

## **BIDIL AND RACIALIZED MEDICINE**

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On June 23, 2005 the Food and Drug Administration (FDA) approved a drug to treat heart failure in African-Americans, and only African-Americans. This race-specific drug is called BiDil. BiDil is not a new drug. It is merely a combination into a single pill of two existing generic drugs that have been used to treat heart failure regardless of race for over a decade.

BiDil was brought to the FDA by NitroMed, a hitherto small Massachusetts biotech company with no other products on the market. NitroMed explicitly requested race-specific FDA approval for its drug based on clinical data produced by its “African-American Heart Failure Trial (A-HeFT)” on the grounds that the trial population happened to be all African-American.

BiDil does indeed appear to significantly help many people suffering from heart failure – a debilitating and ultimately fatal disease afflicting several million Americans. There is no scientific evidence, however, that race has anything to do with how BiDil works. This is for the simple reason that A-HeFT enrolled *only* “self identified” African-Americans. With no comparison population, no legitimate claims can be sustained that BiDil works differently or better in African-Americans than in anyone else.

The FDA, however, accepted NitroMed’s argument that because the trial population was African-American then the drug should be labeled as indicated only for African-Americans. This sends the troubling and unsubstantiated message that the subject population’s race was somehow a relevant biological variable in assessing the safety and efficacy of BiDil. Ominously, it also gives the federal government’s imprimatur to the use of race as, in effect, a genetic or biological category. By seeking and granting approval of BiDil as a drug solely to treat African Americans, NitroMed and the FDA thus opened a Pandora’s box of racial politics without fully appreciating the implications of what they were doing.

### **Basic Concerns**

First, most drugs on the market today were tested almost exclusively in overwhelmingly white male populations. But we do not call these “white” drugs – nor should we. Rather, the operating assumption for approving these drugs was that the unmarked racial category of “white” was coextensive with the category “human being.” That is, a drug tested on white people was good enough for everybody. In approving BiDil as a drug only for African-Americans, the FDA has also implicitly adopted an assumption that drugs tested in black people are only good for black people. This sends the unintended but nonetheless powerful message that black people are somehow less fully representative of humanity than are white people.

Second, given that the BiDil researchers admit that their drug will work in non-African Americans, the most plausible reason for conducting a race-specific clinical trial is that NitroMed holds the rights to a race-specific patent that will give them control over profits from

BiDil until 2020. Of course, this hardly constitutes a sound scientific basis for designing a clinical trial. But it's a good economic one. An older patent, which does not refer to race, expired in 2007; if BiDil had been approved for treatment regardless of race, NitroMed's patent protection would have expired in a mere two years.<sup>1</sup>

Third, there is the problem of who "counts" as African-American. In an increasingly intermixed and complex society, one might ask just "how much" of an African-American one has to be to get the drug – 1/2, 1/4 (quadroon), 1/8 (octoroon)? This starts sounding suspiciously like the blood quantum thinking of the Jim Crow era. Moreover, the label itself also refers to "black" people. Does this include dark skinned peoples from South Asia, or Australian Aborigines? The trails and label of BiDil are based on the concept of "self-identification." Self-identification, however, is a subjective social judgment. It has nothing to do with the biological phenomena of drug metabolism and response.

Fourth, race-specific labeling will make it more likely that non-African Americans who might benefit from the drug will not get it. Health care providers simply may not think of prescribing it to non-African Americans, and insurance carriers may not cover such "off-label" use. Alternatively, what happens if someone who would typically be socially identified as white decides to self identify as African-American in order to get insurance coverage for the drug? Are insurance companies then going to become arbiters of racial identity?

Fifth, marketing a race-specific drug can lead to a misallocation of health care resources. To the extent that we reduce the very real racial disparities that exist in health care to a function of genetic difference, we risk diverting political will and economic support away from addressing the pressing social, economic and political causes of racial inequality in our society. Racialized medicine presents us with the superficially appealing and misguided message that instead of fixing injustice, we can simply fix molecules.

Finally, if the FDA approves BiDil only for African-Americans, it will be giving the federal government's stamp of approval to using race as, in effect, a genetic category. But race is not genetic, as even the BiDil researchers admit. Moreover, there is no accepted biological definition of race. Given our nation's troubled history of racial oppression, this is not something that should be taken lightly.

### **What is Racialized Medicine?**

At the outset, it is important to distinguish between the use of race in medical practice as opposed to racialized medicine. It may be entirely appropriate, even necessary, to use race when tracking and addressing broad issues such as health disparities in American society. Understanding race as a social construct is entirely consistent with recognizing and addressing race-based inequalities in access to or quality of medical care in our society. Such inequalities reflect the biological implications of the social and historical phenomenon of racial discrimination.

Social understandings of race vary over time and across space. In the past, the U.S. Census has included racial categories ranging from Mulatto to Hindu. In the Jim Crow south,

children of Armenian or Greek immigrants were sometimes mandated to go to schools designated for black children. Today, someone of light brown complexion who is socially identified as “black” in the U.S. (say, for example, someone with a white mother from Kansas and a black father from Kenya) might be identified as “white” in Jamaica or Brazil. In the U.S., the concept of “self-identification” has become the norm in assigning racial identities to individuals. As a social practice for collecting census data this makes sense. But as a medical or scientific practice it is far more problematic.

In medical practice what matters is our shifting understanding of the correlations between such evolving social identities and the evolving economic, political and environmental conditions to which they may be related. For example, what are we to make of the fact that African-Americans suffer from disproportionately high rates of hypertension, but Africans in Nigeria have among the world’s lowest rates of hypertension, far lower than the overwhelmingly white population of Germany? Genetics certainly plays a role in hypertension. But any role it plays in explaining such differences must surely be vanishingly small.

There may be occasions where race can be productively used even in genetic research, but in such cases it is very important to differentiate between using a racial group to characterize a gene versus using a gene to characterize a racial group. Thus, for example, a researcher trying to understand the genetics of diabetes may choose to study the Pima Indians in the Southwest United States because that group has a very high incidence of diabetes. This is an example of using a socially identified racial or ethnic group in order to try to characterize a gene (here for diabetes). It is quite another thing, however, for a researcher who finds such a gene to use it to characterize the identity of Pima Indians as a group with “the gene for diabetes”. The former use does not necessarily stigmatize or define a group in terms of genetics, the latter use does.

In such situations, medical practitioners need not, indeed often should not, ignore race. The issue is not primarily one of *whether* to use racial categories in medical practice but *how*. Carefully taking account of race to help understand broader social or environmental factors that may be influencing health disparities can be warranted in certain situations. But it is always important to understand that race itself is not an inherent causal factor in such conditions.

In contrast, *racialized* medicine is premised on an implicit, and sometimes explicit, understanding of race as a genetic construct. Such an understanding is both scientifically flawed and politically dangerous. Since the inception of the Human Genome Project, much time and attention has been devoted to insuring that biological knowledge emerging from advances in genetic research is not used inappropriately to make socially constructed racial categories appear biologically given or “natural”. Since Richard Lewontin’s ground-breaking work on blood group polymorphisms in different groups and races in the 1970s, scientists have understood that race will statistically explain only a small portion of genetic variations. As a 2001 editorial in the journal *Nature Genetics* put it, “scientists have long been saying that at the genetic level there is more variation between two individuals in the same population than between populations and that there is no biological basis for ‘race.’”<sup>2</sup> More recently, an editorial in *Nature Biotechnology* asserted that, “Race is simply a poor proxy for the environmental and genetic causes of disease or drug response. . . . Pooling people in race silos is akin to zoologists grouping raccoons, tigers and okapis on the basis that they are all stripey.”<sup>3</sup>

Politically, history teaches us that constructing races as genetically bounded and discrete categories is only one short step from constructing races as inferior and superior. Racism feeds on biologically reductive constructions of racial difference. It is imperative to recognize the significance of race to understand and address the real and persistent health disparities that plague our country. But these disparities are the result of social, economic and political histories of injustice. They demand social, economic and political responses. If we falsely reduce health disparities among socially defined racial groups to a function of genetic difference to be addressed through race-specific medicine, we risk diverting valuable resources and will away from developing policies and practices to confront the true causes of health disparities.

Unlike *racialized* medicine, which treats race as genetic, the *use* of race in medical practice has many legitimate and important places. Collecting broad-based epidemiological data is perhaps foremost among these. Only by using social categories of race is it possible to identify and track racial disparities in health, healthcare access and outcomes. Such information is needed to address on-going issues of racial justice in society. It may also be appropriate for individual health practitioners to take race into account under certain circumstances in trying to assess the needs of their patients. To the extent that health practitioners understand that race, as a social phenomenon, has biological consequences – such as where higher incidence of hypertension might in part be due to an array of environmental, social, or economic factors disproportionately associated with being a racial minority in the United States – it may be legitimate and important to take race into account in formulating appropriate medical interventions.

### **BiDil: A Cautionary Tale of Exploiting Race in Drug Development**

Why then did NitroMed seek race-specific approval for its drug? At the FDA approval hearing much was made of following the “signal” from two trials conducted in the 1980’s that first tested the generic components of BiDil as a treatment for heart failure. As discussions at the hearings progressed, however, it became clear that reviewers were relying primarily on data from the first trial, which placed only 49 African-Americans on the two BiDil generic components. Given that most valid clinical trials test a drug in thousands of subjects, results from 49 African-Americans seem a slender reed indeed upon which to weigh the value of a new drug. Perhaps then the answer lies not in such tenuous medical evidence but in stouter commercial considerations. It turns out that NitroMed holds two key patents to BiDil. The first covers the non-race-specific use of BiDil. This patent, however, expired in 2007. The second patent is race-specific and just happens to last until 2020. (How and why a race-specific patent was granted will be addressed in the next section.) This extra thirteen years of patent protection may present a compelling commercial reason for seeking to cast BiDil as a racial drug – but it is not supported by the medical evidence.

### **BiDil’s Origins**

How did we get to this point? If we go back to its origins, we find that BiDil did not begin as an ethnic drug. Rather it became ethnic over time and through a complex array of legal,

commercial, and medical interventions that transformed the drug's identity. Over the past twenty years a revolution has occurred in heart failure treatment with the development of a wide array of pharmaceutical interventions to improve both the quality of life and longevity of people suffering from heart failure. One of the earliest breakthroughs came in the 1980s with the first Vasodilator Heart Failure Trial (V-HeFT I). This trial lasted from 1980 to 1985. It was led by Dr. Jay Cohn of the University of Minnesota and involved cardiologists from around the country working together with the U.S. Veterans Administration. The trials found that patients receiving a combination of two vasodilators called hydralazine and isosorbide dinitrate (H/I) seemed to have a lower rate of mortality. These generic drugs – H/I - would later become “BiDil.” It is this trial that placed 49 African-Americans on the H/I combination that would later become the “signal” followed by NitroMed in seeking race-specific approval for BiDil.

The V-HeFT I trial was soon followed by V-HeFT II, which lasted from 1986 to 1989. This trial compared the efficacy of the H/I combination against the drug, enalapril, an ACE inhibitor. It found an even more pronounced beneficial effect on mortality in the enalapril group, establishing ACE inhibitors as a front line therapy for heart failure. ACE inhibitors, however, did not totally supplant H/I because not everyone responds well to them and some others cannot tolerate the side effects.

The V-HeFT investigators did not build the trials around race or ethnicity. They enrolled both black and white patients but in the published reports of the trials' successes they did not break down the data by race. Rather, they presented H/I (the BiDil drugs) as generally efficacious in the population at large, without regard to race.

### **The Legal and Commercial Construction of BiDil as a Race-Specific Drug**

The role of law as player in the emergence of BiDil as a race-specific drug began in 1980, more or less coincidentally with the initiation of V-HeFT I. That year, President Jimmy Carter signed into law two pieces of legislation that would come to transform relations between industry and academic researchers. The first, the Stevenson-Wydler Technology Transfer Act (15 U.S.C. § 3701 (1994)), encouraged interaction and cooperation among government laboratories, universities, big industries and small businesses. The second, the Bayh-Dole Patent and Trademark Laws Amendment (35 U.S.C. §§ 200-212 (1994)), allowed institutions conducting research with federal funds, such as universities, to retain the intellectual property rights to their discoveries. It is in this context that the research findings of V-HeFT, produced in cooperation with the United States Veterans Administration, could be commercialized through patent and trademark law. Thus, lead cardiologists in the V-Heft trials, Jay Cohn and Peter Carson, later were able to obtain intellectual property rights in BiDil-related patents and thereupon enter into deals with the likes of NitroMed to commercialize the discoveries made through the V-HeFT trials.

In 1989, Cohn obtained a patent on a “method of reducing mortality associated with congestive heart failure using hydralazine and isosorbide dinitrate,” (U.S. Pat. #4,868,179). He then licensed the rights to a company called Medco which developed BiDil as a *new* drug – being a combination of H/I in single dose form. BiDil was a breakthrough of convenience - it

made it easier to use and dispense the drug – but it was not itself a new therapy. Again, at this point it was still a drug for everyone, *regardless of race*. In the early 1990s Medco invested time and money to conduct bioequivalence tests and develop marketing strategies in preparation for submitting a New Drug Application (NDA) for BiDil to the FDA in 1996.

Even at this early stage the true breakthrough of BiDil was not the combination of two generic drugs into a single pill, it was the development of new intellectual property rights whose value was contingent on FDA approval of the new drug. With a patentable therapy in hand, drug companies would have an incentive to educate physicians and market the new drug. In contrast to the classic justification for patents as incentives to develop new drugs, intellectual property rights here provided instead an incentive for developing a new marketing strategy based on existing therapy. Moreover, given that the two drugs comprising BiDil were already available as generics, this also indicates how patent law and regulatory approval may distort a market, potentially obscuring less expensive generic alternatives that have the same therapeutic value.

The FDA ultimately rejected this first NDA in 1997 because it found the retrospective analysis of data from the V-Heft trial was insufficiently powered to meet the regulatory criteria of statistical significance. It is important to note here that the FDA advisory committee reviewing the drug did not think BiDil didn't work. To the contrary, many of the doctors on the panel were generally convinced of its clinical efficacy. They turned down the application because V-HeFT trials were not designed as *new* drug trials and so the data they produced could not meet the regulatory criteria of statistical significance required for new drug approval.

Following the FDA rejection in 1997, the value of the intellectual property rights to BiDil plummeted along with Medco's stock. The rights reverted to Cohn, and Medco exited the story of BiDil's development. It was at this point that Cohn, together with Carson and others, went back to the V-Heft data and broke it out by race for the first time.

*The intervention of the federal regulatory system to deny the NDA marks the turning point on BiDil's journey toward ethnicity.* The regulatory action taken by the Advisory Committee impelled the BiDil researchers to re-conceptualize their drug along racial lines in order to get a “second bite” at the apple of FDA approval. After the publication of an article purporting to show that BiDil worked better in African-Americans, the value of the intellectual property rights to BiDil rebounded – not because of any changes to the underlying molecular structure or biological effects of BiDil as a drug, but through the reanalysis of the old V-HeFT data along racial lines.

NitroMed acquired the intellectual property rights to BiDil in September 1999. In the hands of its new corporate handlers, together with their public relations consultants, BiDil soon was reborn as an ethnic drug. The subsequent spate of publicity attending the inauguration of A-HeFT marks how the renewed value of the patent to BiDil provided an incentive for NitroMed to educate doctors and the public about the nature and value of this “new” drug for African Americans.

In the next logical extension of patent rights into the process of creating an ethnic drug, Cohn and Carson jointly filed for a new BiDil-related patent on September 8, 2000. With the

title “Methods of treating and preventing congestive heart failure with hydralazine compounds and isosorbide dinitrate or isosorbide mononitrate,” the patent appears much the same as Cohn’s original 1989 patent. Upon closer inspection, however, the abstract to the patent specifies that the “present invention provides methods for treating and preventing mortality associated with heart failure in an *African American* patient.”<sup>4</sup> The issuance of the new patent is commercially important because the original patent was set to expire in 2007. The new race-based patent will not expire until 2020. In this chapter in BiDil’s development, *patent law did not spur the invention of a new drug, but rather the reinvention of an existing therapy as race-specific.*

In 2001, NitroMed approached the FDA with its proposal to obtain race-specific approval for BiDil. The FDA responded with a letter stating that BiDil might be “approvable” pending the successful completion of a race-specific confirmatory drug trial. With the FDA letter in hand, NitroMed was able to raise over \$30 million in venture capital during the nadir of the dot com bust in 2001 to initiate A-HeFT, the African-American Heart Failure Trial. A-HeFT enrolled only “self-identified African-American” subjects. After a slow start, 1,050 subjects were ultimately enrolled. The trial was halted early, in July 2004, by NitroMed’s Data Safety Monitoring Board because it found a striking degree of efficacy in early results indicating that BiDil reduced mortality by some 43%. Such strong positive results suggested that all trial participants should get the drug. NitroMed’s stock price more than tripled on the announcement. This was followed in June 2005 by the FDA’s approval of the new race-specific NDA for BiDil.

### **The Complex Racial Politics of Race-Specific Medicine**

Given such striking results, it is perhaps not surprising that many prominent health activists and organizations in the African-American community strongly supported the approval of BiDil by the FDA. Prominent among these were the Association of Black Cardiologists (ABC), the NAACP, and the National Minority Health Month Foundation (NMHMF). Each of these groups doubtless saw BiDil as an efficacious drug that promised to help their constituents. But it should also be noted that each also received substantial funding from NitroMed. The ABC received \$200,000, the NMHMF received an undisclosed amount of an “unrestricted educational grant to undertake epidemiological research on chronic heart failure patients” and NitroMed also provided \$1.5 million to fund an NAACP “health justice” campaign.

Significantly, however, many of the groups also argued that while BiDil should be approved, it should be approved for use *regardless* of race. Notably, the day before the FDA Advisory Committee meeting, the National Minority Health Month Foundation staged a press conference with an array of African-American identified interest groups including representatives from the Alliance of Minority Medical Associations; Association of Black Cardiologists; Genetic Alliance, Inc.; International Society on Hypertension in Blacks; Joint Center for Political and Economic Studies; Health Policy Institute; National Association for the Advancement of Colored People; and the National Medical Association. These groups issued a joint press statement calling for FDA approval of BiDil. The announcement garnered much media attention. Less noticed however, was the fact that the press release contained such statements as, “The assertion that this is a race drug is misguided,” by Randall W. Maxey, M.D., President, Alliance of Minority Medical Associations, and another by Dr. Gail Christopher, Vice President of the Office of Health, Women and Family, Joint Center for Political and Economic

Studies, stating, “It would be ‘bad science’ to label or market this drug as a ‘Black’ drug. More importantly, race-based claims are not credible in the face of modern genetic science.” The press release itself was titled, “Organizations Unite to Support BiDil’s Approval for Heart Failure. Rebuff Designation as “Race-Only Drug”. In the end, though, the FDA heard only NitroMed’s voice and acceded to its request for a race-specific approval of BiDil.

## **Conclusion**

The story of BiDil clearly raises concerns over the dangers of reifying race in a manner that could lead to new forms of discrimination. BiDil, however, is part of a much larger dynamic of reification in which the purported “reality of race” as genetic may be used to obscure the social reality of “racism.” To the extent that this dynamic succeeds in reductively reconfiguring health and other types of disparity in terms of genetic difference, it casts personal responsibility and the market as the appropriate arenas for addressing differential outcomes. It also undermines the rationale for deliberate state or institutional interventions to address discrimination.

This is not to advocate "color blind" medicine. To the contrary, there are very real health disparities in the country that correlate with race. African-Americans suffer a disproportionate burden of a number of diseases, including hypertension and diabetes. Like heart failure, these are complex conditions caused by an array of environmental, social, and economic as well as genetic factors. Central among these is the fact that African-Americans experience discrimination, both in society at large and in the health care system specifically. The question is: once society identifies these disparities in health outcomes, how does it address the underlying causes? Of course, outcomes can have multiple causes, both social and genetic. But health disparities are not caused by an absence of "black" drugs. As studies by the Institute of Medicine, among others, make clear, they are caused by social discrimination and economic inequality. The problem with marketing race-specific drugs is that it becomes easier to ignore the social realities and focus on the molecules.

For all the legitimate concerns that the genomics revolution might lead to new forms of discrimination, we must also be alert to the potential appropriation of genetics to obscure or justify existing inequalities.

## **References**

Institute of Medicine. 2002. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*.

Kahn, J. (2004). “How a Drug Becomes ‘Ethnic’: Law, Commerce and the Production of Racial Categories in Medicine.” *Yale J. of Health Policy, Law & Ethics* 4: 1-46.

Kahn, J. (August 2007). “Race in a Bottle.” *Scientific American*, 40-45.

Sandra S. Lee et al., (2001) “The Meanings of ‘Race’ in the New Genomics: Implications for Health Disparities Research”, *Yale J. Health Pol’y L. & Ethics* 1: 33-75.

Taylor, A., et al. (2004) "Combination of isosorbide dinitrate and hydralazine in blacks with heart failure." *N. Engl. J. Med.* 351: 2049-2057.

### **Endnotes**

1 Kahn, J. *From Disparity to Difference: How Race Specific Medicines May Undermine Policies to Address Inequalities in Health Care*, 15 *Southern California Interdisciplinary Law Journal* 105-129 (2005).

2 Editorial. *Genes, Drugs and Race*. 29 *Nat. Gen.* 239, 239 (2001).

3 Editorial. *Illuminating BiDil*. 23 *Nat. Biotech.* 903,903 (2005).

4 (U.S. Patent #6,465,463, emphasis added)

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