Group-Based and Personalized Care in an Age of Genomic and Evidence-Based Medicine

a reappraisal

Koffi N. Maglo

ABSTRACT This article addresses the philosophical and moral foundations of group-based and individualized therapy in connection with population care equality. The U.S. Food and Drug Administration (FDA) recently modified its public health policy by seeking to enhance the efficacy and equality of care through the approval of group-specific prescriptions and doses for some drugs. In the age of genomics, when individualization of care increasingly has become a major concern, investigating the relationship between population health, stratified medicine, and personalized therapy can improve our understanding of the ethical and biomedical implications of genomic medicine. I suggest that the need to optimize population health through population substructure-sensitive research and the need to individualize care through genetically targeted therapies are not necessarily incompatible. Accordingly, the article reconceptualizes a unified goal for modern scientific medicine in terms of individualized equal care.

Department of Philosophy, University of Cincinnati, 206 McMicken Hall, PO Box 210374, University of Cincinnati, Cincinnati, OH 45221-0374.
E-mail: maglokn@ucmail.uc.edu.

Earlier versions of this article were presented in 2011 at the "Philosophy and Race Speaker Series," organized jointly by Columbia University's Department of Philosophy and the Institute for Research in African-American Studies, and at the "Papers in Progress" series organized by the Division of Epidemiology and Biostatistics at the University of Cincinnati's College of Medicine and Children's Hospital. This article partly constitutes the philosophical background of the empirical bioethical research The author is currently conducting on "BiDil in the Patient-Physician Relationship" with internal medicine residents and physicians at the University of Cincinnati.

Perspectives in Biology and Medicine, volume 55, number 1 (winter 2012):137–54

INDIVIDUALIZED CARE AND EQUALITY of care remain two imperatives for formulating any scientifically and morally informed public health policy. Yet both continue to be elusive goals, even in the age of genomics, proteomics, and evidence-based medicine. Nonetheless, with the rapid growth and improvement of human biotechnologies, the need to individualize therapies while allocating medical care equally may result partly from our biological constitution. Human beings are all unique, and their biological differences significantly influence variability in disease causation and therapeutic response to treatments. However, because humans have equal moral worth, there is no ethically justifiable reason to establish an a priori triage among humans with respect to the distribution of health resources.[1] That is, no human being qua human being has a stronger moral claim to good health than do others. Interestingly, the same can be said more or less about human populations. Since every breeding human population qua breeding population is unique, population differences, whether at the genotypic or phenotypic level, affect health outcomes in varying degrees. But here too, there is no morally valid reason to defend an a priori triage among human populations. No breeding human population is morally more entitled to good health than another such breeding human population. The recognition of these interconnected biological and moral facts provides a rationale for defining a unifying goal for modern scientific medicine in terms of individualized equal care.[2] Achieving this goal may require meticulous research that is sensitive to various population substructure levels.

Personalized medicine is based on the core principle of tailoring care to the individual clinical needs of a patient. It aims to optimize individual health and, as such, may require a delineation of the clinical categories of individual beneficiaries of a treatment. Determining beneficiary categories based on patients' clinical biomarkers is called "stratified medicine," a prelude to personalized medicine (Trusheim et al. 2007). Yet, due to human population substructure, the clin-

[1] Triage may occur a posteriori depending on various criteria. For example, we may be morally justified in determining restrictive qualifying conditions for life-saving treatments in situations of scarce resources, and issues such as self-inflicted wounds are fraught with a posteriori moral considerations that may justifiably influence how we allocate care in the healing arts. However, my concern here is how we justify the aims of modern scientific medicine. Disease is sometimes defined as an adverse departure from the species' typical normal functioning (Buchanan et al. 2004). If so, the goal of medicine is to help the sick individual recover a lost or impaired species' normal functioning. Beside factors such as resources constraints, inefficiency, or unavailability of therapeutic means, however, there is no justifiable moral reason to hold that some individuals may not be entitled to a recovery of a lost function no matter what.

[2] The conjunction of the terms *individualized* and *equal* signals that justice in modern scientific medicine involves both "sameness" and "difference." Although achieving justice under current health-care situations undoubtedly often necessitates merely that we reasonably strive to "do more of the same, not more differently" (Bibbins-Domingo and Fernandez 2007, p. 55), it likewise requires at times that we *not* do more of the same, but more differently.

ical beneficiaries of a given treatment may be more or less represented in certain populations compared to others. Since each population, and each individual within any population, has equal moral claim to health, we are morally obligated to maximize the availability of treatment types for different clinical categories of patients, the determination of which may call for substructure sensitivity. Thus both scientific necessity (for example, the avoidance of confounding factors in research design) and the moral imperative of health equality converge to justify human population substructure-sensitive research. This sort of research may facilitate the optimization of population health by maximizing the range of available therapy types. Achieving modern scientific medicine's unified goal of individualized equal care necessitates, both at the individual and populational levels, a dialectical process of optimization and maximization of care.

Complicating matters is the fact that some researchers simply refer, rather crudely, to human population substructure as *race*, a stratification concept that has both biological and social underpinnings. Nevertheless, as a crude label for population substructure, race (rather paradoxically) is likely to be both conspicuously useful and scientifically wanting in biomedical research. Accordingly, a nonnuanced philosophical framework may be inadequate for properly explaining the theoretical status and function of this double-edged-sword-like concept in contemporary biological and biomedical research. In fact, its recent "successful" use in evidence-based medicine sparked a controversy about whether it has any functionality to help revise problematic universalist assumptions, such as "one dose fits all," that have traditionally dominated medical practice. The questions that experts must now address range from the scientific and ontological status of race to the moral permissibility of race-based therapeutics, a crude form of stratified medicine. In the following discussion, I first clarify the assumptions underlying some currently competing clinical concepts in biomedicine. I then document the theoretical status of race in the biological sciences. Finally, I suggest that normative ethical attempts to prevent the use of race must show that race-based therapies raise non-benign moral concerns for competent patient decision making to either accept or forego treatment.

Shifting the Therapeutic Paradigm

The success of the African American Heart Failure Trial (A-HeFT), and the subsequent changes in public health policy brought about by the approval of BiDil for race-specific prescription by the Food and Drug Administration (FDA) in 2005, inaugurated an era of competing clinical concepts. The dominant concept known as "one dose fits all" now seems to compete with a rival concept that we may characterize as "each race, its dose." Various assumptions underlie the dominant concept, but I shall focus on the central tenet of the "species therapeutic similarity assumption," or simply, the universalist clinical assumption. This assumption holds that, with some variations based on age and sex, drug reactions

are generally similar across the human species. Therapeutic goals are best met, therefore, when treatment is guided by clinical rather than demographic characteristics (Bibbins-Domingo and Fernandez 2007; Cooper et al. 2003; Tate and Goldstein 2004).

Yet biomedical researchers have become aware of the limits of the universalist assumption just as they have come to realize that the common variants/common disease hypothesis is untenable. The subject matter of this dual biomedical awareness can be stated as follows: similarity in biological constitution does not always entail similarity in disease risk or reaction to therapeutic agents. Researchers thus have become more informed about the influence of environmental factors on disease causation and drug response. Growing awareness of an expanding repertoire of social and ecological factors in the complex etiology of many chronic diseases, whose prevalence varies along population substructure lines, underscores the limitations of the dominant clinical concept. The need to further stratify medicine beyond age and gender characteristics essentially became a moral imperative driven by a scientific necessity. Race-based therapies emerged out of precisely this scientific and social context, generated in part by genomic claims about the existence of biological human races as a means to overcome the limits of the universalist assumption.

The competing race-based stratification concept embodies the following three-part assumption: (1) there are biologically real human races that formed during human evolutionary history; (2) biological human races are branching continental populations on the human evolutionary tree; and (3) continental ancestry is therapeutically significant. I shall call this three-part assumption the "evolutionary race therapeutic similarity assumption." This assumption presupposes the convergence of phylogenomics (the study of the evolutionary relationship between groups of organisms based on their genomes) and pharmacogenomics, or the convergence between phylogenomics and evidence-based medicine (Burchard et al. 2003; Risch et al. 2002; Taylor et al. 2004). Yet the goal of phylogenomic classification is to study organisms by first mapping their genomic constitutions and then grouping them into taxa based on their evolutionary relatedness. Evidence-based medicine, on the other hand, aims to provide through randomized controlled trials (RCTs) the best scientific evidence for therapeutic decision making. Heated disputes persist over the alleged convergence between these two scientific pursuits and over the resultant rationale of using continental genetic clusters to categorize patients for research and therapy choice (Burchard et al. 2003; Cooper et al. 2003; Maglo 2010; Rosenberg et al. 2002).

Clearly, genomics contributes to evidence-based medicine. But at the theoretical level, evidence-based medicine currently ranks bench research close to the bottom of its hierarchy of evidential sources (Borgerson 2009). N-of-1 randomized trials (involving a patient and a clinician) and systematic reviews of RCTs (involving larger samples of patients) stand at the top of the hierarchy, followed by individual RCTs. It is the clinical trial that tests the effectiveness of a given

therapy in patients and therefore represents the most reliable source of evidence for health-care practitioners' therapeutic decision making. Systematic reviews of observational studies, followed by individual observational studies, come next in the hierarchical ordering of scientific evidence in biomedical research. Observational studies, unlike clinical trials, are particularly expedient for assessing long-term therapeutic harmful effects. Yet the ranking order of clinical studies in evidence-based medicine "is not absolute" (Guyatt et al. 2002, p. 12). For instance, in a recent breakthrough in molecular medicine, the FDA approved Crizotinib (Xalkori) for the 3 to 5% of lung cancer patients carrying the defective ALK gene detectable by a companion test (Rockoff 2011). Genomic medicine increasingly provides tools to stratify patients, to choose therapy, and, of course, to continually revise the evidential hierarchy.

Nevertheless, the hierarchy can operate here as a helpful theoretical shortcut to drive home the following point: there is no reason a priori to believe that phylogenomic groupings and clinical determination of patient categories will necessarily match. Moreover, there is a clear distinction between the goal of phylogenomic classification and that of genomic medicine. The goal of the latter is to understand the functions and interactions of genetic and environmental factors in disease causation and drug response. As critics have repeatedly noted, the functions of much of the genetic material used to classify humans into alleged evolutionary races are unknown. That is, there is no reason a priori to believe that phylogenomic groupings will necessarily coincide with actual medical genetic categorizations (Bibbins-Domingo and Fernandez 2007; Cooper et al. 2003; Maglo 2010; Tate and Goldstein 2004).

Genomic medicine is still in its infancy, and despite encouraging results, many researchers caution that "for both viewers and participants, the race for discoveries from genomic medicine will likely be a marathon, not a sprint" (Newton-Cheh and O'Donnell 2004, p. 3010; see also Royal Society 2005). In the course of this marathon, caution is advisable when one extrapolates from phylogenomic studies to clinical medicine. Genomic findings have confirmed the unity of the human species, as indicated by recent estimates showing that humans are 99.9% genetically similar. Still, the same studies have also confirmed the existence of population substructure within our species, both at continental and subcontinental levels, accounting for 5 to 10% of the 0.1% of our genetic differences. Similarly, views about the uniqueness of each individual are reinforced by research demonstrating considerable individual variability, nearly 90 to 95% of our 0.1% variance in DNA, within continentally and subcontinentally defined groups (King and Motulsky 2002; Rosenberg et al. 2002; Rotimi and Jorde 2010).

An earlier biomedical extrapolation from these data laid the foundation for the common variant/common disease—rare variant/rare disease hypothesis mentioned above. This hypothesis posited that genetic variants causing common diseases are prevalent among humans, while rare variants explain diseases occurring only in some populations (King and Motulsky 2002). While mounting

empirical evidence eventually refuted this hypothesis, scientific findings increasingly suggested that population substructure may have greater epidemiological and clinical significance than previously realized (Burchard et al. 2003; Risch et al. 2002). A turning point in this debate came from the success of the African American Heart Failure Trial (A-HeFT). Yet a close scrutiny of the pertinent literature suggests that we can grant continental genetic ancestry some utility in stratified medicine without necessarily accepting the first two parts of the evolutionary race clinical assumption.

Consider the case of Gencaro (Bucindolol hydrochloride), a genetically targeted therapy currently under development by ARCA Biopharma for the treatment of chronic heart failure. In 2009, the FDA refused to approve certain submissions of the company's New Drug Application (NDA), due to a purported lack of adequate clinical and nonclinical evidence for Gencaro's reduction in all-cause mortality in patients with genotype-defined heart failure. Especially contentious was the FDA's concern over ARCA Biopharma's claim that genotype can predict individual patient response to Gencaro. Consequently, the FDA instructed ARCA Biopharma to conduct further clinical and nonclinical studies to determine the efficacy and safety of the drug. Despite the FDA's cautionary stance, Gencaro is poised to become a genetically targeted treatment for heart failure; in 2010 ARCA obtained a European patent on its treatment methods. The Beta-Blocker Evaluation of Survival Trial (BEST) failed to show that bucindolol hydrochloride, the active pharmaceutical agent later baptized as Gencaro, is efficient in treating heart failure (BEST Investigators 2001). Subsequent analyses of DNA collected from participants in this trial suggested a survival effect in patients carrying the ß1-adrenergic receptor gene and alpha-2C-adrenergic receptor genetic biomarkers. If approved, Gencaro will signal important milestones in both stratified medicine and the path toward personalized medicine.

The irony, however, is that Gencaro strengthens a clinical concept whereby a specific treatment will be directly targeted to a particular category of patients, regardless of their racial membership, while at the same time demonstrating the clinical importance of human population substructure (typically misconstrued as race) in biomedicine. In the initial BEST reports, bucindolol hydrochloride revealed no significant overall survival benefit in a "demographically diverse group of patients with NYHA class III and IV heart failure" (BEST Investigators 2001, p. 1659). The failure of BEST is explained by a lack of sensitivity to human population substructure in the initial sampling strategy. While earlier trials of beta-blockers recruited only about 5% of African Americans, BEST's sample comprised about 23% of African American patients (Reinhart and White 2009). Only 38% of African American patients compared to 53% of European American patients in the study carried the ß1-adrenergic receptor genetic polymorphism putatively responsible for the favorable response to bucindolol hydrochloride (Bibbins-Domingo and Fernandez 2007; Ferdinand and Ferdinand 2009). The category of patient-beneficiaries of bucindolol hydrochloride cuts across

divisions of continental genetic ancestry as well as social groups corresponding to races. Nevertheless, rather than showing that demography-based stratification concepts are irrelevant in biomedicine, Gencaro's story illustrates the relevance of these concepts for research and public policy. The evidence to date suggests that many heart failure patients in certain demographic groups may not benefit from this drug.

If genetic polymorphisms are unevenly distributed across the species, or if their influences on drug metabolism (and disease causation) differ across populations, then the moral imperatives of health equality require standards of proportionality and equivalence in human population research. Accordingly, there may be specific moral obligations deriving in part from the occurrence of population substructure within our species, just as there are compelling obligations to achieve personalized medicine that emanate partly from human individual variation. Presumably all human populations, just like all individual humans, are born equal, with comparable aspirations to pursue and attain improved health.[3] Thus there are at least three types of population differences that may still justify the use of population stratification concepts in biomedicine even in the age of personalized medicine. These are (1) population substructure difference; (2) population research inequality, evidenced by the finding that some populations are less studied than others and are thus less likely to benefit from evidence-based personalized medicine (Rotimi and Jorde 2010); and (3) population care access inequality, or the unavailability, for patients in some populations, of genetically targeted therapies yet available for others.

Improvements in individualized care are by themselves unlikely to resolve these issues, simply because personalized medicine is not synonymous with health equality, and personalized medicine may still shine over blatant health injustices. While personalized medicine seeks to optimize treatment efficacy for the individual patient, the health equality goal is to maximize both populational and individual access to optimal individualized therapies. In the age of genomics and evidence-based medicine, however, individuals in some populations may have access to optimally personalized treatments even though such treatments are nonexistent for other populations even within the same nation. The unified goal of modern scientific medicine, when understood in terms of personalized equal care, fosters an optimization-maximization dialectical moral obligation that can be termed the "opti-max imperative." This imperative morally compels us to promote personalized medicine in order to optimize individual health. But at the same time, it requires that we promote population substructure-sensitive research in order to optimize "subpopulation" health in a demographically diverse group (or world) of patients, by maximizing both the availability and access to optimally individualized treatments. Regardless, our present task is to assess the theoretical justification of substructure-sensitive research.

[3] Thus a human population qua human population has a moral status with group right implications.

Human Population Substructure and the Ontological Status of Race in Biomedicine

An appropriate theoretical understanding of human population substructure is necessary to avoid negative consequences of its use or nonuse in biomedicine. For example, if we conceptualize population substructure within our species as reflecting discrete evolutionary groups that are clinically significant, then we may tend to favor race-specific clinical concepts. Yet therapeutic profiles often cut across subgroups, though in varying degrees. Thus, failure to understand how population substructure affects the configuration of clinical categories may diminish appreciation of the biomedical correlates of population research disparities. However, the quarrel about whether or not genetic substructures within our species define independent biological realities remains. Because human population differences are often conceptualized in terms of racial differences, the pivotal issue is whether human races constitute a biological reality. Put differently, the question is whether human races are evolutionary differentiated into what philosophers call natural kinds (Hacking 1999, 2005; Kitcher 2007; Maglo 2011; Root 2010).[4]

Contemporary defenders of biological realism about human population differences provide at least three accounts of race as an evolutionary kind. One group maintains that despite the small degree of variation between humans, current technologies allow us to subdivide our species into biologically distinct continental groups allegedly reflecting an evolutionarily diverging phenomenon (Burchard et al. 2003; Risch et al. 2002; Rosenberg et al. 2002). As in phenetic classification—which assesses the overall similarity between organisms—the goal of racial groupings is to evaluate the overall genetic similarity and differences among human populations. Critics sharply charge that these continental groups are not discrete but instead depict a smooth gradation of human population genetic profiles. Ontologically speaking, they maintain, there is nothing natural about human races so defined, since their putative boundaries are at best fuzzy (Bolnick 2008; Keita et al. 2004; Royal et al. 2010; Serre and Pääble 2004).

To overcome the non-discreteness problem, some race realists have turned away from genetic similarity assessments in favor of the search for ancestral lineages, a taxonomic approach known as *cladistics*. They contend that human races are clades or monophyletic groups—that is, each group comprises a common ancestor and all the descendants of that ancestor (Andreasen 1998; Templeton 1999). The problem with this line of argumentation is that human evolutionary history and migration patterns are such that population history does not correspond to gene history. While gene history in the human species readily translates

[4]Roughly speaking, natural kinds such as water or gold are determined by their microstructures H_2O and the atomic number 79, respectively. In the same vein, genomics, it is said, allows us to determine the "microstructure" of human races and to reveal that they are in fact what we may call evolutionary kinds (see Maglo 2011).

into clades, world human populations are formed partly through fusion and reveal crisscrossing genetic lineages. For a classification to have an evolutionary meaning in cladistic theories, the groups should be defined as monophyletic. Human populations tend rather to comprise the descendents of more than one common ancestor. Otherwise put, they are not naturally divided by evolutionary processes. Ontologically, they are not evolutionary kinds (Long et al. 2009; Maglo 2011; Templeton 1999).

The pitfalls of similarity-based and lineage-based classifications in the race debate have led other race realists to maintain that any two human groups differentiated by a trait that arose through natural selection under specific ecological pressures are biologically real human races, or evolutionary kinds. Any single naturally selected trait is sufficient to identify human races. Because human populations face different evolutionary pressures in different ecological niches, some naturally selected advantageous traits and the genetic mechanisms controlling for them differ from population to population. The problem, however, is that, under the "one evolutionary trait" scenario, two different adaptive traits may cross-classify the same population, hence the same individual. For example hemoglobin S mutation and LCT gene controlling for sickle-cell anemia trait and lactose metabolism, respectively, may allow for the classification of a single West African population and an individual into two different races. In a word, racial membership will be unstable, varying according to the trait under study (Maglo 2010; Oubré 2011).

However, it does not follow from the denial of human races as evolutionary kinds that population substructure is illusory. With the emergence of genomic technologies, populations once thought to be homogeneous can now be shown to exhibit genetic substructures. For example, genome-wide association studies allow scientists to distinguish northern from central Swedes and both of these groups from southern Swedes, based on their varying genetic profiles (Salmela et al. 2011). These findings may have epidemiological significance, even though they do not support biological race realism. But whether racial or ethnic categories should be predicated at all on these genomic studies remains an open issue. I have proposed elsewhere that population substructures are best conceptualized in terms of divisionary levels (DLs). The divisionary level taxonomic scheme would enable describing, for example, the Swedish population in terms of a DL-5 population, and each of its subpopulations mentioned above as DL-6 populations (see Maglo 2010). This might help alleviate the problem of predicating race (and all of its confounding sociopolitical connotations) on human population genetic substructures. That said, whether an alternative terminology will ever succeed in dislodging this time-honored concept in science is hard to predict. About a century and half ago, Darwin (1871) disappointedly wrote about attempts to substitute more appropriate notions for race when he stated: "But from long habit the term 'race' will perhaps always be employed" (p. 204).

The sticking philosophical point here is that when, under these epistemic

conditions, race has functionality in biomedicine, it is best understood as an instrumental kind—in other words, as a mere convenient device. This simultaneously suggests that there is no a priori reason to adamantly oppose the use of race in biomedicine on epistemic grounds alone. In biology, as in the case of physics, there are concepts and theories that have only instrumental value. For instance, empiricists like Rudolph Carnap (1991), post-empiricists like Thomas Kuhn (1962), and postmodernists like Michel Foucault (1970) all acknowledge that some theoretical frameworks are accepted in science based only on the criteria of expediency, efficiency and fruitfulness. As Carnap (1991) once said: "Let us grant to those who work in any special field of investigation the freedom to use any form of expression which seems useful to them; the work in that field will sooner or later lead to the elimination of those forms which have no useful function" (p. 96). Although Carnap's concern was theoretical physics, his empiricist stance on freedom of inquiry may help to explain the instrumentalist standpoint taken in this paper. On epistemic grounds, whether the concept of race should be embraced in specialized fields like human genetics and medical genetics hinges on its heuristic nature or problem-solving potential to resolve relevant case study queries, rather than on the validity of this concept in light of evolutionary biology. My approach here is therefore a casuistic instrumentalism or epistemology (that is, an approach revolving around case-based reasoning).

Casuistic instrumentalism maintains that the belief—whether social constructivist, postmodernist, or otherwise—that we divide and label all scientifically known phenomena in the natural world into distinctive structures only because of our interaction with the world is as problematic as the ancient Platonic metaphor that nature is all carved at its joints (Hacking 2005; Kitcher 2007). This belief resembles the traditional pragmatist and principled instrumentalist/anti-realist view that properties we recognize in the natural world are by no means independent from us or discretely distributed, but instead appear to exist as such only because of our interests and because of the divisions, or scientific categorizations, that we impose on nature. Casuistic instrumentalism differs from these views and beliefs in the sense that it does not hold that all biological kinds, and hence all scientific kinds, are instrumental kinds (Maglo 2011). Implicit in this view is the idea that at least some biological kinds are naturally or evolutionary differentiated, and thus independent from our human inclination to categorize nature into manmade divisions. Yet casuistic instrumentalists also recognize that in the course of our interaction with the biological world we sometimes create biological and biomedical kinds, some of which we call human races. Casuistic instrumentalism has other ramifications as well. Just as the use of the term species does not imply that all the groups to which taxonomists apply this term have the same ontological status, use of the term *race* in lieu of *human populations* does not imply that human races necessarily meet the criteria of subspecies differentiation in nonhuman species. As Darwin (1871) noted with respect to the use of the term *species*:

> Nevertheless it must be confessed that there are forms, at least in the vegetable kingdom, which we cannot avoid naming as species, but which are connected together, independently of intercrossing, by numberless gradations. . . . The choice of terms is only so far important in that it is desirable to use, as far as possible, the same terms for the same degrees of difference. Unfortunately this can rarely be done. . . . So again the species within the same large genus by no means resemble each other to the same degree: on the contrary, in most cases some of them can be arranged in little group round other species, like satellites round planets. (p. 204)

My argument against biological realists is, quite simply, that just as not all astronomical kinds are planetary kinds, not all biological kinds are evolutionary kinds. Likewise, I maintain against opponents of the concept of race in biology and biomedicine that we may be justified in applying the term *race* to humans on taxonomic grounds, even if the degree of variation between human subpopulations is far less than the comparable degree of differentiation between subpopulations in other species. As Carnap (1991) has already bluntly put it in regard to physics: "To decree dogmatic prohibitions of certain linguistic forms instead of testing them by their success or failure in practical use, is worse than futile. It is positively harmful because it may obstruct scientific progress" (p. 95). However, in contrast to linguistic forms in physics, the instrumental use of race in biomedicine impacts issues beyond scientific progress. It has the potential to affect human health either positively or negatively, raising far more daunting ethical concerns than the issue of freedom of inquiry. Thus it does not follow from the fact that freedom of inquiry in race research may be justified on epistemic grounds that it would automatically be justified on ethical grounds as well. Indeed, we may be morally obligated to eliminate race from science and medicine if its use negatively affects humans. The instrumental use of race therefore requires a combined empirical and normative ethical justificatory framework which I have dubbed "axiological empiricism" (Maglo 2010).

Freedom of Inquiry and the Axiological Empiricist Stance

I have argued that group-based therapy cannot be justified on the ground that race is an evolutionary kind, for the simple reason that there is no such definable thing as evolutionary human races. But even some researchers, Darwin included, who deny that race has any evolutionary meaning still believe that it may have epidemiological and medical significance (Maglo 2010, 2011). Furthermore, over the last 10 years, a growing amount of clinical evidence suggests that drug reactions may vary according to race. But even supporters of race-based therapies maintain that "racial/ethnic pharmacogenetics does not justify withholding appropriate medications" from patients who may not share membership in a particular population for which a race-based drug is approved

(Ferdinand and Ferdinand 2009, pp. 187, 189). These various attitudes toward race are not contradictory within an instrumentalist framework.

The enigma confronting biomedical researchers was described by a group of scientists about a decade ago as follows: "Many drugs that show therapeutic potential never reach the market because of adverse reactions in some individuals, whereas other drugs in common use are effective for only a fraction of the population in which they are prescribed" (Wilson et al. 2001, p. 265). Biomedical researchers attempt to resolve this brainteaser in various ways. In recent years, some experts have reconceptualized race in an effort to revise the universalist clinical assumption, thereby delineating the category of beneficiary entities of a given treatment. However, the end does not justify the means unless the means in itself is not evil. Wilson and his colleagues who described so vividly the biomedical poser also believed that, unlike genetic clusters, demographic categories are "insufficient" and "inaccurate" to help resolve this puzzle. But over the past decade, these "defective" stratification categories have sometimes been used with relative success in clinical trials to get some drugs to bedside. In other cases, the medications were administered in combination with genotypic information, thereby minimizing the potential for dangerous side effects by determining (demographic) group-specific doses. For instance, different doses of warfarin, an anticoagulant drug whose metabolism varies according to genotype but which is also highly sensitive to drug-drug interaction and other environmental conditions, are currently prescribed to different populations (International Warfarin Pharmacogenetics Consortium 2009; Limdi et al. 2008; Yuan et al. 2005). For some, this only compounds the conundrum: how can a scientifically "invalid" concept be useful in science? Yet, as I have been arguing, there is nothing in modern scientific knowledge and practice that precludes a concept that has been invalidated in, for example, evolutionary biology to have practical benefit in specific cases of developmental biology or biomedicine.

To illustrate this point, let us return to the case of BiDil, a drug used in cardiac medicine that represents the most striking instrumental application of the race concept in modern biomedical therapeutics. The road to the approval of this drug by the FDA for race-based therapy was paved by three different clinical trials surrounded by scientific controversies. The Vasodilator Heart Failure Trial I (V-HeFT I), conducted from 1980 to 1985, compared a combination of two generic drugs, hydralazine hydrochoride and isosorbide dinitrate (H/I), to placebo. Though no significant difference was observed between H/I and placebo, retrospective analysis suggested that the combined therapy might be efficient in African Americans. During V-HeFT II, conducted between 1986 and 1991, the efficacy of BiDil was compared with the active agent, enalapril, an ACE inhibitor. The phase II trial revealed that enalapril was more efficient in treating congestive heart failure than BiDil. In a retrospective analysis, however, no difference was observed between BiDil and enalpril in African Americans. The ACE inhibitor produced better clinical outcomes in European American patients. As

critics point out, for both clinical and nonclinical reasons, it was at this juncture that a phase III, placebo-controlled cross-population trial was needed to evaluate the therapeutic effect of adding BiDil and ACE inhibitors to the standard therapeutic regimen. Because corporate rationale prevailed over scientific logic, the phase III trial became a race-based trial that included only African American patients (Bloche 2004; Kahn 2004, 2007, 2011).

The sample sizes of African Americans in V-HeFT I and II were 128 and 215, respectively. Between 2001 and 2004, more than 1,000 African Americans diagnosed with congestive heart failure were recruited to participate in the African-American Heart Failure Trial (A-HeFT). The vast majority of the participants were NYHA class III patients. Despite the widely reported alleged lack of efficacy of ACE inhibitors in African Americans,[5] inclusion criteria in A-HeFT required that eligible patients receive ACE inhibitors in conjunction with other standard therapies. In fact, 69.4% of the participants in the experimental group were taking ACE inhibitors. A-HeFT tested the efficacy of BiDil in an experimental cohort (n = 518) compared with a placebo group (n = 532). The results showed a 43% reduction in mortality rate, and 33% reduction in first hospitalization (Taylor et al. 2004). Despite the controversial clinical concept that led to the A-HeFT, this trial helped bring to the bedside a fixed dose of two race-blind and already available generic drugs that otherwise may not have reached patients. It thus maximized therapy-type availability at the bedside and, therefore, may have contributed to optimization of population health.

Race consciousness provided a way out of the biomedical brainteaser by bringing a fixed dose type of BiDil to clinical beneficiaries. Nonetheless, race, crudely predicated here on human population substructure, offered only a partial solution to our clinical brainteaser. The fact is that to date, there is still no convincing evidence that BiDil works exclusively on all patients with African ancestry. The current issue is about how we should theoretically cash out the like findings, and how we should create the ethical safety nets that may be required if studies like this continue.

I submit that the success of A-HeFT in getting BiDil to the bedside, rather than vindicating biological race realism—the view that race is an evolutionary kind—merely illustrates an instrumental utilization of race. First, the decision to use the A-HeFT study design was motivated partly by economic imperatives, rather than by scientific necessity (Kahn 2004, 2007, 2011). Second, the problem raised by BiDil for the drug companies Medco and NitroMed parallels the challenges that more recently have confronted ARCA Biopharma over a negative therapeutic response to Bucindolol hydrochloride (Gencaro) in a subset of the general population. Yet the clinical concept deployed in each case to bring the drug to the bedside is radically different. Third, the FDA's rationale for support-

[5] It has been widely reported that the differential effect of ACE inhibitors in blacks and whites is as dramatic as a ratio of 1 to 2 (see Kahn 2004).

ing and approving BiDil seemed to rest primarily on the moral imperative of health equality in the treatment of cardiovascular diseases. Fourth, even if it is plausible that the efficacy of BiDil in patients with African ancestry may be due to some particular genetic variants, there is no reason to presume that these variants will be squarely limited to one racial group and simultaneously carried by every individual member of that racial group.

My arguments are not directed simply against biological race realism but also against race eliminativism, or the view that race should be banished from science and biomedicine. In reality, we need to distinguish between epistemic eliminativism and ethical eliminativism (Maglo 2010). *Epistemic* eliminativism holds that the concept of race should be rejected in science and medicine because it is meaningless in light of evolutionary biology. But as I have shown, there is no compelling theoretical justification for using the concept of race only if it corresponds to a proper evolutionary kind. Rather, *ethical* eliminativism maintains that it is morally justified to eliminate from science and medicine a concept, whether foundationally important or only occasionally useful, if its use causes harm or violates some fundamental moral norms.

Accordingly, I maintain that the ethical conflict over race in biomedicine needs to be resolved mainly from the patient perspective. Our primary and ultimate goal in the biomedical sciences is to help discharge a duty to the patient qua patient. This is not to deny that the societal, corporate, scientific, and patient perspectives are intertwined in biomedical research. But this four-dimensional entanglement cannot obscure the essential rationale that justifies the existence of medical practice and biomedical research in the first place—that is, the hope and obligation to deliver care to the patient qua patient. Ethical eliminativists' concerns typically focus on the overall well-being of society (Hacking 2005; Kitcher 2007; Root 2010). Their concerns are sufficiently well-founded and serious to warrant close scrutiny. These concerns range from racial stereotyping and the unintended consequence of creating the impression that science and medicine validate the social meaning of race to the fear that the search for race-oriented drugs will lead to economic exploitation by pharmaceutical companies.

However, from the patient perspective, ethical eliminativist arguments do not provide a compelling justification for withholding a potentially efficacious therapy from a patient. They fail to show why such a patient should, out of a sense of moral obligation, be willing to sacrifice him- or herself to avoid hypothetical and unforeseeable collective harm. Indeed, lessons from race-based historical wrongs are teachable moments in navigating the sociopolitical environment of human development and well-being, both of which may be enhanced by biomedicine. Yet with respect to life-threatening epidemiological and clinical conditions, if societal moral arguments rest primarily on speculative scenarios, it seems reasonable to assume that the patient perspective ought to be the overriding consideration. Our duty to the patient should lie at the heart of our endeavor to establish regulative ethical rules. This is not to suggest that the patient perspective is nec-

essarily patient-centric. The appropriate regulative rules wangled from this perspective ought to meet at least the following three conditions: (1) they should be acceptable for the reasonably healthy person; (2) the competent patient, in the bioethical sense, should see them as fair despite the serious nature of the health condition; and (3) they should be relevant to the competent patient's decision to undergo or forego treatment, should the treatment be available. The latter point is not a minor consideration. If societal concerns are benign from the competent patient perspective, then ethical eliminativism may be unjustified.

Competence on the part of a patient involves not only the capacity to reason but also the ability to understand one's health situation, to make a decision and express preferences. It encompasses altogether the state of the mind, the will, and the body (Beauchamp and Childress 2009). Thus a competent patient would, for example, realize that it is contradictory and morally objectionable to seek health by causing others harm similar to the adverse conditions she or he is not prepared to endure. No healthy human being is morally obligated to consent, for the sake of patients' well-being, to a state of compromised health to which a competent patient would not consent. Likewise, the clinical needs of a patient with a severe and debilitating condition may not be sacrificed for societal concerns that are benign from the competent patient perspective. An informed competent patient with a severe and debilitating health condition may still object to an efficient treatment, on moral grounds, should the treatment be obtained at severe or ethically unjustifiable health costs to others. From the competent patient perspective, a treatment is permissible not only because it is therapeutically efficient and safe, but also because it is morally unobjectionable. If so, ethical eliminativists must demonstrate from the patient perspective the morally objectionable nature of race-based therapeutics. Ethical eliminativism needs to provide a competent patient with a debilitating health condition compelling moral reasons to refuse a race-based therapy, if such a therapy were available at the bedside.

It is my belief that both healthy reasonable persons and reasonably competent patients would see a regulative rule that fully captures these considerations as fair. I call such a rule the *patient standpoint rule* and suggest the following formulation:

> In case of conflict over unintended societal consequences of a health policy, the obligation to satisfy the need for efficient (and safe) treatment of patients with debilitating or life threatening conditions is prima facie overriding, unless receiving that treatment will directly and severely affect the health conditions of other bodily independent human beings.

The patient standpoint rule so stated may offer an ethical justification for a casuistic instrumental use of race, provided that the case necessitating the use of race is equally justifiable in a sound empirical framework. However, it may be an incomplete regulative principle for race research, because the category of likely beneficiary patients of a given treatment, as we have seen, usually cuts across racial groups.

While the patient standpoint rule may justifiably supply an ethical grounding for substructure-sensitive research and equality-oriented health policy, it needs to be complemented by a rule that likewise places unambiguously cross population research at the center of our endeavor to achieve personalized equal medicine. I refer to such a rule as the *excluded beneficiary rule*, and it may be stated as follows:

> In the context of study design and theory-choice, the most robust model or clinical trial concept is the one that meets the requirement of improving the health status of orphan populations whose therapeutic needs may be discounted by race market-driven research. (see Maglo 2010)

The excluded beneficiary rule certainly constrains the corporate perspective. But by stressing, consistently with the Hippocratic oath, that our duty is not to "epidemiological charts" or, in keeping with the terminology of this paper, to "population substructure" or "race," but rather to the "sick individual" or patient qua patient, it also holds implications for study design and the interpretation of scientific findings. Taken together, both the patient standpoint rule and the excluded beneficiary rule indicate that while an instrumental use of race may be permissible under some circumstances, it is at the same time limiting in our endeavor to achieve the unified goal of personalized equal care in modern scientific medicine.

CONCLUSION

I have argued that the universalist clinical assumption, according to which one therapeutic dose supposedly fits all human populations, needs revision. To achieve this, however, does not require scientific evidence establishing human races as evolutionary divergent groups. Because race is construed in research as a proxy for population substructure, it may be useful under some circumstances. Yet, as a crude indicator, it is unlikely to help further our theoretical understanding of the subtle ways in which proper population substructure-sensitive research contributes to advancing the unified goal of personalized equal care in modern scientific medicine. This epistemic issue, however, does not provide a sufficient reason to eliminate the concept of race from biomedicine. For race eliminativism to be justified, one also needs to show, on ethical grounds, that biomedical race research and race-based therapeutics are morally objectionable from the patient perspective. Ethical eliminativists have yet to meet this challenge.

References

Andreasen, R. 1998. A new perspective on the race debate. *Br J Philos Sci* 49(2):199–225.

Beauchamp, T., and J. Childress. 2009. *Principles of biomedical ethics*. Oxford: Oxford Univ. Press.

BEST Investigators. 2001. A trial of the beta-blocker Bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 344:1659–67.

Bibbins-Domingo, K., and A. Fernandez. 2007. BiDil for heart failure in black patients: Implications of the U.S. Food and Drug Administration approval. *Ann Intern Med* 146: 52–56.

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*, ed. B. Koenig, S. S-J. Lee, and S. S. Richardson, 70–85. Rutgers: Rutgers Univ. Press.

Borgerson, K. 2009. Valuing evidence: Bias and the evidence hierarchy of evidence-based medicine. *Perspect Biol Med* 52(2):218–33.

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.

Carnap, R. 1991. Empiricism, semantics, and ontology. In *The philosophy of science*, ed. R. Boyd, 85–97. Cambridge: MIT Press.

Cooper, R. S., et al. 2003. Race and genomics. *N Engl J Med* 348(12):1166–70.

Darwin, C. 1871. *The descent of man and selection in relation to sex*. Repr. London: Penguin Books, 2004.

Ferdinand, K., and D. Ferdinand. 2009. Cardiovascular disease disparities: Racial/ethnic factors and potential solutions. *Curr Cardiovasc Risk Rep* 3:187–93.

Foucault, M. 1970. *The order of things: An archaeology of the human sciences*. New York: Pantheon.

Guyatt, G., et al. 2002. *Users' guides to the medical literature: A manual for evidence-based clinical practice*, 2nd ed. New York: McGraw-Hill.

Hacking, I. 1999. *The social construction of what?* Cambridge: Harvard Univ. Press.

Hacking, I. 2005. Why race still matters. *Daedalus* 134(1):102–16.

International Warfarin Pharmacogenetics Consortium. 2009. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 360(8):753–64.

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.

Kahn, J. 2007. Race in a bottle. *Sci Am* (Aug.):40–45.

Kahn, J. 2011. Mandating race: How the USPTO is forcing race into biotech patents. *Nat Biotechnol* 29(5):401–3.

Keita, S. O. Y., et al. 2004. Conceptualizing human variation. *Nat Genet* 36(suppl. 11): S17–S20.

King, M.-C., and A. Motulsky. 2002. Mapping human history. *Science* 298:2342–43. http://www.sciencemag.org.

Kitcher, P. 2007. Does "race" have a future? *Philos Public Aff* 35(4):293–317.

Kuhn, T. 1962. *The structure of scientific revolutions*. Chicago: Univ. of Chicago Press.

Limdi, N. A., et al. 2008. Influence of CYP2C9 and VKORC1 1173C/T genotype on the risk of hemorrhagic complications in African-American and European-American patients on warfarin. *Clin Pharmacol Ther* 83(2):312–21.

Long, J., et al. 2009. Human DNA sequences: More variation less race. *Am J Phys Anthropol* 139(1):23–34.

Maglo, K. 2010. Genomics and the conundrum of race: Some epistemic and ethical considerations. *Perspect Biol Med* 53(3):357–72.

Maglo, K. 2011. The case against biological realism about race: From Darwin to the postgenomic era. *Perspect Sci* 19(4):361–90.

Newton-Cheh, C., and C. J. O'Donnell. 2004. Sex differences and genetic associations with myocardial infarction. *JAMA* 291(24):3008–10.

Oubré, A. 2011. *Race, genes and ability: Rethinking ethnic differences*, vol. 1. Woodland Hills, CA: BTI Press.

Reinhart, K., and M. White. 2009. Bucindolol: A beta-blocker for the treatment of heart failure. *Formulary* 44(6):166–71.

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

Rockoff, J. 2011. FDA approves Pfizer lung-cancer drug. *Wall Street J*, Aug. 26.

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

Root, M. 2010. Stratifying population by race. *J Soc Philos* 41(3):260–71.

Rotimi, C. N., and L. B. Jorde. 2010. Ancestry and disease in the age of genomic medicine. *N Engl J Med* 363(16):1551–58.

Royal, C. D., et al. 2010. Inferring genetic ancestry: Opportunities, challenges, and implications. *Am J Hum Genet* 86: 661–73.

Royal Society. 2005. Personalized medicine: Hopes and realities. http://royalsociety.org/Personalised-medicines-hopes-and-realities/.

Salmela, E., et al. 2011. Swedish population substructure revealed by genome-wide single nucleotide polymorphism data. *PLoS One* 6:2:e16747.

Serre, D., and S. Pääble. 2004. Evidence for gradients of human genetic diversity within and among continents. *Cold Spring Harb Lab Press* 14:1679–85.

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

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

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

Trusheim, M. R., et al. 2007. Stratified medicine: Strategic and economic implications of combining drugs and clinical biomarkers. *Nat Rev Drug Discov* 6:287–93.

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

Yuan, H.Y., et al. 2005. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. *Hum Mol Genet* 14, 1745-51.