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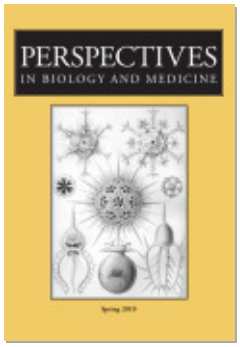

Perspectives in Biology and Medicine, Volume 53, Number 3, Summer 2010, pp. 357-372 (Article)

Published by The Johns Hopkins University Press
DOI: 10.1353/pbm.0.0171

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ABSTRACT This article addresses the question of whether race is a biological category and whether it is permissible to use it in biomedicine. I suggest that instrumentalism, a view that race is a problem-solving tool rather than a concept with an objective referent in nature, may be more consistent with the available scientific evidence. I argue that, to be morally permissible, the instrumentalist use of race in research and medicine requires stringent guidelines. I then provide four normative rules to guide race research in the biomedical sciences. The paper gathers evidence from philosophy of science, genomics, legal history, and normative ethics in order to ground the biomedical use of race in a converging ethical and epistemic framework.

The utility of a notion testifies not to its clarity but rather to the philosophic importance of clarifying it.

—Nelson Goodman (1983)

Even mistaken hypotheses and theories are of use in leading to discoveries. This remark is true in all the sciences.

—Claude Bernard (1865)

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The author wishes to thank Luisa Borrell, Richard Burian, Philip Kitcher, Lisa Lloyd, Peter Machamer, Sandra Mitchell, and James Woodward for their comments on this article. Earlier versions were presented at the roundtable on genetics and race at Harvard University (2004), at the Annual Meeting of the American College of Epidemiology in Boston (2004), at the Clinical and Translational Research Ethics Conference organized by Cincinnati Children's Hospital at the University of Cincinnati (2008), as well as at various universities, including the Program in Science, Technology, and Society at MIT (2004), the University of South Florida, USF (2006), and Pennsylvania State University (2008).

Perspectives in Biology and Medicine, volume 53, number 3 (summer 2010):357–72

THE GENOMIC REVOLUTION raised hopes that the putative utility of race in biomedicine could be grounded in the view that race has a biological reality and scientific validity (Burchard et al. 2003; Risch et al. 2002). However, the rebuttal of the contention that race is a biological category has been sharp among genomic scientists (Cooper, Kaufman, and Ward 2003; Long and Kittles 2003; Serre and Pääbo 2004). Some researchers worry about the reification of race in science and medicine (Bolnick 2008; Duster 2005; Gannett 2004; Lee, Mountain, and Koenig 2001). Still others warn that false assumptions about subgroup differences may undermine the goals of evidence-based medicine (Rogers and Ballantyne 2009). In what follows, I suggest that despite the new momentum the DNA revolution gave the concept, race in the biomedical sciences appears to be more of a convenient designator for multiple presumed layers of human population structures and, in public health settings, a multipurpose managerial tool. For instance, it may help probe environmental and genetic risk factors in disease etiology and surveillance, assess fairness in healthcare allocation across social groups, and tailor care to group needs.

Accordingly, I suggest an instrumentalist conception of race, which holds that racial partitions in the biomedical sciences need not be predicated on a putative match with evolutionary differentiations within our species, but rather on their usefulness at solving concrete, relevant problems. I construe instrumentalism as an alternative to the belief that race is a fact of nature, as well as an alternative to "eliminativism," or calls for a straightforward elimination of the concept from biomedicine. In addition to examining the notions of reality, validity, and utility that underlie the dispute, I scrutinize their ethical implications. Even if the view that race has a biological reality and scientific validity is false, eliminativism may still be unjustified. However, eliminativism might still be justified even if race were biologically real and scientifically valid, because validity, let alone reality or utility, does not entail permissibility. To be permissible, the instrumental use of race requires moral constraints. I therefore provide four normative rules to safeguard its biomedical use.

Debating the Biological Reality, Scientific Validity, and Medical Utility of Race

An Unexamined Assumption

The conflict over race in human population genetics is not new. For instance, Ashley Montagu (1941) declared race a whitened sepulcher which "in the light of modern experimental genetics is utterly erroneous and meaningless" (p. 101). For Theodosius Dobzhansky (1962), however, racial differences were "objectively ascertainable" and "facts of nature" (pp. 266–67). However, with the completion of the Human Genome Project, human population genetics seems to have entered a kind of Kuhnian crisis, in that the current situation sparks even more

intense controversies. Consider, for example, the following recent dispute between two teams of genomic scientists. Studying about 4,682 alleles from 377 autosomal microsatellite loci in 1,056 individuals from 52 worldwide populations, Rosenberg et al. (2002, 2005) were able to split these individuals into different sets of clusters. When the number K of clusters was set at 2, the partition seemed to show the migration event from Africa into the rest of the world. At K = 5, the split was among (Tropical) Africans, Eurasians, East Asians, Oceanic populations, and Native Americans. The finding seemed to suggest that these continental groups might reflect an evolutionary process of differentiation into subspecies.

However, Serre and Pääbo (2004) countered that these continental genetic clusters, rather than reflecting natural subdivisions of our species into discrete groups, are simply study design artifacts, and that "there is no reason to assume that major genetic discontinuities exist between continents" (p. 1679). According to this line of reasoning, to obtain relatively sharp allele frequency breaks between the five continental genetic clusters, ancestral membership identification studies adopt an "island model" sampling strategy rather than a regional continuity model. The island model considers our species to be a collection of well-defined groups living far apart from one another. Samples based on this model reflect preselected and isolated or "extreme" populations, rather than reflecting the relatively contiguous spread of populations around the world (Bamshad et al. 2004). Briefly, some researchers have argued that continental clusters are merely sampling and computational artifacts (Bolnick 2008; Serre and Pääbo 2004).

The clash over race has persisted throughout the DNA revolution to the post-genomic era. Careful scrutiny reveals that the debate revolves around the following questions: (1) did human evolutionary history lead to a natural division of our species into subspecies, the so-called biological races? (2) do genetic taxa correspond to racial identities defined at a social level? (3) does race have a biomedical utility? and (4) is it morally permissible to use race in biomedicine? Researchers answer questions one through three by either arguing or denying that race has a biological reality or is a valid scientific category and a useful notion. While many reject the idea that race is a valid primary or foundational category in human population genetics (Keita et al. 2004; Templeton 1999), a major source of confusion in the debate stems from the unexamined notion of the "biological significance" of race and the equally unexamined assumption that a biomedical utility of race must somehow necessarily derive from its putative reality in evolutionary biology and putative validity as a primary notion in human population genetics. As Cooper et al. (2003) noted:

> Into this storm of controversy rides genomics. *With the acknowledgment that race is the product of a marriage of social and biologic influences, it has been proposed that genomics now at least offers the opportunity to put its biologic claims to an objective test. If those claims are validated, race will become a way to choose drug therapy for patients,*

> *categorize persons for genetic research, and understand the causes of disease*. Genomics, with its technological innovations and authority as 'big science', might thereby solve the conundrum of race and bring peace to the warring factions. (p. 1166, my emphasis)

Thus, the disputed issues are not simply whether race has a biological reality and scientific validity, but also whether it is a useful category in virtue of this presumed validity and reality. Let's call this "validity-derived utility" in contrast with "validity-neutral utility," which characterizes some flawed theories.

First, as the zoologist and evolutionary biologist Ernst Mayr (1954) once said: "The subspecies is merely a strictly utilitarian classificatory device for the pigeonholing of population samples" (p. 87). This statement is particularly applicable to divisions within the human species (Maglo n.d.; Templeton 1999). Second, as indicated above, the claim that race has a biological reality and scientific validity is at best controversial. Third, as I have shown elsewhere, there is a strong line of researchers, starting with Darwin in *The Descent of Man*, who emphatically deny that human races are evolutionarily distinct groups but who nonetheless view race as a problem-solving device. For Darwin, human races were not sufficiently differentiated to represent distinct evolutionary branches (Maglo n.d.). Fourth, over the last two centuries, morphometric and epidemiological studies have indicated that human races are very likely not adaptively discrete phenotypic taxa (Cooper et al. 2005; Gould 1996; Graves 2001).

That said, there are, however, many well-controlled situations in which race may be a useful proxy. Note that Darwin, for one, already attempted to probe the correlation between race and disease susceptibility while at the same time forcefully denying that race, as applied to humans, has any evolutionary meaning. Thus just like occupation or socioeconomic status, race may serve as a useful variable in biomedicine without necessarily being a biological category. In fact, because of genetic evidential underdetermination, race has somehow become shorthand for population substructure, whether that substructure is associated with isolation by distance, social history, language, advantageous selection, or the like. Now, although population substructure occurs at different divisionary levels within our species, there is apparently no objectively natural division that is uniquely useful (Wilson et al. 2001). Thus, we may conveniently stratify humans into various divisionary levels (DLs), none of which encompasses naturally discrete taxa (see Table 1).

Leaving aside the tangential issue of the distinctiveness of the causes of differentiation—such as geography or linguistics—such divisionary levels reflect the effects of various types of isolating mechanisms operating within our species. They map varying population substructures and are thus biologically significant despite the lack of sharp natural boundaries. Proponents of the continental race concept privilege DL-2 populations as reflecting biological human races, while others suggest that DL-5 (or lower) divisionary level populations—correspon-

TABLE 1 ILLUSTRATION OF THE CONCEPT OF DIVISIONARY LEVELS (DLS) WITH THREE CONTINENTAL GROUPS

Divisionary levels (DL)	*Populations*		
DL-1		Human species	
DL-2	Africans	Eurasians	East Asians
DL-3	Bantu	Europeans	Sino-Tibetans
DL-4	Western/Southern Bantu	Northern/Southern Europeans	Chinese
DL-5	Bamileke/Zulu	Finns/Basques	Han

ding roughly to breeding populations—substantiate the existence of biological human races (Dobzhansky 1962; Kitcher 2003; Mayr 2002). The question of which divisionary level actually corresponds to biological human races is an unresolved theoretical issue. For example, on the one hand, equating race with breeding populations could lead to the assignment of two castes in India to different races, because of reduced interbreeding; on the other hand, proponents of the continental race concept would classify them as members of one single race, "Caucasian" (Burchard et al. 2003; Risch et al. 2002). To be sure, race does seem to lack any scientific necessity (for more details, see Maglo n.d.).

An Alternative Framework

The instrumentalist conception of race I am suggesting is informed in part by the fact that even an utterly flawed scientific concept—one that is invalid in its domain of (presumed) validity—may still prove to be, under certain circumstances, more pragmatically useful than a competing scientifically valid concept. For instance, although the geocentric concept remains an adequate conceptual tool in geodesy and navigational settings (for the World Geodetic System), reliable inferences obtained in special cases by assuming a stationary earth do not validate geocentricity in astronomy. So, there is a distinction between the utility that derives from the validity of a concept or theory—validity-supported utility—and the validity-indifferent utility that may stem even from a concept proven flawed in its domain of validity. To put it differently, the inference from success to truth or reality is not always reliable. In any event, the idea that some flawed scientific theories, concepts, and models may still have some scientific significance and utility has already been acknowledged not only by Enlightenment scientists but also by 19th-century biomedical researchers such as Claude Bernard (1865) and mathematical physicists such as Henri Poincaré (2001), as well as by contemporary researchers (e.g., Wimsatt 2007).

There is no agreement among researchers about the criteria of biological real-

ity. Social and biomedical researchers speak of predictive, external, internal, analytic, and clinical validity, and so forth. For example, income may predict health outcomes and thus have a predictive validity, or we may assess the clinical effects of a phenylketonuric-free diet on the brain development of newborns diagnosed with the PKU syndrome. But we do not say that income or diet is a valid biological concept. To say that race is a valid biological concept is therefore to say something theoretically deeper—that race is a primary or foundational concept in human population genetics (Gannett 2004). I am suggesting that race may have, for example, clinical "validity" without being real in light of evolutionary biology or a primary concept in human population genetics. Race may just be, in Mayr's (1954) terminology, a "strictly utilitarian" methodological apparatus. My point therefore is not that researching the putative validity-based utility of the concept of race is epistemically unjustified. Quite the contrary! To repeat, and as detailed below with the case of A-HeFT and BiDil, my claim is simply that the presumed medical utility of race does not necessarily imply that race has an evolutionary meaning or is a fundamental concept in human population genetics.

Indeed, while a claim about reality is a claim about the ontological structure of the world, a claim about validity is a claim about the explanatory value of a model, concept or theory. For instance, to say that electrons or genes are real, as opposed to unicorns and centaurs, is to claim that the former, unlike the latter, have objective referents in nature. But to say that the concept of force is a valid physical concept or that natural selection is a valid biological concept, as opposed to the phlogistic concept in chemistry or the humoral in biomedicine, is to claim that the former, unlike the latter, satisfy reasonable epistemic criteria of scientific justification in domains or disciplines relevant to the testing of their explanatory value as a primary concept. The relevant and required domain of validity of geocentricity as a primary category, for example, is astronomy but not geological survey.

Likewise, the utility of race does not necessarily require the reality or even the validity of race as a fundamental biological category. Just as invalid scientific concepts such as geocentricity may be useful under certain circumstances, race may be a useful proxy yielding reliable inferences or sound probabilistic reasoning in some specifically well-defined biomedical contexts without necessarily being a valid primary concept in human population genetics. To illustrate this point further, suppose for the sake of argument that Montagu is right, that from the point of view of experimental genetics, race is an invalid scientific concept. Does it follow that a researcher who finds a correlation between self-identified racial groupings and traits such as intestinal disaccharidase activities or hypertension in a given country is delusional? Not necessarily, and for the purpose of disease surveillance, we need to take these findings seriously. But suppose that Montagu is wrong, and Dobzhansky is right that experimental genetics provides a scientific justification for race. Why does it not follow that a medical doctor would be justified in transplanting a heart or kidney from one Asian American to another

Asian American without testing for an HLA (human lymphocyte antigen) match, given that both self-identify in the same way? Or why does it not follow that in the emergency room a doctor would be justified in refusing to consider, for example, a blood transfusion from a Native American to a Pacific Islander on racial grounds alone? The answer is simply that in sound scientific medicine, individual response to treatment is understood as colorblind; even siblings have only one chance in four to be an HLA match. Nonetheless, it does not follow that it is a wrong policy to use race to foster interest in organ donation or as a research variable to probe, for example, social biases in tissue transplantation or access to health care across social groups.

In the same vein, neither the biological significance nor the medical relevance of race is a sufficient criterion with which to establish the objective reality and validity of race. Take, for example, the once widely held division of Europeans into Mediterranean, Alpine, and Nordic races. This division was deemed so significant biologically that the 1921 *Emergency Quota Act* and the *Immigration Act of 1924* aimed to reduce the migration of the "Alpine" and "Mediterranean" races, among others, into the United States. Although this racial scheme eventually became obsolete, very few scientists today would deny that there are significant biological and epidemiological differences between the social groups so defined. In fact, this categorization scheme, roughly speaking, corresponds to the DL-4 grouping mentioned in Table 1. Alleles associated with lactase persistence seem to demarcate Europeans along the lines suggested by the old racial categories. In Scandinavia (Nordic race), the frequency of the persistent allele -13910T is 81.5%. In France (Alpine), it is 43.1%, while it varies in Italy (Mediterranean) between 35.5% and 6.3% (Bersaglieri et al. 2004; Enattah et al. 2002). The CYP2D6 ultra-rapid drug metabolizer allele variance also separates these populations. While this allele is found at a frequency of 1–2% in Sweden (Nordic), in Spain (Mediterranean) it is about 10% (Wilson et al. 2001). ß-thalassemia is associated with the Mediterranean region, with an incidence rate as high as 8% in Greece and 16% in Cyprus, but it is vanishing (with an incidence rate of about 0.1%) in Northern Europe. In Greece, sickle cell anemia varies from 0% to 32%, according to district (Athanassiou-Metaxa et al. 2002). The CCR5 delta 32 allele that protects against HIV infection is found at a high rate (25%) in Nordic countries but at a lower rate in the Mediterranean. The delta 508-CFTR allele responsible for cystic fibrosis and the C282Y-HFE allele associated with hemochromatosis vary among Europeans (Bamshad et al. 2004; Cooper, Kaufman, and Ward 2003).

So, are there European races and, if so, how many are there? To rehash the taxonomic change from fish to mammals in the classification of whales and the like by suggesting that early subdivisions of Europeans into multiple races were mistakes rectified by genomics would be missing my point about inferring the reality and validity of race merely from the notion of biological significance or population substructure. In the age of genomics, there are plenty of sociopolitical

categorizations into race that may be said to have biological significance and medical relevance due to various isolating mechanisms. But as the European example reveals, "races" can fade away by simple conceptual changes. Thus, some scientists have argued that "'race' and 'ethnicity' are poorly defined terms that serve as flawed surrogates for multiple environmental and genetic factors in disease causation" (Collins 2004, p. 13; see also Wilson et al. 2001). In a word, race is not a thin but a thick notion, and its use hinges on its problem-solving potential.

Instrumentalism and Race as a Social Construct

Instrumentalism about race is not vulnerable to the criticism that race is a social construct, because instrumentalism, as construed here, only requires that race be an efficient, safe, and ethically defensible biomedical problem-solving device. Indeed, social constructivism aims above all at challenging the naturalistic claims embedded in scientific taxonomies and legal classifications into race. For instance, anti-miscegenation laws were among the causes of assortative mating in the United States. But not only were they infringements on human rights, they were also incoherent. Although interracial marriage was deemed unnatural and a violation of natural "racial" boundaries, Native Americans, for example, were banned from marrying "Whites" in Tennessee and Oregon but were defined as white in Oklahoma (Wallenstein 2002, p. 178). Otherwise put, though supposedly based on fundamental and obvious natural characteristics, racial identity seemed to change from state to state like automobile registration plates. In the landmark case *Plessy v. Ferguson*, Plessy was described as "seven-eighths Caucasian and one-eighth African blood" and was considered nonwhite in Louisiana. But under the Ohio "predominance of blood" rule, for example, he would have been defined as white. Challenging the taxonomic naturalistic assumption, Plessy's defense "advanced a single proposition: no reasonable law could exist to categorize Plessy, or anyone else, as colored or white or as a member of any race because race was indefinable; it was not a physical fact but, rather, a social construct" (Davis 2002, pp. 70–71).

As one scholar recently put it, "By the end of the 1930s, the list of races named in miscegenation law was so complex and convoluted that its logic was apparent to no one" (Pascoe 2009, p. 199; see also Browne-Marshall 2007; Gross 2008). Interestingly, until the 1930s, scientists were still actively investigating the existence of numerous European races (Coon 1939). Throughout the 19th and early 20th centuries, they argued that moral concerns should not interfere with objective scientific inquiry into race, and that quantification and experiment provide an antidote against researchers' biases. Yet not only were their works underwritten by social factors, but they also helped pave the way for ominous biomedical practices (Duster 2006; Gould 1996; Graves 2001). Be that as it may, it is important to define the morally permissible conditions for an instrumental use of race (Kitcher 2007).

Race in Biomedicine: Towards an Axiological Empiricist Approach

Determining the Permissibility Conditions

By "axiological empiricism," I simply mean an account of scientific research grounded in converging epistemic and normative ethical frameworks. Although axiology refers to the study of values, I will not lurch into a general debate over values and their role in science here. My focus is rather on the ethical implications of the above theoretical developments. Even a fierce critic of the biological reality and scientific validity of race, à la Montagu, might still defend its use under certain circumstances. Anti-naturalism is compatible with apologism, or the defense of race. Likewise, eliminativism is compatible with naturalism about race. One may hold the view that race is a fact of nature and still oppose its use, for example, on ethical grounds. For instance, in *Plessy v. Ferguson*, the defense found a powerful ally in Supreme Court Justice John Marshall Harlan, who, in his famous dissenting opinion, declared that the American constitution is color-blind. But though

> Harlan embraced Plessey's attack on de jure racial segregation, even he abandoned Plessy's assault on the law of racial identity. Like his fellows on the Supreme Court, Harlan accepted the concept of race, the idea of humanity grouped by "distinctions based upon physical differences." Where Plessy's defense insisted that race did not exist as fact [in nature], Harlan insisted only that the Constitution restricted government from recognizing race as a basis for any public action. (Davis 2002, p. 72).

Leaving the constitutional point for constitutionalists, the interest of this historical court case for our discussion is that it allows me to drive home a crucial point: validity, let alone reality or utility, does not entail permissibility. Even if race were proven to be a biological reality and a valid scientific concept, eliminativism might still be justified if its use caused harm or violated certain moral ideals and values. As some genomic researchers have warned, "race already has a meaning. To invoke the authority of genomic science in the debate over the value of race as a category of nature is to accept the social meaning as well" (Cooper, Kaufman, and Ward 2003, p. 1169). In the current controversy, overt and hidden axiological factors drive a wedge between eliminativism and apologism.

Consider, for example, the conflict over some recent findings about heart failure. First came the manufacturing of the drug BiDil by Nitromed and its subsequent approval by the Food and Drug Administration (FDA) for race-specific prescription (Kahn 2004; Tate and Goldstein 2004; Taylor et al. 2004). Next came the discovery that the possession of the haplotype Hapk, an allelic variant of the leukotriene A4 hydrolase gene associated with leukotriene production and inflammatory response in the arterial wall, increases the risk of myocardial infarc-

tion by 1.16 in European Americans but by 3.5 in African Americans (Hegadottir et al. 2006). Because DeCode, the company behind the study, was testing the drug veliflapon (DG-031) on the effects of another gene that also controls for leukotriene production, it sought a clinical trial of DG-031 in an African American cohort. This prompted an overt axiological clash between eliminativists and apologists (Grens 2007; Wade 2005).

After the African American Heart Failure Trial (A-HeFT) and the approval of BiDil, the question is whether it is permissible to conduct a new clinical trial on African Americans. Keeping in mind the legitimate concerns about the reification of race, how should we adjudicate between eliminativism and apologism in situations like this? The putative biological reality and validity of race by themselves supply no answer to this question. Moreover, it would be misleading to suggest that BiDil works because race is a valid biological category. Actually, it may just be the case that it works in an alleged "racial" framework because of the scientific limitations of the study. Indeed, it has been forcefully argued that the Vasodilator Heart Failure Trials (V-HeFT I and II) did not clear the road for A-HeFT, as is usually claimed. Rather, the whole process seems to have been driven by regulatory and market incentives (Kahn 2004). As one researcher stated:

> it might have made clinical and scientific sense to add isosorbide dinitrate and hydralazine to conventional therapy (which by now typically included an ACE inhibitor) and compare this combination to conventional therapy alone—for all patients with heart failure, regardless of race. Such a trial had not been performed, since the standard therapies used in earlier trials did not include ACE inhibitors. But race consciousness offered a faster way through the FDA's regulatory maze. (Bloche 2004, p. 2035).

The charge against the approval of BiDil as a racial drug is twofold. First is the objection that A-HeFT targeted only a segment of the cluster of populations referred to in the U.S. 2000 Census as Blacks or as Africans in genetic studies. Because A-HeFT testing did not attempt to establish that membership in this cluster is stable for this particular treatment, there is no scientific ground on which to generalize its results to the whole continental group or "race." Second is the objection that the "race consciousness" embedded in the approval and marketing process of BiDil de facto excludes potential non-black beneficiaries. In sum, although the FDA approval of BiDil as a racial drug may be satisfactory from some societal perspectives, there is no scientific justification for substituting the tempting clinical concept of "each race, its dose" to the now decried concept of "one dose fits all." In other words, normative constraints are necessary to guide the use of race in the biomedical sciences. But what might they be?

Taking the DL-2 partition scheme discussed above as an example, I suggest the following rules:

Rule 1, or The Cluster Stability Rule: It is legitimate in rational scientific practice to target a subset of a given continental population in research and clinical

trials, but researchers who aim to generalize their findings (or those of other studies) to all the members of the continental cluster are obliged, by the membership stability burden of proof (see below), to provide in their study designs tests for the stability of the cluster.

Rule 2, or The Patient Standpoint Rule: The patient perspective is prima facie overriding unless it conflicts with the permissibility principle.

Rule 3, or The Excluded Beneficiary Rule: In the context of theory-choice, the most robust model or clinical trial concept is the one that meets the requirement of improving the status of orphan populations.[1]

Permissibility Principle: It is morally justified to prevent the availability of treatment or care that is necessary for the well-being of a category of patients within the limit of "species-typical normal functioning," *if* access to that treatment or care will predictably severely upset the "species-typical normal functioning" of fellow humans.[2]

These rules are relevant not just to clinical trials and drug marketing. They also constitute hidden sources of conflict in genomics. I suggested above that there is no uniquely useful divisionary level within our species. A local population on a given continent may show similarities with another on a different continent depending on the goals, criteria, and methods of the study. Even when allele frequencies remain similar for a given continental group, phenotypic plasticity may render group membership unstable. This weakens the common variants–common diseases/rare variants–rare diseases hypothesis. We simply cannot safely infer from the lone fact that two populations belong to the same genetic cluster that they necessarily have the same clinical priorities. For example, given that the Fulani and African Americans belong to the same continental genetic cluster, and that African Americans are in the main lactose intolerant and have a higher prevalence of hypertension compared to European Americans, we cannot infer that the Fulani have clinical priorities similar to those of African Americans. Knowledge of an epidemiological condition among Swedes does not necessarily translate into a predictive tool about Greeks or Asian Indians. This situation creates what we may call a membership stability burden of proof on researchers using the continental race concept as a proxy. For example, it would be misleading and potentially harmful to use racial designators to suggest or imply that one has observed Asians (a DL-2 population), when one has in fact studied only a subset of the Asian populations, Han (a DL-5 population). If a practical goal of

[1]By orphan populations, I refer primarily to two categories of populations that we may call "non-falsifying" and "falsifying" in the debate over race. A *non-falsifying* orphan population is one whose health needs are discounted because its inclusion or noninclusion in a study do not significantly change the outcome of the study. A *falsifying* orphan population is one whose health needs are discounted for the sake of the race niche market and which is not included in a race-based study because it might falsify the racial assumptions and undermine the economical rationale of pharmaceutical companies.

[2]For more details on the notion of species-typical normal functioning, see Buchanan et al. 2000.

race studies is, as Dobzhansky (1962) maintained, to facilitate communication among scientists "who must be able to indicate which peoples they have observed" (p. 266), then Rule 1 is justified by that fact alone. In fact, "there is not a single 'representative' African population'" (Tishkoff and Verrelli 2003, p. 612) nor is there one for any continental cluster. What should be clear here is that genomic evidence can be fraught with axiological background assumptions.

Hidden Ethical Clashes

At the height of the genomic dispute, a study of the population genetic structure of drug metabolizing enzyme (DME) showed that average differences in drug response do not correspond to the commonly defined racial boundaries. For instance, at K = 4 clusters, 62% of the Ethiopians in the study, rather than clustering with the Bantu as racial categorization would predict, clustered instead with the Ashkenazi Jews, Norwegians, and Armenians. Likewise, Chinese and New Guineans formed two different clusters at K = 4, but at K = 3 both populations merged into one single cluster. The authors concluded that due to the complex patterns of human migration "there is no obvious natural clustering scheme" (Wilson et al. 2001, p. 265). From the perspective I have taken in this paper, the findings of the DME study are noteworthy in two respects. First, the clustering schemes of Chinese and New Guineans indicate that even the defunct U.S. racial classification that merged Asians and Pacific Islanders into one group may be said to have biological significance and medical relevance. Second, continental ancestral membership identification studies have shown that Ethiopians are primarily Africans, sharing about 60% of their genetic material with the other African groups (Cavalli-Sforza et al. 1994; Semino et al. 2002; Tishkoff and Verrelli 2003). So, the findings of the DME study either result from a sample bias or corroborate the membership instability argument. This argument forbids us, consistent with Rule 1, to infer with confidence and without scientific testing (clinical or genetic) that a treatment that is efficient in a given DL-5 population within one continent will automatically and exclusively work for all populations in the same continental cluster.

In fact, there are conflicting interpretations of the findings of the DME study. For eliminativists and advocates of personalized treatment, the study simply shows that racial categories are "insufficient" and "inaccurate." For apologists and advocates of group-based treatment, the study vindicates race-based medicine. Hence, it is important to realize that neither the New Guineans nor the Ethiopians "would have much impact on studies in the U.S., as these groups represent only a tiny fraction of the U.S. population" (Risch et al. 2002, p. 7). A clarification of the axiological background assumptions underwriting the conflicting genomic interpretations is in order. On the one hand are assumptions stemming from the deontological formalist standpoint generally associated with Kant, according to which moral norms are universal and place an equal burden on each individual. From the deontological formalist genomic perspective, a public-

health policy that condones sacrificing a subset of the population for the general well-being is morally unsound. On the other hand are assumptions deriving from consequentialist ethics, championed in particular by Jeremy Bentham and John Stuart Mill, according to which the morally sound action is the one that maximizes the general outcome, even if it sacrifices some individuals. From the consequentialist genomic perspective, a public-health policy guided by considerations of the best outcome for the greatest number of people, particularly when resources are scarce, is morally defensible. But there is more to this debate than these abstract considerations.

At least four perspectives are often at odds with one another in the debate over the usefulness of race in biomedicine. I shall call them, roughly speaking, the societal, scientific, patient, and industrial or corporative perspectives. In the current bioethical context, the patient perspective requires further elaboration. For the purpose of this article, one needs to distinguish between the patient's psycho-therapeutic situation, his or her perception of a given disease and available treatments; patient autonomy, defined as the patient's right to choose; and the patient's existential health condition, understood as his or her basic need and hope for access to efficient treatment. It is this latter understanding of the patient's perspective that justifies the existence of medical practice in the first place, while the concept of patient autonomy was the cornerstone concept in the birth of bioethics. I define the patient perspective here not primarily in terms of the patient's right to choose but rather in terms of the patient's basic need and hope for access to efficient treatment. I further claim, in accordance with Rule 2, that our obligation to the patient is a prima facie obligation.

The societal and patient perspectives furnish different axiological demands. From the patient perspective, the right question to ask about findings similar to those of the DME study is not whether a given population significantly falsifies studies in a given country, but whether there is an alternative conceivable model, mathematically accurate and empirically adequate, that improves on the condition of the orphan groups created by competing models. That is, the patient perspective places stringent obligations on our choice of scientific models. What this perspective builds into theory-choice is a weighting scale that values mathematical accuracy, empirical adequacy, and ethical soundness. Consistent with Rule 3, this scale is construed in terms of the extent to which a given model ameliorates the status of an orphan population by extending the boundaries of what competing models indicate as scientifically satisfactory.

My point is that both race apologists and race eliminativists have unexamined axiological assumptions. For instance, admitting for the sake of argument that race is a useful category in biomedicine but that there are social risks attached to its use, when is it morally justified to press a utilitarian duty on patients—in Nussbaum's (2005) words, a duty to be "just engines of maximization" (p. 213)? That is, when is it morally permissible to ask patients to give up their existential hope for efficient treatment for the sake of the general well-being of society? A

morally consistent regulative principle would look like the permissibility principle stated above—that is, not just any negative externalities provide moral grounds for eliminativism. Although I cannot fully develop this principle here, the message I am trying to convey is that in our legitimate fight against social "evils," we need to be wary of the patient being the loser.

Conclusion

I have defended a view that, for simplicity, I call instrumentalism about race. However, I did not (or have not intended to) make broad philosophical statements about whether instrumentalism is generally true for any scientific concept or theory. My position is best understood as casuistic epistemology, the view that case-study conclusions hold for the relevant case only, or if a paradigm case, for similar cases only. I also suggested that the clash over race cannot be fully understood and resolved in either a purely epistemic or a purely ethical framework. Rather, it must be understood in a converging empirical and normative framework that I term an axiological empiricist framework. Normative issues sometimes influence what kind of scientific resolution a researcher is prepared to accept as satisfactory. Thus, although it is structured by epistemic parameters, genomic science is also fraught with value assumptions.

References

Athanassiou-Metaxa, M., et al. 2002. A vascular necrosis of the femoral head among children and adolescents with sickle cell disease in Greece. *Haematologica* 87(7):771–72.

Bamshad, M., et al. 2004. Deconstructing the relation between genetics and race. *Nat Rev Genet* 5:598–609.

Bernard, C. 1865. *An introduction to the study of experimental medicine*, trans. H. C. Greene. Repr. New York: Dover, 1957.

Bersaglieri, T., et al. 2004. Genetic signatures of strong recent positive selection at the lactase gene. *Am J Hum Genet* 74(6):1111–20.

Bloche, G. 2004. Race-based therapeutics. *N Engl J Med* 351(20):2035–37.

Bolnick, D. 2008. Individual ancestry inference and the reification of race as a biological phenomenon. In *Revisiting race in a genomic age*, eds. B. Koenig, S. S.-J. Lee, and S. S. Richardson, 70–85. New Brunswick: Rutgers Univ. Press.

Browne-Marshall, G. J. 2007. *Race, law and American society: 1607 to present*. New York: Routledge.

Buchanan, A., et al. 2000. *From chance to choice: Genetics and justice*. Cambridge: Cambridge Univ. Press.

Burchard, E. G., et al. 2003. The importance of race and ethnic background in biomedical research and clinical practice. *N Engl J Med* 348(12):1170–75.

Cavalli-Sforza L. L., et al. 1994. *The history and geography of human genes*. Princeton: Princeton Univ. Press.

Collins, F. 2004. What do we and don't know about "race," "ethnicity," genetics and health at the dawn of the genome era. *Nat Genet* 36(11):S13–S15.

Coon, C. 1939. *The races of Europe*. New York: Macmillan.
Cooper, R. S., J. S. Kaufman, and R. Ward. 2003. Race and genomics. *N Engl J Med* 348(12):1166–70.
Cooper, R. S., et al. 2005. An international comparative study of blood pressure in populations of European vs. African descent. *BMC Med* 3(2).
Davis, T. 2002. Race, identity and the law. In *Race on trial: Law and justice in American history*, ed. A. Gordon-Reed, 61–76. Oxford: Oxford Univ. Press.
Dobzhansky, T. 1962. *Mankind evolving: The evolution of the human species*. New Haven: Yale Univ. Press.
Duster, T. 2005. Race and reification. *Science* 307:1150–51.
Duster, T. 2006. Lessons from history: Why race and ethnicity have played a major role in biomedical research. *J Law Med Ethics* 34(3):487–96.
Enattah, N. S., et al. 2002. Identification of a variant associated with adult-type hypolactasia. *Nat Genet* 30(2):233–37.
Gannett, L. 2004. The biological reification of race. *Br J Philos Sci* 55:323–45.
Goodman, N. 1983. *Facts, fiction and forecast*. Cambridge: Harvard Univ. Press.
Gould, S. J. 1996. *The mismeasure of man*. New York: Norton.
Graves, J., Jr. 2001. *The emperor's new clothes: Biological theories of race at the millennium*. New Brunswick: Rutgers Univ. Press.
Grens, K. 2007. Race-based medicine? African-American heart drug study raises questions about benefits of racially targeted trials. *Scientist*, Nov. 19. http://www.the-scientist.com/news/display/53869/.
Gross, A. 2008. *What blood won't tell: A history of race on trial in America*. Cambridge: Harvard Univ. Press.
Hegadottir, A., et al. 2006. A variant of the gene encoding leukotriene A4 hydrolase confers ethnicity-specific risk of myocardial infarction. *Nat Genet* 38(1):68–74.
Kahn, J. 2004. How a drug becomes "ethnic": Law, commerce and the production of racial categories in medicine. *Yale J Health Policy Law Ethics* 4(1):1–46.
Keita, S. O.Y., et al. 2004. Conceptualizing human variation. *Nat Genet* 36(11):S17–S20.
Kitcher, P. 2003. Race, ethnicity, biology, culture. In *Mendel's mirror: Philosophical reflections on biology*, 230–57. Oxford: Oxford Univ. Press.
Kitcher, P. 2007. Does "race" have a future? *Philos Public Aff* 35(4):293–317.
Lee S. S-J., J. Mountain, and B. A. Koenig. 2001. The meanings of "race" in the new genomics: Implications for health disparities research. *Yale J Health Policy Law Ethics* 1: 33–75.
Long, J., and R. Kittles. 2003. Human genetic diversity and the nonexistence of biological races. *Hum Biol* 75(4):449–71.
Maglo, K. n.d. The case against biological realism about race: From Darwin to the postgenomic era. *Perspect Sci* 19(2), forthcoming.
Mayr, E. 1954. Notes on nomenclature and classification. *Syst Zool* 3(2):86–89.
Mayr, E. 2002. The biology of race and the concept of equality. *Daedalus* 131(1):89–94.
Montagu, A. 1941. The concept of race in the human species in the light of genetics. In *The idea of race*, ed. R. Bernasconi and T. Lott, 100–107. Cambridge: Hackett, 2000.
Nussbaum, M. 2005. Beyond the social contract: Capabilities and global justice. In *The political philosophy of cosmopolitanism*, ed. G. Brock and H. Brighouse, 196–218. Cambridge: Cambridge Univ. Press.

Pascoe, P. 2009. *What comes naturally: Miscegenation law and the making of race in America*. Oxford: Oxford Univ. Press.

Poincaré, H. 2001. *The value of science: Essential work of Henri Poincaré*, ed. S. J. Gould. New York: Modern Library.

Risch, N., et al. 2002. Categorization of humans in biomedical research: Genes, race and disease. *Genome Biol* 3:7.

Rogers, W., and A. Ballantyne. 2009. Justice in health research: What is the role of evidence-based medicine? *Perspect Biol Med* 52(2):188–202.

Rosenberg, N. A., et al. 2002. Genetic structure of human populations. *Science* 298:2381–84.

Rosenberg, N. A., et al. 2005. Clines, clusters, and the effect of study design on the inference of human population structure. *PLoS Genetics* 1:660–71.

Serre, D., and S. Pääbo. 2004. Evidence for gradients of human genetic diversity within and among continents. *Genome Res* 14:1679–85.

Semino, O., et al. 2002. Ethiopians and Khoisan share the deepest clades of the human Y-chromosome phylogeny. *Am J Hum Genet* 70(1):265–68.

Tate, S., and D. Goldstein. 2004. Will tomorrow's medicine work for everyone *Nat Genet* 36(11) :S34–S42.

Taylor A. L., et al. 2004. Combination of isosorbide dinitrate and hydralazine in blacks with hearth failure. *New Engl J Med* 351(20):2049–57.

Templeton, A. 1999. Human races: A genetic and evolutionary perspective. *Am Anthropol* 100(3):632–50.

Tishkoff, S., and K. Kidd. 2004. Implications of biogeography of human populations for race, and medicine. *Nat Genet* 36(11):S21–S27.

Tishkoff, S., and B. C. Verrelli. 2003. Patterns of human genetic diversity: Implications for human evolutionary history and disease. *Annu Rev Genomics Hum Genet* 4:293–340.

Wade, N. 2005. Genetic find stirs debate on race-based medicine. *NY Times*, Nov., 11.

Wallenstein, P. 2002. Interracial marriage and the law. In *Race on trial: Law and justice in American history*, ed. A. Gordon-Reed, 177–96. Oxford: Oxford Univ. Press.

Wilson, J. E., et al. 2001. Population genetic structure of variable drug response. *Nat Genet* 29:265–69.

Wimsatt, W. 2007. *Re-engineering philosophy for limited beings: Piecewise approximations to reality*. Cambridge: Harvard Univ. Press.