Racializing Drug Design: Implications of Pharmacogenomics for Health Disparities

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Current practices of using “race” in pharmacogenomics research demands consideration of the ethical and social implications for understandings of group difference and for efforts to eliminate health disparities. This discussion focuses on an “infrastructure of racialization” created by current trajectories of research on genetic differences among racially identified groups, the use of race as a proxy for risk in clinical practice, and increasing interest in new market niches by the pharmaceutical industry.

The confluence of these factors has resulted in the conflation of genes, disease, and race. I argue that public investment in pharmacogenomics requires careful consideration of current inequities in health status and social and ethical concerns over reifying race and issues of distributive justice. (Am J Public Health. 2005;95:2133–2138. doi:10.2105/AJPH.2005.068676.)

THE COMPLETION OF THE Human Genome Project has heightened public anticipation of the potential fruits of genomic medicine. The era of “personalized medicine” and the development of differentiated strategies for the prevention of disease at the molecular level has fueled expectations of improved health through targeted therapeutics. These technological developments have fostered the burgeoning field of pharmacogenomics in the study of gene-to-gene interactions using high-throughput technologies.

One goal of pharmacogenomics is to identify drug response for molecular subgroups using differential diagnosis during the early stages of drug development to create “tailored” drugs of greater efficacy.

How such molecular subgroups are characterized reveals the continued salience of “race,” despite the widely publicized conclusion of the Human Genome Project that humans share 99.9% of their genetic makeup. A review of the pharmacogenomics literature indicates a particular emphasis on stratifying patient populations by race or ethnicity. In the absence of cost-effective methods of sequencing individual genomes in clinical settings, research on human genetic variation is increasingly conducted among racially identified populations.

This approach mimics the long-standing practice in clinical medicine of identifying patients by race and ethnicity. Clinical care, including disease risk analysis, has often incorporated perceptions of race in clinical judgment and decisionmaking. Building on these practices, pharmaceutical companies may easily adopt conventional notions of race in marketing pharmacogenomic products. The use of race as a proxy for genetic relatedness has been widely criticized.

The conflation of race with genetics opens the door to prejudice, racial stereotyping, and overly simplistic conceptualizations of pharmacogenomic interactions, which could ultimately lead to poor health care.

I discuss an “infrastructure for racialization” in biomedicine and drug development and its implications for public health. This infrastructure includes research on human genetic variation that maps genes to social categories of race as used in the United States, the pervasive use of race as a proxy for risk in clinical medicine, and the search for new “racially inscribed” market niches by the pharmaceutical industry. Although it has been predicted that pharmacogenomics will usher in an era of personalized medicine, population—rather than individual—differences continue to be the focus of much of current research.

In research design, race and ethnicity remain important factors in identifying study populations. Numerous studies in the pharmacogenomics literature conclude that racial and ethnic differences exist among drug-related enzymes. Most of these studies categorize research participants by self-identified race or ethnicity and compare frequencies of candidate alleles. Although several studies have suggested that race will be rendered obsolete once underlying genetic mechanisms are identified and that the use of race in genomic research is merely an interim solution, much evidence suggests that the current infrastructure built up around racialization may stymie efforts to use genetics to counter notions of a racial biology. This debate over the relationship between race and genes is more than merely academic: at stake are struggles over equity, access, and resources for public health.
WHY PHARMACOGENOMICS?

Reducing Adverse Drug Reactions

The efficacy and toxicity of most drug therapies vary widely among individuals. In their meta-analysis, Lazarou et al. estimated that in the United States, more than 100,000 patients die and 2.2 million are injured annually from adverse drug reactions. Incidence of serious and fatal cases among hospitalized patients has been reported at 6% to 7%, making adverse drug reactions the fourth leading cause of death in the United States. Currently, negative effects from medications are monitored only after the drugs are prescribed to patients. On a case-by-case basis, clinicians adjust dosage and treatment type according to the reported reactions of individual patients to initial prescriptions. This trial-and-error approach has been criticized for exposing patients to potentially harmful drug therapies as well as making inefficient use of costly clinical consultation time.

The health care cost of drug-related morbidity and mortality in the United States is estimated to be $177.4 billion annually. Of this total figure, approximately $101 billion is believed to be avoidable. By studying human genetic variation, researchers hope that adverse drug reactions will be minimized and that safety and efficacy will be improved for genome-based medications. The promise is one of a personalized medicine in which individuals will receive the “right” medication as dictated by their unique genetic signatures.

Efficiency in Drug Development

The pharmaceutical industry, which invests approximately $24 billion annually in the research and development of new drug therapies, has suggested that pharmacogenomics research may produce more efficient and effective medications. Savings could reach 60% of current costs, which now average $880 million to bring 1 drug from bench to market. These savings would not be limited to the pharmaceutical industry but are expected to dramatically reduce the overall cost of health care in the United States. Pharmacogenomics could potentially allow significant recovery by pharmaceutical companies of money spent on “orphan drugs.” Orphan drugs are products that either have been abandoned because the costs of bringing them to market would exceed expected earnings from their sales or have failed tests because of side effects experienced by subjects in clinical trials. By identifying specific populations that may benefit from these drugs, pharmaceutical companies may be able to salvage drugs, labeling them for and marketing them directly to the people who would benefit most.

In developing new drugs, pharmacogenomic testing could be used in clinical trials to identify potential study participants with genotypes associated with an intended drug response. Costs of recruiting participants for phase II clinical trials—in which drugs are examined for efficacy, dosage, and side effects—and phase III clinical trials—in which drugs are further tested against current standards of care and for rare side effects—could decrease by “enriching” the study population with people having the candidate genotypes. As a result, fewer participants would be needed to achieve the anticipated effect, and the time spent on these stages of drug development would decrease. The drug would then be labeled for use only by people with the genotypes in question. Although such approaches may prove to be efficacious, the question remains of whose genotypes will be the focus of interest for these newly tailored therapeutics. Unless the entire population is genotyped, how will race and ethnicity influence decisions to selectively enroll individuals into clinical trials? What are the scientific, economic, and medically relevant issues that will inform such decisions? And how will such decisions affect current health disparities?

THE INFRASTRUCTURE OF RACIALIZATION

Several researchers have argued that recent developments in genetic variation research will render race, as defined by distinctive genetic signatures, obsolete (S. Lee, PhD, unpublished data, 2005). The argument is that race and its proxies, including skin color, eye shape, and enzyme metabolism, will no longer be necessary for research once specific genetic correlates are identified. Underlying this prediction of a race-free genomic era is the assumption that research on human genetic variation will proceed untainted by dominant social ideas and values regarding what constitutes human difference. Whereas much of the focus on race in science has formed a largely harmonious chorus against the concept’s use as a biological category for human groups, little attention has been given to the ways in which bodies and bodily materials are nonetheless racialized institutionally. Closer inspection of the infrastructure of racialization is needed to fully understand how race may be produced and inscribed onto human DNA, as opposed to being “discovered” in the research process.

I discuss 3 areas from which the infrastructure of racialization emerges. The first is current research on human genetic variation—specifically, efforts to create national DNA repositories within which genetic samples are catalogued by racial and ethnic identifying information. The second is the embedded practice in clinical medicine of incorporating perceptions of racial and ethnic identification and concomitant assumptions of biological difference into clinical decisionmaking. The third is the pharmaceutical industry’s increasing interest in racially identified patient populations as profitable market niches. These areas of research, clinical practice, and commercial development build an infrastructure of racialization whereby race becomes a central focus in the search for meaningful differences.
among groups. The confluence of these efforts and practices might not foreshadow the predicted era of personalized medicine; rather, the current trajectory may be one of race-based medicine that further reifies race as a naturalized, immutable biological reality.

**Mapping Race and Genes**

Critical to the realization of personalized medicine is the creation of large population databases that store both genotypic and phenotypic information. The inclusion of demographic details with disease history will be crucial in expediting disease association studies that support pharmacogenomics. A challenge of such research is identifying specific candidate genes associated with drug response. Many scientists have called for the creation of large databases similar to the Icelandic deCode genetics project and the emerging UK Biobank to further these trajectories of research.2,21 Francis Collins, director of the National Human Genome Research Institute of the National Institutes of Health, has stressed the need for large-scale mapping efforts to engage with ethical raw material for research on human genetic variation.

The National Human Genome Research Institute is currently engaged in a project called International HapMap, which the institute hopes will enhance disease association and drug response studies by providing a reference map for identifying common haplotypes from the DNA of individuals of Chinese, Japanese, Yoruban, and Northern European ancestry. The decision to identify participating populations by racial and ethnic categories was justified by the institute in part by research suggesting that common haplotypes differ in frequency between populations of different continents. The institute defended its decision by stating that “genetic data from more than one population will enhance the ability of researchers to study the genetic contributions to diseases that are more or less prevalent in different groups.”22

Whereas the selection of the populations resulted in part from sociopolitical concerns and efforts to engage with ethical concerns over DNA sampling (S. Lee, PhD, unpublished data, 2005), the resulting sampling strategy closely parallels notions of race as understood in the United States, thus providing critical raw material for research on the relationship between race and genes.

This publicly funded effort to create a haplotype map that captures genetic diversity has found echoes in the private sector. In February 2005, the journal Science published an article reporting on the genome sequencing of 71 individuals of European, African, and Asian ancestry by the Silicon Valley company Perlegen.23 Although the authors concluded that the 3 populations shared approximately 80% of common haplotypes, this map, like the HapMap, provides further tools for comparative research that links genes to race.

The lingering question is, if there is no genetic basis for race, then why do large-scale mapping projects continue to use racial categories in identifying research populations? Furthermore, by selecting populations that are geographically separated from one another, the genetic distance between groups is accentuated, which results in a recapitulation of the stereotypical prism of race as White, Yellow, and Black. If critical tools such as the HapMap and the Perlegen map were to include populations with ancestries from the Middle East, South Asia, and multiple areas of Africa, which reflect more nuanced, gradual differences among populations, research on human genetic variation might uproot conventional notions of racial boundaries and inspire new trajectories of research that dispense with age-old notions of racial difference.

**Racial Profiling in Biomedicine**

The use of racial categories in human genetic research parallels the use of race in clinical medicine. In medical practice, race often is used as the best available proxy for risk. In an article in the New York Times Magazine, Sally Satel, a practicing psychiatrist and author of PC, MD: How Political Correctness Is Corrupting Medicine,24 asserted:

In practicing medicine, I am not colorblind. I always take note of my patient’s “race.” So do many of my colleagues. We do it because certain diseases and treatment responses cluster by ethnicity. Recognizing these patterns can help us diagnose disease more efficiently and prescribe medications more effectively. When it comes to practicing medicine, stereotyping often works.25

Satel further argued in her essay that enzymes associated with drug response differ among racial groups and that not paying attention to race does a disservice to patients.

Although Satel defended the use of race as a morally justified practice in medicine, pervasive but inexplicit use of race in clinical practice may result in disparities in standards of care. For example, studies have indicated that clinicians are less likely to prescribe pain medication to Black patients than to White patients with the same clinical presentation.26,27 Although little research has been done on why such differences persist, social knowledge about race may significantly affect clinical decision-making, reflecting prevailing assumptions of biological differences among groups. Such entrenched practices are powerful precedents for the translation of research findings that link genetic differences to race into health care approaches and policies.

**Racialized Populations: The New Market Niche?**

The third critical component of the infrastructure of racialization that may significantly affect directions in pharmacogenomics is the increasing demands of the marketplace. Much of the success of the pharmaceutical industry is the result of a focus on common disorders such as heart disease, depression, and diabetes and the creation of “blockbuster drugs”
intended for the general population. However, over the past several years, increasing interest has focused on drugs intended for much narrower patient populations. This interest has been motivated by several factors, including greater competition among companies that produce drugs within the same class and fear of liability from severe side effects. Although the potential market share of a particular drug may be limited, the number of drugs available to the smaller patient population also may be reduced, and companies thus stand a better chance of being one of a few suppliers in a smaller market. The challenge for companies interested in diversifying their drug markets will be to identify narrow market segments for which few therapeutic choices are available.

The use of race may prove to be an effective way of identifying therapeutic populations. By using race as a proxy for genetic variation in targeting patient populations, companies may seek to bypass the need for costly pharmacogenomic testing. The launch of BiDil, an antihypertensive drug that was approved by the US Food and Drug Administration (FDA) in June 2005 for use among self-identified African Americans, reflects the reality of race-based therapeutics. In explaining the drug’s effectiveness among African Americans, Nitromed Inc, the maker of BiDil, cites a “distinctive pathophysiology found primarily in African American patients” that causes nitric oxide insufficiency.28

Upon FDA approval, BiDil became the first drug labeled exclusively for a racially identified population, thus setting a precedent for the use of race as a proxy for biological variation.

During a recent international conference on the biotechnology industry, a session titled “Drug Development and Minority Populations” was organized to focus attendees’ attention on the new market niche of racial and ethnic groups. During this session, Michael Loberg, president and chief executive officer of Nitromed, emphasized that developing drugs for underserved populations such as Blacks and Hispanics makes “good business sense,” as these populations have been largely untapped by the pharmaceutical industry.28 Although the launch of BiDil may not portend the development of further drugs targeted for minority populations, BiDil’s success clearly rests on assumptions of distinctive racial biologies.

IMPLICATIONS OF RACE IN PHARMACOGENOMICS

The pervasive use of race in biomedical research and practice, coupled with increasing corporate interest in “ethnic minority markets,” may significantly shape the direction of pharmacogenomics, in which race is tied more closely to conceptions of genes, medicine, and disease than to sociopolitical histories that create group boundaries. Although pharmacogenomics is still in its nascent, we must consider the implications of race in the field’s development—in particular, how the deployment of race affects ethical and social principles and values of privacy, equity, and distributive justice.

Central to this discussion is the tension between the needs of individuals and responsibilities to the larger social body. Rhetoric about pharmacogenomics has focused on the delivery of individualized medicine. Although greater drug efficacy and efficiency are desirable goals for improving human health, investment in such efforts may come at the expense of other public health objectives. Is it ethically justified to devote scarce resources to tailoring drugs to individuals when millions lack access to routine health care services? Is race a legitimate axis for differentiating patient populations and distributing pharmacogenomic products? If so, would developing drugs for use exclusively in White patients be an equally legitimate use of public investment? And if not, what principles determine who should be the recipients of the anticipated benefits of pharmacogenomic products?

Unintended Consequences and the Reification of Race

The reality is that although the rhetoric about personalized medicine focuses on notions of “individualized therapy,”29 population-based differences continue to serve as the bedrock of ongoing research. Defining populations therefore becomes a central dilemma in which the significance of race looms large as a controversial issue. Responding to an editorial in the New England Journal of Medicine claiming that “race” is biologically meaningless,30 Risch et al. asserted that self-reported “race” and ethnicity are significantly correlated to human genetic substructure.31 The authors defended the use of race as a legitimate and necessary research variable by claiming its importance in mitigating health disparities. They argued that “Every race and even ethnic group within the races has its own collection of clinical priorities based on differing prevalence of diseases.”31 If this assertion is true, are those differences the result of distinct biologies or are other factors occluded by dominant ideas of racially distinct groups? And, if the clinical priorities of groups tend to overlap, is it dangerous and dishonest approach to label as “racial” the minor differences in allele frequencies that do exist?

Confusion regarding the meanings of difference, disparity, and race as they relate to health and disease warrants careful scrutiny of how “race,” in the name of eliminating health disparities, has been framed. The Institute of Medicine’s report on health disparities makes clear that race has a significant impact on health status and emphasizes that many of these differences are environmental and coincide with racial identity in the United States.32 Although the government has institutionalized “race counting” to ensure that racially and ethnically identified individuals are included in federally funded biomedical research, researchers feel little pressure to be explicit about the meaning and significance of racial and ethnic identity in framing their research hypotheses.
Although institutional mandates may have been created to redress exclusion and exploitation in biomedical research, the practice of sorting and counting without explicit working definitions of what race means for specific research questions can cause confusion and misinterpretation of research results. An unintended consequence may be that notions of a racial biology are favored, and the role of environmental conditions that give rise to inequitable distribution of resources and access to opportunities—and thus to population-based differences in health status—are deemphasized.

Furthermore, the use of US census categories to identify research subjects is problematic. Increasing the participation of historically underrepresented groups in biomedical research is an important public health goal that requires policy interventions. Although using census categories provides administrative continuity, this is not the best taxonomy to use to answer questions of genetic differences between groups in pharmacogenomic research. A national interdisciplinary dialogue on the use of racial and ethnic categories in biomedical research and clinical practice that critically analyzes the implications of such categorizing practices is long overdue.

Need for Greater Institutional Oversight of Race-Based Scientific Claims

Although open dialogue is a necessary step toward better understanding of the meaning of race for health care, addressing the infrastructure of racialization will require changes on an institutional level. The case of BiDil provides a useful illustration of the need for gatekeepers such as the FDA to provide institutional guidance when race-based findings are included in applications for therapeutics.

In its review and ultimate approval of BiDil, the FDA advisory committee put forth 2 seemingly contradictory arguments. The first was the claim that the approval of BiDil was morally imperative because of significant health disparities among Blacks. The logic is that an antihypertensive medication with greater efficacy among Blacks is an important step toward addressing the greater burden of disease among this group. The second argument was that race is the “best available proxy” for genetics, suggesting that use of race is acceptable only until further research reveals the biological mechanisms underlying differential drug response. As such, race is justified as merely a way station on the road to personalized medicine.

The juxtaposition of these 2 claims reveals a recurrent paradox in discussions of race and pharmacogenomics and biomedicine more generally. The first claim suggests that some racially identified populations respond particularly well to certain drugs because of biological differences and that these differences also may contribute to health disparities. The argument simultaneously frames both race and health disparities as having biological bases. However, the second claim asserts that race will be rendered obsolete once underlying variables are identified. The paradox emerges when the use of race is justified in the first instance by a “racial biology” and yet, in the second instance, is qualified as a temporary solution, ultimately having little explanatory power.

What is most disturbing about the paradoxical use of race is the effect it may have on the trajectory of ongoing human genetic variation research. By making the moral argument that race-based therapeutics address injustice in health care, and at the same time maintaining that genetics research will ultimately eliminate the need for racial categories, racialization is allowed to proceed unchallenged despite its inherent contradictory claims that race is both biologically meaningful and meaningless. Rather than serving as a way station, the use of race is allowed to become more fully embedded in the production of scientific knowledge and medical practice.

Institutional leadership must look past race to the specific variables that cause differential findings among groups. The FDA should require investigators and companies that attribute differential drug response to race to pursue additional research that further explicates the underlying mechanisms. At a minimum, research data used to draw race-based conclusions should be made available to enable other researchers to further study the basis for findings of difference among groups. Without measures to make these data available for examination, race is allowed to remain the explanatory tool in interpreting such differences.

Balancing Market Segmentation With Equitable Benefit Sharing

Leadership by federal agencies, including the NIH, FDA, and the Department of Health and Human Services, that have adopted the use of census categories in biomedical research is needed to fully consider the social and ethical implications of pharmacogenomic research and development. Although the rhetoric for pharmacogenomics has focused on a utopian era of personalized medicine, little consideration has occurred regarding how pharmacogenomic medicine may affect the principle of distributive justice, and, in particular, who will benefit from newly developed tailored drugs. Pharmacogenomic research has the potential of stratifying individuals into patient groups on the basis of a combination of genotypic and phenotypic information.33,34 Smaller groups who have rare alleles could be perceived as unattractive for pharmaceutical investment.35,36 Pharmacogenomic research may be pursued to a greater extent among populations that are believed to constitute larger, more profitable market shares. Currently, regulatory measures are lacking that would counter disincentives to develop pharmacogenomic products and services for potential orphan patients.37,38 Regulatory guidance of pharmacogenomic research, including industrial development, is needed to ensure that larger public health goals are met. Such guidance could balance the potentially conflicting priorities of national health initiatives and commercial
interests. The FDA has recently taken steps to work with pharmaceutical companies on policies regulating the submission of pharmacogenomic data for clinical trials. Further discussions on policies regarding the segmentation of potential markets (e.g., the emergence of orphan patient populations and equity issues pertinent to racially identified populations) are necessary. Such discussions may provide answers to the question of what should be the most critical public health goals for research on human genetic variation. Public discourse may trigger institutional changes that would dismantle the infrastructure of racialization, which leads to paradoxical thinking and practices regarding the use of race. The starting point may be to ask how our ideas of human difference will inform processes to justice in genomic medicine. Only after answering this question can work toward eliminating health disparities begin.

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References