a predominant European or Native American genetic contribution to ancestry (Shriver et al., 2003). This same study documented the significant incongruence between skin color and genetic contribution to ancestry (Shriver et al., 2003), underscoring the poor validity of classification based on skin color. The use of self-identified Hispanic or Latino identity as a construct of human variation in genetic studies is similarly problematic. Puerto Ricans, for example, on average have an admixture comprised of about 37% African ancestry, 45% European ancestry, and 18% Native American ancestry, while Mexican Americans on average have ancestry that is 31% Native American, 61% European, and 8% African (Hanis, Hewett-Emmett, Bertin, & Schull, 1991). Self-identified race and ethnicity are thus both unacceptably poor proxies of human genetic variation.

Third, the traditional use of "race" in biomedicine implies the typological view of humanity, discussed above, wherein individuals can be neatly categorized into a few clusters that possess distinctive genetic, social, and environmental characteristics. Such a view is increasingly outmoded in many countries in the world, including the United States, and may already be antiquated given the increasing prevalence of admixture (see Figure 1). By 2050, analysts project that approximately one in five Americans will identify as multiracial (Smith & Edmonston, 1997). It is worth noting that measures of continent of origin are similarly limited by being locked into a typological framework with

**Figure 1**  
*Map of the United States Showing Multiracial Population From the 2000 Census*



Note. From CensusScope (2000): [http://www.censuscope.org/us/map\\_multiracial.html](http://www.censuscope.org/us/map_multiracial.html). Copyright by Social Science Data Analysis Network ([www.ssdan.net](http://www.ssdan.net)), University of Michigan. Reprinted with permission.

rigid boundaries that do not reflect the continuous nature of any measure of human genetic variation (Serre & Paabo, 2004).

Fourth, the use of “race” as a variable does not facilitate the development of the types of mechanistic hypotheses that characterize biomedical research and thus does not lead to greater understanding about the disease pathways that in turn might lead to effective interventions. If the presence of a disorder or some outcome is significantly associated with “race,” the explanatory power of the research finding is highly limited; it is not possible to determine whether the finding indexes genetic differences, cultural effects, and/or differential environmental exposures.

Finally, with respect to the ultimate goal of using genetic research to improve health, “race” most often proves an unacceptably poor clinical test. Although there are occasional exceptions, most genetic markers do not differ sufficiently by racial or ancestral group to be useful in directing clinical care. For example, N-acetyltransferase 2 (NAT2) has an important role in drug metabolism and carcinogen inactivation. Poor NAT2 function (“slow-acetylator”) is present in 14% of East Asians, 34% of African Americans, and 54% of European Americans (Yu et al., 1994). Clinical decisions based on the inference of acetylator phenotype solely on race would often be erroneous. The distributions of clinically relevant polymorphisms across racial communities will be such that clinicians will not be able to rely on them to guide clinical practice. A recent study identified 33 significant and replicated associations for drug response among European, African, and

Asian populations (Goldstein, Tate, & Sisodiya, 2003). We plotted the frequency of genetic variants across these populations (see Figure 2). We would posit that, to meaningfully guide clinical practice, the differential pattern of allele frequencies would have to be more along the lines of our hypothesized frequency distribution, shown via the dotted line on Figure 2. The complexity of the genetics of complex traits will rarely if ever yield group prevalence rates useful to guide treatment decisions for individual patients without further individual assessment.

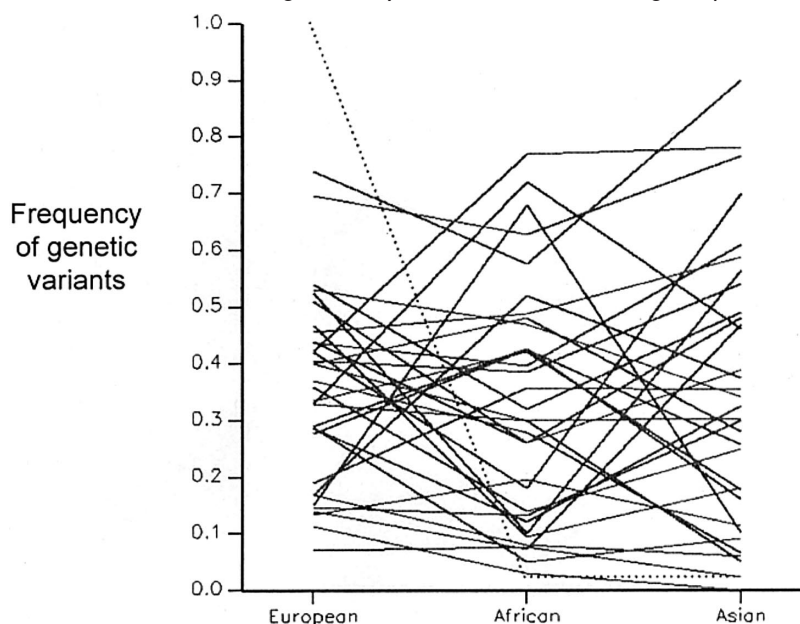
### **Socioethical Arguments Against the Use of Race Variables in Genetic Studies**

There are also several socioethical arguments against using race categories in genetic analyses, when other more sophisticated strategies for controlling for population stratification have become available (A. E. Shields, Lerman, & Sullivan, 2004). First, racializing disease leads to stigma. Once a particular socially defined group is identified as having a higher prevalence of risk-conferring genotypes, there is increased concern regarding discrimination and stigmatization of individuals and their particular communities (Foster, Bernsten, & Carter, 1998; P. A. King, 1992b; Lehrman, 1997; Proctor, 1988; Stolberg, 1998). Early screening efforts for sickle cell hemoglobin, for example, resulted in substantial racial stigmatization and discrimination against African Americans in both insurance and employment settings, despite the fact that other subpopulations had a similarly high prevalence of sickle cell traits and that the initial tests were not able to distinguish between sickle cell trait and sickle cell disease (Bowman & Murray, 1990; P. A. King, 1992b). Meanwhile, Whites and other groups not associated with sickle cell disease often went undiagnosed, until screening for sickle cell was finally implemented for all newborn infants. Given the extreme approbation with which substance abuse is viewed in our society, similar misunderstandings of the meaning of a higher frequency of addiction-related “susceptibility” genotypes among identified racial subpopulations could be far more destructive.

Second, the pleiotropic nature of many of the genes associated with complex behaviors such as addiction poses additional risks of discrimination and stigmatization of subpopulations identified as having a higher prevalence of putative alleles. One of the most promising applications of genetic research on smoking is to individually tailor smoking treatment by genotype, thereby increasing a patient’s chances of successfully quitting smoking. However, genes implicated in smoking behavior have also been associated with a variety of far more socially stigmatizing behaviors and psychiatric conditions, including substance abuse (Comings, Muhleman, Ahn, Gysin, & Flanagan, 1994), sexual activity (Miller et al., 1999), novelty seeking (Noble et al., 1998), and other psychiatric conditions (Billett et al., 1998; Comings, Muhleman, & Gysin, 1996; Muglia, Jain, Macciardi, & Kennedy, 2000; see Table 1). Thus, a genetic test to match patients to optimal nicotine replacement treatment would simultaneously generate information related to

**Figure 2**

*Pharmacogenetic Variants That Have Been Significantly Associated With Drug Response in at Least Two Studies*



Note. The dotted line represents a hypothesized frequency distribution of the differential pattern of allele frequencies that would meaningfully guide clinical practice, and the solid lines represent mapped allele frequencies from Goldstein et al. (2003) for select polymorphisms across racial groups.

a patient's genetic risk for other addictions and psychiatric conditions.

Social risks related to unauthorized uses of genetic information cannot be assessed without attending to the current policy environment and specifically the strength of current privacy and antidiscrimination protections that govern access and authorized uses of patients' genetic information. Even though the genetic variants associated with complex behaviors have very low penetrance and thus do not directly predict risk of developing a particular condition, this complexity may escape those with access to patients' genetic test results (e.g., insurers, employers, family members) and still may lead to individual harm. Currently, no federal law in the United States bans genetic discrimination in the general population (Hustead, 2002). State laws remain the primary source of protection, yet only 41 states currently ban genetic discrimination in group health insurance and only 37 states have passed laws that ban the misuse of genetic information by employers (National Human Genome Research Institute, 2003a, 2003b). Given inadequate privacy protections and antidiscrimination statutes at the state and federal level (National Human Genome Research Institute, 2003a, 2003b), genetic information has substantial abusive potential.

Further, the conflation of reported racial differences in putative alleles associated with smoking but also implicated in addiction to cocaine and other substances might easily be misconstrued to reinforce persistent racist stereotypes regarding African Americans and substance abuse.

Several studies have shown, for example, that physicians often prescribe inadequate pain medication for African American patients relative to White patients with similar conditions and severity of illness, possibly due to concerns about potential drug abuse by minority patients (Cleland, Gonin, Baez, Loehrer, & Pandya, 1997; Todd, Deaton, D'Adamo, & Goe, 2000).

For all of these reasons, the potential social harms associated with framing genetic studies of addiction along racial lines must be closely evaluated. If there are other, more scientifically valid ways of meeting methodological evaluation of underlying population structure that do not have these same attendant risks of generating social harm, it is difficult to see how the continued use of race variables can be justified. Further, if race variables in fact function as sponge variables that reflect a host of unmeasured factors that do affect one's health but do not provide the information needed to address health disparities, is there not an ethical obligation to attempt to identify and measure these factors directly?

Third, the use of race variables in genetic research exacerbates an existing problem: Biological factors in disease etiology and health outcomes are often overemphasized relative to social and environmental determinants underlying health disparities. When genetic research results are framed in racial terms, they often have the effect of inscribing racial categories with biological meaning, thereby obscuring cultural, social, and environmental factors also affecting health and behavior. For example, ge-



**Table 1**  
*Select Pleiotropic Associations of Genes Implicated in Nicotine Addiction*

Genetic variant	Complex traits			
	Tobacco use	Addictive behaviors	Psychiatric conditions	Behavior patterns
	Dopamine pathway			
<b>DRD1</b> (dopamine D1 receptor)	<b>Smoking</b> (Comings et al., 1997)	<b>Cocaine, alcohol</b> (Comings et al., 1997)	<b>Tourette's syndrome</b> (Comings et al., 1997)	<b>Gambling</b> (Comings et al., 1997)
<b>DRD2</b> (dopamine D2 receptor)	<b>Smoking</b> (Comings, Muhleman, & Gysin, 1996; Spitz et al., 1998)	<b>Alcohol</b> (Comings, Muhleman, Ahn, Gysin, & Flanagan, 1994), <b>cocaine</b> (Noble et al., 1993)	<b>PTSD</b> (Comings et al., 1996) <b>ADHD</b> (Comings et al., 1991)	<b>Sexual activity</b> (Miller et al., 1999)
<b>DRD4</b> (dopamine D4 receptor)	<b>Smoking</b> (P. G. Shields et al., 1998)	<b>Alcohol</b> (Bau et al., 2001)	<b>ADHD</b> (Muglia, Jain, Macciardi, & Kennedy, 2000) <b>OCD</b> (Billett et al., 1998)	<b>Novelty seeking</b> (Bau et al., 2001; Noble et al., 1998)
<b>SLC6A3</b> (dopamine transporter [DAT])	<b>Smoking</b> (Lerman et al., 1999; Sabol et al., 1999)	<b>Alcohol</b> (Schmidt, Harms, Kuhn, Rommelspacher, & Sander, 1998)	<b>Anxiety, Tourette's syndrome</b> (Rowe et al., 1998)	
<b>DBH</b> (dopamine beta-hydroxylase)	<b>Smoking</b> (McKinney et al., 2000)		<b>Paranoia</b> (Cubells et al., 2000)	
	Serotonin pathway			
<b>5HTTLPR</b> (serotonin transporter)	<b>Smoking</b> (Hu et al., 2000; Lerman et al., 2000)	<b>Alcohol</b> (Hallikainen et al., 1999; Lichtermann et al., 2000)	<b>Depression</b> (Bellivier et al., 1998) <b>Anxiety</b> (Lesch et al., 1996)	
<b>TPH</b> (tryptophan hydroxylase)	<b>Smoking</b> (Lerman et al., 2001; Sullivan, Jiang, Neale, Kendler, & Straub, 2001)	<b>Alcohol</b> (Nielsen et al., 1998)	<b>Suicide</b> (Nielsen et al., 1998) <b>Depression</b> (Bellivier et al., 1998)	<b>Aggression</b> (Manuck et al., 1999)

Note. ADHD = attention-deficit/hyperactivity disorder; PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder.

netic studies have reported a dramatically higher frequency in Asian populations (approximately 20%) of low or no activity alleles of the *CYP2A6* gene (Ando et al., 2003; Nakajima, Kuroiwa, & Yokoi, 2002), which regulates the rate at which nicotine is metabolized in one's system and is therefore thought to be protective against smoking (Tynedale & Sellers, 2002). On the basis of such data alone, we should anticipate dramatically lower rates of smoking among Asian populations, although the exact opposite is true. Japanese and Chinese men actually have among the highest smoking rates (approximately 53% and 67%, respectively) in the world (World Health Organization, 2002). Scientific knowledge is developing rapidly; our in-

vestigation of social and cultural factors requires equally rigorous attention.

## Working Toward Consensus Regarding the Use of Race Variables in Genetic Studies

### Recommendations for Genetic Researchers

We offer below some specific recommendations to guide researchers' use of race variables in genetic studies of complex traits. These recommendations are based on a synthesis of the current literature. As the available knowledge and technology are constantly evolving, the best ap-

proach must always be determined in light of the specific characteristics of the polymorphism under study, the state of scientific knowledge, and the most current methods available to address these concerns.

First, consensus that is developed from within the field is likely to be far more effective than anything imposed externally. While external critiques from those in other disciplines can provide novel insights and prompt closer examination of the social implications of research practices in genetics, a thoughtful and workable resolution of these matters will require active engagement from the genetic research community, and we encourage such engagement. Second, it is essential to specify and use the correct terms. A substantial portion of disagreement stems from imprecise use of racial terms. For example, the difference between *self-identified race* and *self-identified ancestry* is seldom clarified in the published literature. We suggest the following definitions. In genetic research, *ancestry* (“ancestral lineage or descent”) is usually the most appropriate term in reference to the issues in relation to population stratification. Specific definitions should be explicitly noted (e.g., Was ancestry self-reported on the basis of ancestry of four grandparents?). *Ethnicity* is often a reasonable choice of terms for referring to cultural identity and influences (“ethnic character or peculiarity”). With the exception of the health disparities context, in which self-identified race remains a socially important metric, *race* should be avoided

or used with caution and clarification, as its meaning encompasses both ancestry (“a group of persons, animals, or plants, connected by common descent or origin”) and ethnicity (“a group or class of persons, animals, or things, having some common feature or features”; Oxford English Dictionary, 2004).

Third, we support the ongoing collection of self-identified race from study subjects to meet the requirements of NIH inclusion criteria policies. It will be years before the complex intersection of racial self-identity, socioeconomic position, genetic status, and health outcomes are unraveled. In the meantime, we think maintaining the capacity to track participation in clinical trials, response to treatment, and health outcomes across racially defined populations remains an important public health objective, in service to the larger social goal of reducing health disparities. We now turn to specific recommendations pertinent to each stage of the research process (see Table 2).

**1. Study design.** Researchers should avoid the use of racial variables as a proxy for ancestry and instead use empirical methods for assessing population structure as a first choice, self-reported ancestry as a second choice, and self-identified race only if there is no other reasonable choice. We acknowledge the practical challenges of getting accurate information regarding ancestry but feel it is within the power of all investigators to do better than to rely on self-identified race/ethnicity. We propose that self-reported

**Table 2**  
*Recommendations Regarding the Use of Race Variables in Genetic Studies of Complex Traits*

Stage of research	Recommendations	Tools and resources
1. Study design	Establish ancestry empirically; self-reported ancestry based on all 4 grandparents is an acceptable alternative when resource constraints are at issue.	Genotype all subjects for ~50 markers to assess degree of continental ancestry.
2. Recruitment	Recruitment based on self-identified race or other phenotype is acceptable.	
3. Phenotyping	Assess ancestry, pertinent aspects of SES directly.	Ancestry of grandparents; measures of social context (discrimination, education, income/poverty, social class); ethnic identity; appropriate environmental exposures.
4. Genotyping	Assess ancestry empirically.	Diagnostic test for presence of stratification (20 genetic markers/\$15 per subject). Individual determination (60 selected SNPs per subject, cluster with STRUCTURE, \$20 per subject).
5. Statistical analysis	Avoid the use of self-identified race variables. Include necessary covariates to capture relevant phenotypes directly.	
6. Interpretation and dissemination of research findings	Anticipate implications; explicitly raise, explain, and avert what may be racist interpretations of data.	Review findings with multidisciplinary team; attend to press.

*Note.* SES = socioeconomic status; SNP = single nucleotide polymorphism; STRUCTURE = computer program used to assess degree of population admixture based on multilocus SNP genotype data.

race no longer be used in genetic analyses as a proxy for ancestry if at all possible. In addressing population stratification, and given the ultimate goal of individualized medicine, we feel the first-line approach should be to use a sufficient number of random genetic markers to determine ancestry empirically. This approach addresses the valid methodological concerns without investing self-identified racial/ethnic categories with biological significance and is likely to represent a more accurate assessment of ancestry than self-report. In instances where resource constraints make direct empirical assessment of ancestry difficult, we support the use of self-reported ancestry based on four grandparents as a reasonable option.

## **2. Recruitment: Self-identified race will remain a practical approach for recruitment.**

Beyond meeting the laudable social goal of ensuring equal access to clinical trials and research results applicable to the full diversity of our population, we see several practical reasons for the continued use of self-identified racial categories in recruiting study subjects. Pragmatically, establishing ancestry using an empirical genotyping strategy is not feasible in the context of recruitment into clinical trials or many types of clinical research. We also acknowledge that self-identified racial categories do have some degree of overlap with genetically meaningful groupings based on continent of origin and that, further, certain rare alleles have been found to be enriched in specific populations so identified. We therefore believe that the use of self-identified race will remain a reasonably efficient and acceptable tool for recruiting subjects.

## **3. Phenotyping: Use more refined phenotypes in genetic analyses.**

Using more refined phenotypes would go a long way in both reducing the potential for social harm and increasing the explanatory power of genetic studies of complex traits. Socially relevant constructs should also be measured directly. A substantial amount of work has been done critiquing available measures of social status known to have a measurable impact on health. More work needs to be done to reach consensus on a minimum set of measures that adequately capture key influences and support provided in using and interpreting such measures. Key constructs include local level measures of poverty, individuals' social class and standing, experiences of racism, education, and ethnic identity, as discussed in greater detail below (Barbeau et al., 2004; Braveman, Cubbin, Marchi, Egerter, & Chavez, 2001; Krieger et al., 1997; Blank, Dabady, & Citro, 2004; Williams, Neighbors, & Jackson, 2003; Wright, 1996). Further, depending on the trait under study, key measures of relevant environmental exposures will also need to be included in analyses.

## **4. Genotyping: Establish continental ancestry empirically.**

Best practices for genotyping in association studies of complex human traits are constantly evolving. Several currently available approaches to establish ancestry empirically have been described (Bacanu, Devlin, & Roeder, 2000; Devlin & Roeder, 1999; Hoggart et al., 2003; Reich & Goldstein, 2001; N. A. Rosenberg et al., 2002; Satten, Flanders, & Yang, 2001; Wilson et al., 2001). We provide an example of one approach (Hoggart et al., 2003). First, 26,530 single nucleotide polymorphisms

(SNPs) have been screened in three populations (European, African American, and East Asian) to identify those with the greatest differences among these three populations (Akey, Zhang, Zhang, Jin, & Shriver, 2002; Shriver et al., 2003). Starting with 174 SNPs with the highest differences across groups (Akey et al., 2002), select the 60 SNPs with the highest  $F_{st}$  (i.e., quantitative measure of the degree to which a genetic marker can distinguish several populations) values ( $Mdn = 0.65$ , interquartile range = .60–.74) and genotype for these 60 SNPs. Many high-throughput academic and commercial genotyping facilities can accomplish this for less than \$20 per subject. If the NIH were to make this a priority and support a generally available resource dedicated to this purpose (see policy recommendations below), the cost could drop to under \$5 per subject.

Statistical clustering follows individual genotyping. This area is evolving, but at the current time, the program STRUCTURE (Pritchard & Rosenberg, 1999; Pritchard et al., 2000; Pritchard, Stephens, Rosenberg, & Donnelly, 2000) can be used to determine the degree of continental ancestry based on multilocus SNP genotype data. From prior results (Hoggart et al., 2003), these 60 selected SNPs will yield a series of continuous variables representing the percentage of continental ancestry (e.g., African, Asian, and European; Serre & Paabo, 2004). The accuracy of this approach should exceed 90% (Bamshad et al., 2003; Hoggart et al., 2003). We acknowledge that continental ancestry may be too imprecise for some genetic applications.

This approach can also be used empirically to determine the presence of population stratification. The number of subgroups in the sample (the STRUCTURE parameter  $K$ ) is a key estimate: If  $K$  equals 1, the data do not support the presence of genetic substructure, and if  $K$  is greater than or equal to 2, then there is empirical support for the existence of substructure.

## **5. Statistical analysis: Do not include self-identified race variables.**

If at all possible, the use of self-identified race in statistical analyses should be avoided—in addressing population stratification or as a proxy measure of cultural or environmental effects, as more direct assessments are preferable.

## **6. Interpretation and dissemination: Anticipate potential misinterpretations of study results.**

Many potential misinterpretations of genetic research results stem from the widespread lack of genetic literacy in the media and in the general public. Studies have documented distortions and misrepresentations of genetic research presented in the media and subsequent controversies (Geller, Bernhardt, & Holtzman, 2002). The problematic intersection of race and genetics—particularly in the context of behavior—requires a heightened sense of social responsibility among researchers, not only with respect to research practices but also with respect to how research results are framed and how they are likely to be interpreted and understood. Even if self-identified race variables are no longer used in genetic studies of complex traits, as we have suggested, there remains the potential for widespread misinterpretation of population differences based on continent of origin. To the extent that human variation is reported

along these lines, we encourage researchers to contextualize any reported results by clearly defining how these variables were constructed (“Census, race and science,” 2000; R. S. Schwartz, 2001), emphasizing that these categories reflect disciplinary practices but are somewhat arbitrary categorical measures of constructs that are continuous by nature (Serre & Paabo, 2004) and providing appropriate caveats that situate such findings within current debates within the field. Considerable social harm can be avoided with thoughtful efforts to anticipate and address potential misinterpretations of genetic research results.

## **Recommendations for Policymakers**

**1. Review of the NIH inclusion guidelines in the context of genetics research on complex traits.** The initial intention of the NIH inclusionary criteria was to ensure that subjects in clinical trials and other research reflect the diversity of the U.S. population. This appropriately but incompletely reflects the principles of beneficence and justice. The OMB classification scheme remains the dominant framework for monitoring and measuring health disparities. We question whether framing measures of “genetic risk” along these same lines will ultimately serve the goal of distributive justice and fear it may in fact generate additional harm for already overburdened and marginalized groups. Clinical trials should include diverse populations so that differential progression of disease or response to treatment among diverse groups of patients can be studied and understood. At issue is the underlying rationale for the grouping metric to be used.

We question whether the current OMB categories serve the purpose of reducing health disparities in the context of genetic research. Reducing disparities requires understanding the complex gene-gene and gene-environment interactions that together comprise disease risk and severity. The small number of putative alleles that have a higher frequency among minority groups using self-identified race according to the OMB classification will not offer significant explanatory power in explaining racial disparities in health. Rather, we should be focusing on the distribution of social and environmental risk factors known to interact with key genetic predispositions and direct intervention efforts to reduce these social and environmental risk burdens that often are distributed along racial lines in our society.

To the extent that genetic research identifies a higher frequency of alleles directly useful for tailoring prevention or treatment in racially defined subpopulations (according to the OMB categories), might this information be useful for targeting resources and interventions and tracking the impact of such on health outcomes? The answer, it seems to us, depends on the calculus of likely benefits versus harms accruing to a community so identified. If history were rife with examples of documented disproportionate burdens of illness being followed up with parallel disproportionate expenditure of effort and resources to eliminate such disparities, the answer to this question might be positive. History in this instance, however, is not reassuring. We fear framing genetic research in terms of the frequency

of putative alleles across racial groups risks widespread stereotyping of minority populations as inherently unhealthy in the minds of policymakers, providers, patients, and larger communities—and outweighs the potential benefits.

**2. Support research, development, and validation of a robust set of measures that directly measure specific social dimensions known to have an impact on health and health outcomes.** To support researchers’ efforts to abstain from using race variables as “sponge” proxies to control for numerous social, economic, and environmental factors that disproportionately affect minority populations in the United States and instead measure these constructs directly, we recommend that the NIH take leadership in reaching consensus on a core set of measures that address SES and in disseminating and promoting the use of such measures in genetic studies as well as federal and state data collection efforts. Further, appropriate measures of relevant environmental exposures for use in genetic studies of complex traits should also be developed, validated, and promoted (e.g., area-level measures of exposures such as diesel particles or level of overcrowding for inclusion in genetic studies of asthma). Responding to health disparities, a number of federal initiatives have already acknowledged the need to build national consensus on core measures addressing inequity and its determinants and to disaggregate populations beyond the global OMB racial/ethnic categories in order to assess disparities at the local level and target effective interventions to alleviate them (Ver Ploeg & Perrin, 2004). The global OMB racial/ethnic categories remain too gross to inform local level efforts to measure and address health disparities, and the lack of sufficiently nuanced measures of SES impede our understanding of the complex relationship among race/ethnicity, poverty, and health disparities. The Trans-HHS Cancer Health Disparities Initiative has issued several recommendations, including the development and adoption of a minimum core set of measures of race and ethnicity and SES in the collection and reporting of data, and the geocoding of all health records to latitude and longitude or to census tract to facilitate linkage to other geo-referenced data (U.S. Department of Health and Human Services & Trans-HHS Cancer Health Disparities Progress Review Group, 2004). An earlier multiagency initiative on health statistics in the 21st century (Friedman, Hunger, & Parrish, 2002) and the recent report by the National Academy of Sciences on measurement and data needs to eliminate disparities (Ver Ploeg & Perrin, 2004) are two more examples.

Questions have also been raised about resistance to incorporating measures of social class or social standing into public data collection efforts in the United States. Social class, as expressing a social relationship, is logically and materially prior to expression in distribution of occupations, income, wealth, education, and social status and is manifested empirically in diverse aspects of socioeconomic position, including occupational class and poverty (Krieger et al., 1997). Yet measures of social class or social standing are rarely included in public health surveillance data and only occasionally included in research studies in the United

States. The predominant measure of social class, as reflecting social relations and not simply occupational class, is that developed by Wright (Krieger et al., 1997; Wright, 1996), although this measure is only beginning to be used in U.S. studies. In the United Kingdom, however, measures of occupational class have a long-standing history in public data collection efforts and biomedical research (Peterson & Bunton, 2003). In 2001, the United Kingdom adopted the National Statistics Socioeconomic Classification (NS-SEC) for use in all government statistics and surveys (Office for National Statistics-United Kingdom). This measure, which can be based on self-report or empirical analysis of employment records, classifies individuals in one of five categories based on “aspects of work and market situations and of the labour contract” rather than on one’s skills or education level (Office for National Statistics—United Kingdom, Origins section, para. 4). The NS-SEC schema has only recently begun to appear in health studies in the United States. (Barbeau et al., 2004). A future core set of socioeconomic measures may also need to include this dimension.

Similarly, there are many challenges to be resolved in determining best practices for assessing the impact of discrimination on health (Krieger, 1999; Williams & Neighbors, 2001). A recent review (Williams et al., 2003) identified 53 studies on discrimination and health, the majority documenting a positive association. One of the key challenges in this area involves situating the impact of racism in the context of other measures of chronic, traumatic, and overall stress. Williams and colleagues (2003) have argued for measures that frame exposure to discrimination in terms of “unfair treatment,” believing that repeatedly asking whether a particular event occurred “because of your race” can lead to results that overestimate or underestimate responses, while others contend that such an approach fails to fully capture racial discrimination (p. 204). Development and validation of widely accepted and used measures of discrimination, which can be used to directly measure the impact of racial discrimination on health rather than rely on self-identity as a proxy for this and numerous other constructs, will go a far way in improving the specificity of future research.

While it may not be feasible to incorporate all relevant measures of social and economic standing, consensus should be developed regarding a limited set of appropriate, robust measures that could be easily incorporated into genetic studies. For example, a study analyzed 18 different area-based socioeconomic measures to determine best measures for monitoring socioeconomic inequalities in health (Krieger, Chen, Waterman, Rehkopf, & Subramanian, 2003). It found that census tract poverty level (percentage of persons below federal poverty level) powerfully detected expected socioeconomic gradients in health across seven types of outcomes, allowed maximal geocoding and linkage to other area-based data, and was feasible to implement within state health departments (Krieger, Waterman, Chen, Rehkopf, & Subramanian, 2004). Adjusting for just this one measure, for example, substantially reduced excess risk observed in the African American and Hispanic popula-

tions relative to Whites, and for half the outcomes, more than 50% of cases would have been averted if everyone’s risk were equivalent to those in the least impoverished census tract (Krieger et al., 2004). Collecting data needed to geocode at the census tract data would thus allow for powerful area-level measures of SES to be included in genetic studies with little additional expense to research efforts. Ideally, it would be important to collect individual, household, and area-level data (including data at different points in the life course) to fully elucidate the role of social location in the etiology of disease (Krieger et al., 1997). Genetic researchers are particularly positioned to be able to incorporate such measures into ongoing research initiatives with minimal burden. Clinical trials typically include a survey component, in which address information could easily be obtained to determine census tract. Finally, depending on the particular disease under study, genetic studies of complex diseases should also include relevant measures of pertinent physical environmental exposures. Leadership is needed to identify, test, validate, and promote such measures within the research community.

### **3. Provide additional support to genetic researchers to use empirical approaches to address population stratification.**

The social harms associated with continued use of self-identified race variables in framing genetic research results on complex traits are substantial enough to warrant strong policies to encourage the methodologically superior but far less harmful approach of using direct empirical assessment of ancestry. These approaches, however, are far more costly and burdensome relative to relying solely on self-identified race. We believe the risk of social harms is sufficient to warrant a considerable public investment in providing the resources and/or additional funding to genetic researchers to facilitate the diffusion of these new approaches. This could be accomplished in at least two ways. The NIH could provide grants to support centralized genotyping services, providing the necessary genetic data to address population structure. Alternatively, the NIH could provide supplemental funds to ongoing studies, specifically targeted to supporting researchers’ use of these various empirical methods for directly assessing ancestry. The tremendous power of the 1994 NIH inclusionary policies to shape research practices and culture has been clearly demonstrated. This influence could now be used to identify and promote best practices with respect to the use of race constructs in genetics research.

### **4. Promote interdisciplinary dialogue regarding genetic research practices and social policy.**

As our sophistication in understanding the complex interplay of gene-gene and gene-environment interactions in disease etiology and response to treatment grows, it becomes more apparent that this extraordinary complexity that determines human health requires an equally complex set of concepts, constructs, methods, and measures for incorporation into research designs. We believe the future of all biomedical research will be fundamentally interdisciplinary in nature. Only by tapping the best minds and most promising research across all the sciences, social

sciences, and humanities can we design better studies, interpret their results, and translate those findings into practice effectively. Once again, the NIH can play a tremendously formative role in shaping the research culture. Recent NIH experiments in multi-institute funding of large research centers required to reflect a transdisciplinary approach (Morgan et al., 2003) and the current NIH Roadmap (National Institutes of Health, 2004) both hearken this new future. Further efforts should be made to investigate and invest in the infrastructure, resources, and other supports needed to encourage meaningful interdisciplinary dialogue and research aimed at addressing these most difficult but most challenging questions regarding our potential to understand, treat, and prevent human disease and achieve improved health for all.

## Conclusion

The intersection of emerging genetic research and existing health disparities promises to pose continued challenges for genetic researchers, practitioners, and policymakers. Challenges remain at every stage of the research process, from designing studies and conducting research, to framing and communicating research results, to translating this research into clinical practice. At each point, different dimensions of the problematic intersection of race and genetics arise. Current practices in genetic research often include categorizing research subjects according to the OMB census categories through self-identified race variables. This has important implications for the reporting of genetic research results—framing them in terms of differences in the frequency of risk alleles across racial groups (e.g., African American vs. White) and thereby locating biological difference within socially defined communities. Given the social risks inherent in using such a categorization scheme in the context of behavioral genetics research and given that more elegant and powerful strategies for controlling for population admixture are now available, we call for an end to the use of self-identified race variables in genetics studies and for direct measurement of key underlying effects that race variables have traditionally captured. Insofar as genetic investigations into complex gene-environment interactions underpinning the etiology of complex traits spur the field to identify and use more refined measures of social and environmental factors in their analyses, as opposed to relying on gross proxy measures of race/ethnicity, genetics research may actually achieve a breakthrough in producing the nuanced data needed to strategically intervene and thereby reduce health disparities across socially defined racial/ethnic groups in our society.

The rapid pace of technological advancement in the scientific methods available and in the scientific base of knowledge about the genetics of complex traits promises to make many of our concrete suggestions dated in short order. As newer and better methods for addressing population admixture in studies of complex traits emerge, the overarching principle guiding research practice ought to be using the best strategies available to address valid methodological concerns while consciously reflecting on and minimizing potential social risks associated with the framing,

communication, and translation of genetic research results into clinical practice. As emerging genetic research on complex traits is able to provide new, more effective treatment strategies that have the potential to improve health outcomes and reduce the unacceptable burden of illness on poor and minority communities, translating this new knowledge into effective interventions is a national priority. The extent to which genetic research on complex diseases and behaviors ultimately addresses or exacerbates existing health disparities in the United States is surely one critical measure against which the enormous public investment in genetics research ought to be judged.

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