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Beyond Best Practices: Strict Scrutiny as a Regulatory Model for Race-Specific Medicines

Osagie K. Obasogie

Race is becoming an increasingly common lens through which biomedical researchers are studying the relevance of genes to group predispositions that may affect disease susceptibility and drug response. These investigations contravene decades of research in the natural and social sciences demonstrating that social categories of race have little genetic significance.¹ Nevertheless, a resounding debate has ensued over the utility of race in biomedical research — particularly as new drugs claiming to serve particular racial populations enter the marketplace. Now that the Food and Drug Administration (FDA) has approved BiDil as the first race-specific treatment despite conflicting evidence and unsettled debates, is there a way for federal regulators to promote research that may address minority health concerns without giving undue credence to the dangerous idea that social understandings of race are genetically relevant? It may be useful for the FDA to turn to an area with experience negotiating such dilemmas — constitutional law — and its approach — strict scrutiny — to help guide when and under which circumstances government should give effect to racial categories in biomedicine.

Controversy over the Relevance of Race to Biomedical Research

Much of the 20th century's struggles around race involved challenging the problematic link often made between social categories of race and presumptions surrounding groups' heritable predispositions. Yet new research looking at the genetic underpinnings of disease, health outcomes, and drug response is rethinking this approach, giving renewed credence to arguments suggesting that social categories of race reflect meaningful genetic differences. Though there is considerable evidence demonstrating the social determinants that give rise to racial disparities in health outcomes,² research using race as a proxy for groups' biological predispositions is becoming a remarkable trend at the intersection of population genetics and biomedical research. Some argue this will dramatically reshape clinical interactions and health care delivery.³

This has stirred a heated debate in scientific and bioethical communities over when and how race should be used in biomedical research. Those supporting the use of race and ancestral background point to at least three sets of studies in population genetics that osten-

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sibly show significant genetic variation both within racial and ethnic subpopulations and among the five main racial groups defined by continental ancestry.⁴ First, population genetic data from indigenous groups have enabled researchers to construct ancestral tree diagrams that presumptively show that human genetic diversity can be apportioned along five major branches that roughly correspond to the five main continents.⁵ Second, multi-locus genetic data and cluster analyses have resulted in genetic delineations that roughly map onto self-identified racial groups and continental ancestry.⁶ Third, researchers have shown that alleles (genetic variants) with a frequency of 20% or more in one racial group are likely to appear in others, but alleles appearing less frequently are more likely to be contained within the racial group.⁷ Since Africans have greater genetic variability but more low-frequency alleles, race-specific genetic variants are deemed to be more common among this group. This “indicate[s] that the frequency of variant alleles underlying disease or normal phenotypes can vary substantially among racial groups, leading to differences in the frequency of the phenotype themselves.”⁸

While these studies give the appearance of a correlation between certain genes and social categories of race, there has been a growing critique concerning how these studies might reify rather than reveal race as a genetic category. Evolutionary geneticist James L. Graves has pointed out how physical anthropologists and geneticists have repeatedly demonstrated the principle of discordance since the 1940s: that populations’ physical features and genetic variations do not consistently correlate with one another. Graves notes that “if one attempts to take multiple physical characters to define racial groups, you arrive at categorizations that are not indicative of their evolutionary history.”⁹ And, in a related critique, physical anthropologist Deborah Bolnick has raised important questions concerning the methods used to infer individual ancestry from genetic data — methods that are also used to support arguments that social understandings of race are reflected in populations’ underlying genetic structures.¹⁰ With regards to two oft-cited articles by Noah Rosenberg et al. and Michael Bamshad et al. that use the computer program *structure* to identify genetic clusters that correspond with geographic origin, Bolnick shows how the evidence for genetic clustering around ancestry does not arise organically out of the data but depends heavily upon a series of questionable assumptions — both from the underlying program and its users.¹¹

Others have also raised serious doubts as to whether race, as a social category, is significant to genomic research. Racially targeted therapies are based upon

the presumption that the frequencies of alleles that influence drug efficacy are meaningfully and predictably different for each race. The science supporting this conclusion, however, is far from conclusive. For example, where microsatellite loci have been used to ground classifications that approximate continental groups, the results have been questioned:

[It] depends in part on the cumulative effect of minor differences in the frequencies of common alleles and in part on the effect of population specific alleles. In neither case is it apparent that such differences have relevance for traits that are important to health. Most population-specific microsatellite alleles are unlikely to be functional; rather, like a last name, they merely help to verify the geographic origin of a person’s ancestry.¹²

Moreover, some have argued that allele frequency may not be particularly relevant to pursuing a genetic basis for racial categorizations in biomedical sciences. Using allele frequencies to categorize people is arguably “not the same as apportioning the whole of human diversity into medically relevant categories. The more germane outcome — that the sets of common functional polymorphisms are distributed in discrete racial categories — has not been demonstrated.”¹³ Most population geneticists continue to agree that the vast majority of all genetic variation occurs within continental populations, not between them.¹⁴

Those who question the utility of race to genomic research are not only troubled by what they perceive to be inconclusive and unpersuasive science, but also by the social harms that may result when social categories of race are prematurely accepted as reflecting real genetic divisions among humans. What is particularly troublesome for these commentators is the extent to which minorities in general, and African Americans in particular, are assumed to be genetically predisposed to a remarkably high number of chronic diseases when little genetic data has been systematically analyzed and various social and environmental factors remain inextricably intertwined. To many, the recent trend within the biomedical sciences to demonstrate how blacks are genetically predisposed to adverse health outcomes creates conditions where society stops looking at the often discriminatory environmental and structural conditions that strongly correlate with these health disparities. Troy Duster notes that using *social* categories such as race as an explanatory proxy for *genetic* differences in health outcomes creates a “complex feedback loop and interaction effect between phenotype and social practices related to that

phenotype...[that is] poised to exert a cascading effect — reinscribing taxonomies of race across a broad range of scientific practices and fields.”¹⁵

These debates are as robust as any contemporary discussion in the biomedical sciences. Any reasonable, science-driven resolution or consensus will require decades of clinical research supported by millions of dollars. In the meantime, it is not enough to say that this research should categorically stop given the explosive nature of this conversation; not pursuing race-based medicines may leave the most vulnerable populations without life-saving or life-improving medications. On the other hand, it is similarly important to grapple with the gruesome historical relationship science has had with race and, in particular, the real threat to minority communities when their adverse social or health outcomes are discussed as a function of who they are.

The circumstantial evidence supporting BiDil’s race specific claims may be persuasive to some but is far from conclusive. Though BiDil, a pill containing hydralazine and isosorbide dinitrate, had been tested in two earlier clinical trials (V-HeFT I and V-HeFT II), its FDA approval was propelled in large part by the African-American Heart Failure Trial (A-HeFT). This trial only enrolled patients that self-identified as Black¹⁶ — an unorthodox decision “based on observations of differences in prevalence, risk, profiles, causation, disease severity, outcomes, and response to therapy between black patients and white patients with heart failure.”¹⁷ Though social scientists question the methodological soundness of research findings relying solely on self-identified race,¹⁸ the A-HeFT researchers found the trial results to be promising: the placebo group experienced a significantly higher mortality rate and lower quality of life than patients using BiDil,

Steven Nissen noted that the committee “us[ed] self-identified race as a surrogate for genomics” when they advised the FDA to approve BiDil’s race-specific indication. This is only one example of how race as an entrée to personalized medicines is becoming an increasingly important consideration for federal regulators and why the FDA should prepare for what many predict will be nothing short of a revolution in how we approach health care.

The Emerging Racial Pharmacy

In the midst of these debates, the bricks and mortar of the racial pharmacy are being put into place. BiDil, a drug patented and marketed by NitroMed to treat African American heart failure, arrived on the scene in June 2005 as the first drug to receive FDA approval for treating a specific racial group.

BiDil has been widely cited as exemplifying a breakthrough in personalized medicine. Though not a pharmacogenomic product per se, BiDil lends credibility to race based genomic research by advancing the logic that it is indeed possible, if not preferable, to use race as a presumptively genetic marker to segment drug markets. As the first drug patented as race-specific (a *legal* claim about race and genetics), the first to be approved by the federal government as race-specific (a *state* claim about race and genetics) and the first to be marketed as race specific (an *economic* claim about race and genetics), BiDil represents a remarkable step forward in giving credence to the idea that social categories of race can be an appropriate proxy for yet to be known genes that are both unique to particular racial groups and the cause of specific health outcomes.

suggesting that BiDil works differently in Blacks than other groups. Nonetheless, many have raised serious concerns as to whether a clinical trial that only included blacks can show, as a matter of science, that they respond *differently* to a drug than other racial groups.

A central concern here is as much about how people think about race and racial disparities as it is about particular health outcomes. BiDil’s ostensible effectiveness notwithstanding, the logic underpinning its arrival worries many — particularly in the context of inconclusive research over the utility of race as a predictive category for drug response. Health care practices that fixate on molecular and genetic differences as an explanation for racial disparities in health may prematurely deflect attention from known social determinants of health: economic class, social conditions, and environmental factors among others. Allowing markets to move this discussion to local pharmacies before scientists can come to some reasonable consensus may be premature; some blacks with heart failure may *individually* benefit from BiDil, but the black *community* as a whole may suffer if this leads to

an uncritical acceptance that resuscitates the dangerous idea that differences in phenotype, their adherent social meanings, and racial disparities in health outcomes are observable at a molecular level.

Commentaries on BiDil and the future of race-specific medicines have been predictably heated. Some proponents of race-based therapies concede that race is an imprecise if not crude marker for understanding genetic variance, yet ultimately find it to be a useful proxy until specific genetic markers become available to treat genotypes rather than phenotypes.¹⁹ Others have noted both the cultural and economic difficulties of transcending race once it has been accepted as an explanatory factor in health outcomes and medical treatment. Duster notes that race as an “interim solution” can still do much harm once given scientific legitimacy.²⁰ And, after noting the market incentives leading to BiDil’s development,²¹ M. Gregg Bloche argues that pharmaceutical firms with patent protection and regulatory approval for race-specific medicines have little incentive to sponsor research aimed at finding the relevant genetic variations that would obviate their previous research and devalue their intellectual property.²² Still others hypothesize that blacks may have a genetic predisposition towards nitric oxide deficiency that BiDil can address.²³

Though these commentaries have provoked much thought and discussion, they have largely not offered a way to balance the pragmatic need to remain open to potentially beneficial race-based medicines with the need to minimize misleading conversations over the genetic relevance of race. Is there a way for public policy to take into account both the potential health benefits of race-specific drugs and the attendant social risks of geneticizing race?

Strict Scrutiny as a Regulatory Model

Despite ongoing investigations, BiDil’s effectiveness has not been linked to any genetic mechanism. Remarkably, this did not prevent BiDil’s clinical trial results and race-specific new drug application from being interpreted as such. Steven Nissen, chair of the FDA’s Cardiovascular and Renal Drugs Advisory Committee, noted that the committee “us[ed] self-identified race as a surrogate for genomics”²⁴ when they advised the FDA to approve BiDil’s race-specific indication. This is only one example of how race as an entrée to personalized medicines is becoming an increasingly important consideration for federal regulators and why the FDA should prepare for what many predict will be nothing short of a revolution in how we approach health care.²⁵

Currently, the FDA is without formal regulations or procedures on how to review new drug applications

that target specific races beyond its traditional focus on safety and efficacy, which are informed almost exclusively by clinical observations.²⁶ This limited scope may lead FDA officials to miss key social and ethical concerns that are not immediately demonstrable in a clinical context — particularly when biotechnological innovations are involved. Take as an example the FDA’s claim of regulatory authority over human reproductive cloning.²⁷ Ostensibly, if someone were to attempt to clone a human being and demonstrated that it could be performed safely and effectively, then the FDA could approve the procedure. But, this mandate does not necessarily address broader social concerns over human reproductive cloning that exist regardless of how safe or effective the procedure may be. This is but one example of how biotechnology requires a different sensitivity and sensibility because of its unprecedented power to reshape basic human relationships.

To understand how government can best negotiate this growing relationship between biotechnology and race, constitutional law may offer a bit of guidance. In areas such as employment and education, the United States Supreme Court has subjected the state’s use and approval of racial categories, even for benign purposes, to close examination. The application of this doctrine, known as strict scrutiny, came out of a concern that federal and state governments should neither create nor enforce illegitimate racial classifications that may prove to be discriminatory or unduly burdensome given the troublesome context of American race relations. But, strict scrutiny also recognizes that some racial classifications may not only be helpful, but essential to address ongoing inequalities. Strict scrutiny as applied to race developed in the mid-20th century as a function of the 14th Amendment’s Equal Protection jurisprudence, which had an original “pervading purpose...[to promote] the freedom of the slave race, the security and establishment of freedom, and the protection of [Blacks] from the oppressions of those who had formerly exercised unlimited dominion over him.”²⁸ Though Equal Protection’s contours have certainly changed since the Supreme Court offered this language in 1873, it is important to note that this idea of giving state-enforced racial categories an extra level of scrutiny comes out of a longstanding commitment to racial equality and remedying past injustices.

Strict scrutiny does not hold that all racial classifications are impermissible per se, but only that they should raise of our suspicion. In order to prevent harmful or needless racial categorizations, strict scrutiny requires that when the state gets into the business of racially classifying individuals, these categories should be “narrowly tailored to further compelling

state interests.”²⁹ The state has the burden to demonstrate that its purpose is significant, non-discriminatory, and not exploitive. As the Supreme Court notes in *Richmond v. J. A. Croson*, a case on the constitutionality of so called “minority business set asides,” the purpose of strict scrutiny is to ensure that government is “pursuing a goal important enough to warrant use of a highly suspect tool.”³⁰ This has led to a few remarkable balancing acts in terms of how public entities use racial categories in their daily practices, even when these practices may benefit minority populations. For example, in the affirmative action context, universities can take race into account when reviewing applications for the purpose of increasing racial diversity, but may not use quotas.

As the gatekeeper standing between these powerful technologies and their public impact, strict scrutiny highlights a critical point that the FDA should consider when reviewing pharmacogenomic and other

apply to help ensure that race-specific drug claims meet minorities’ needs in compelling and meaningful ways and are not irresponsibly driven by commercial desires. It can also help make sure that the individuals that benefit the most from the drug continue to have unimpeded access to it.

Since there is no precedent for how Equal Protection should inform the use of race in biomedicine, a number of commentators have discussed its possible relevance. Erik Lillquist and Charles Sullivan have taken an exhaustive look at the legal relevance of this issue, including how Equal Protection jurisprudence might inform the development of race-based medicines and the use of racially exclusive clinical trials.³² Jonathan Kahn draws upon Equal Protection jurisprudence to advocate developing mechanisms within clinical and biomedical research that resists conflating genetic categories of population with social categories of race while requiring a “tight fit” when such claims

Given the vigorous and unsettled debate concerning the genetic relevance of race, the state has a strong interest in approving the use of race-specific indications only when they are used cautiously, are supported by robust scientific studies, and are not simply used as a convenient proxy.

personalized medicines: race is different. The *Richmond* Court aptly notes that “classifications based on race carry a danger of stigmatic harm...[;] they may in fact promote notions of racial inferiority and lead to a politics of racial hostility.”³¹ The appropriate use of race specific treatments must not only look at “safety” and “efficacy” in a clinical or statistical sense, but should be similarly rigorous in its examination of social responsibility. Put differently, the use of race in biomedicine should be held to a heightened standard of proven efficacy and be narrowly tailored — that is, used only when better proxies such as specific genetic markers are not available. A key concern with the use of racial indications in biomedicine, as with other categorizations in Constitutional law, is that they can be both over and under inclusive. Racial indications may be overinclusive, for example, by channeling too many Blacks with heart failure towards BiDil when they might fare better through other treatments. These very same indications may also be underinclusive by “missing” the substantial number of non-Black heart failure patients who may benefit from BiDil in that their doctors may not think to prescribe the medication to them. This additional layer of oversight can

are made.³³ And Dorothy Roberts draws upon Equal Protection norms to suggest a social justice framework that encourages researchers to use racial categories to combat health disparities, but resists its use as a biological category to prevent dangerous racial ideas from being reinforced.³⁴

Each of these and other contributions are useful in helping us think through the issues that arise when race and biotechnological claims arise. They are united by an effort to use Equal Protection norms and commitments to improve clinicians’ and researchers’ use of race in their professional capacities. But perhaps broader framings are similarly appropriate as strict scrutiny is a regulatory approach that is designed to examine *whether the state is using racial categories appropriately* in light of constitutional mandates, not only as an instrument that may suggest professional or ethical guidelines. Thus, analogizing courts’ judicial oversight to a normative scheme of clinical or research best practices may not fully leverage strict scrutiny’s broad regulatory spirit.

David Winickoff and I have drawn upon strict scrutiny to propose an oversight mechanism whereby “race-specific indications should be rejected unless

clinical trials can demonstrate convincingly that the drugs are both better than existing treatments for a specified group and no better than existing treatments for non-specified groups.³⁵ This approach is designed to ensure that the evidence supporting race-specific indications is robust and accessible to the most appropriate groups. Yet, another promising avenue to introduce a strict scrutiny analysis may be through rethinking the role of FDA advisory committees.

FDA advisory committees are routinely used to give expert advice on new drug applications to assist the regulatory process and boost the credibility of the FDA's decision on whether to allow a drug to become publicly available.³⁶ And, as demonstrated by the troubling "race as a surrogate for genomics" comments made by the chair of the FDA advisory committee that recommended BiDil's approval with a race-specific indication, the framing of these committees' inquiry can either affirm or act as a check against certain shortcomings within the narrow review of new drug applications that focus largely on safety and efficacy.

While these committees are typically composed of physicians, scientists, and statisticians with expertise relevant to the drug or device under review, an advisory committee that uses a strict scrutiny framework to review any new drug that proposes a race-specific indication could be a remarkable addition. Once a general finding of safety and efficacy is made, this committee would focus on whether a race specific indication is appropriate by weighing the merits of approving the drug with or without the race-specific label. Much of this can be meaningfully guided by strict scrutiny principles: questioning whether there is a compelling state interest for a race-specific indication (an ongoing health disparity, the ineffectiveness of other treatments, etc.) and if the use of race is narrowly tailored such that race is not uncritically framed by government as a genetic variable while ensuring that other potential beneficiaries are not denied access. These committee members (social scientists, lawyers, bioethicists, and others) could play a critical role in assessing the social impact of a proposed racial indication relative to its benefits — including whether it promotes unfounded genetic theories of racial difference. Though ultimate approval of such drugs would remain with the FDA, much of the uncertainty surrounding the appropriateness of state-enforced racial indications could be mitigated if these committees' decisions concerning the use of race indications enjoyed substantial deference.

Conclusion

Given the vigorous and unsettled debate concerning the genetic relevance of race, the state has a strong interest in approving the use of race-specific indications only when they are used cautiously, are sup-

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ported by robust scientific studies, and are not simply used as a convenient proxy. Like its role in Equal Protection jurisprudence, this article proposes strict scrutiny as a regulatory guidepost for reviewing new drugs seeking race-specific labels to, as the *Richmond Court* notes, "smoke out illegitimate uses of race."³⁷ Whether BiDil itself could survive such scrutiny depends heavily upon how this additional form of oversight is developed and implemented. But, the take-home message is that the use of racial categories in medicine will require remarkable sensitivity and responsibility on the part of corporations, government, clinicians, and consumers. As a result, it may very well be wise for us to have a deeper appreciation for how the battles waged to afford racial minorities Equal Protection of the laws can extend this same sentiment to medical research and health care.

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[A]lthough this body of work emphasizes the individual as the crucial unit of analysis, individual ancestry inference is closely tied to our understanding of human groups and the distribution of genetic variation among them. Inferring an individual's genetic ancestry entails deciding that his or her DNA was inherited from a certain group or groups, and that cannot be accomplished unless one first distinguishes groups that differ genetically in some way. Thus, even such individually-oriented genetic research has implications for our understanding of race and the pattern of human biological diversity.
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the fact that *structure* identifies a particular number of clusters is insignificant: it does so simply because the user told it to do so. What is more important is that *structure* provides a way to determine the value of K that is most appropriate for the dataset in question (i.e. the most likely number of clusters or populations represented.) The 'best' value of K is the one that maximizes the probability of observing that set of data.... However, it is not entirely straightforward to determine the true number of genetic clusters in a given dataset for three reasons...[:] First, because it is computationally difficult, ... *structure* provides only an approximation.... Second, if a dataset is complex, different runs of *structure* may produce substantially different results.... Third, the underlying model used in the *structure* program is not appropriate for all datasets.

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