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How a Drug Becomes 'Ethnic': Law, Commerce, and the Production of Racial Categories in Medicine

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Abstract
A drug called BiDil is poised to become the first drug ever approved by the Food and Drug Administration (FDA) to treat heart failure in African Americans - and only African Americans. This article explores the story of BiDil and considers some of its broader implications for the use of racial categories in law, medicine, and science. It argues that BiDil is an ethnic drug today as much, if not more because of the interventions of law and commerce as because of any biomedical considerations. The article is, first, a retrospective analysis of how law, commerce, science, and medicine interacted to produce a distinctive understanding of BiDil as an ethnic drug, shaping which questions got asked at critical junctures in its development and orienting how they were pursued. Second, it is a prospective consideration of how the science and medicine thus produced may come to affect legal and commercial understandings of the significance of race in relation to biology. The development of BiDil has profound implications for health law and policy, first, because it may be distorting current efforts to address the very real health problems associated with heart failure in America; and second because it implicates federal agencies in inappropriately giving the imprimatur of the state to conceiving and using race as a biological category.

Keywords
Health and race, BiDil, Pharmacogenetics, Pharmaceutical industry

Disciplines
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ARTICLES

How a Drug Becomes "Ethnic": Law, Commerce, and the Production of Racial Categories in Medicine

Jonathan Kahn, J.D., Ph.D.*

INTRODUCTION

A drug called BiDil is poised to become the first pharmaceutical ever approved by the U.S. Food and Drug Administration (FDA) to treat heart failure specifically in African Americans—and only African Americans. On March 8, 2001, NitroMed, then a privately held biotech firm in Massachusetts, issued a press release triumphantly announcing the receipt of a letter from the FDA "describing the regulatory status and ultimate approvability of BiDil®," pending the successful completion of a confirmatory trial of the drug in African Americans with heart failure.[1] Press reports have already touted this breakthrough as the first "ethnic" drug to treat heart failure.[2]

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1. Press Release, NitroMed, Inc., NitroMed Receives FDA Letter on BiDil® NDA, a Treatment for Heart Failure in Black Patients (Mar. 8, 2001), http://www.nitromed.com/newsindex.html (last visited Dec. 7, 2003).

2. *See, e.g.*, Victoria Griffith, *FDA Paves the Way for First 'Ethnic' Drug*, FIN. TIMES, Mar. 8, 2001, at 13; *This Heart Drug Is Designed for African Americans*, BUS. WK., Mar. 26, 2001, at 71; Eliot Marshall, *Trial for "Ethnic" Therapy*, SCI. NOW, Mar. 26, 2001, at 2, *at*

NitroMed framed its announcement with a striking statistic: "[D]eath rates from heart failure are more than twice as high in black patients than in white patients."[3] It heralded BiDil as presenting an opportunity to address "the disparity in outcomes for African American heart failure patients."[4] NitroMed posited that the disparity might be due to "a pathophysiology found primarily in black patients that may involve nitric oxide (NO) insufficiency."[5] A follow-up press release reiterated both the 2:1 statistic and the proposition that "observed racial disparities in mortality and therapeutic response rates in black heart failure patients may be due in part to ethnic differences in the underlying pathophysiology of heart failure."[6]

Since NitroMed's initial announcement, BiDil has emerged as a central player in ongoing debates over whether and how to use race and ethnicity as categories in biomedical research. It has also played a

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http://sciencenow.sciencemag.org/cgi/content/full/2001/326/2 (last visited Dec. 17, 2003); Geraldine Sealey, *Race and the Heart: 1st Drug Developed for Black Heart Failure Patients*, ABCNEWS.COM (Mar. 21, 2003), *at* http://abcnews.go.com/sections/living/DailyNews/bidil010321.html (last visited Dec. 17, 2003).

I use terms for "ethnicity" and "race" interchangeably in this paper, primarily because that is how the main actors in the story use them. In scholarly literature on the subject, there is much discussion about the differences between "race" and "ethnicity." Yet, even those who try to articulate more refined definitions of the two often end up defining each in terms of the other. For example, *Nature Genetics*, in a very well-meaning editorial requiring authors to explain how and why they use racial categories in science, provided as one of several definitions of race: "A distinct *ethnic* group characterized by traits that are transmitted through their offspring." *Census, Race and Science*, 24 NATURE GENETICS 97 (2000) (emphasis added). It then provided as one of several definitions of ethnic groups: "A social group or category of the population that, in a larger society, is set apart and bound together by common ties of *race*, language, nationality or culture." *Id.* (emphasis added). This confusion evidences a need to pay much greater attention to how and why these terms are used in various contexts and what purported meanings get attached to or elided by them. In this Article, I primarily use the term "race," but I also employ the terms "ethnic" and "ethnicity."

3. Press Release, NitroMed, Inc., *supra* note 1.

4. *Id.*

5. *Id.*

6. Press Release, NitroMed, Inc., NitroMed Initiates Confirmatory BiDil® Trial in African American Heart Failure Patients (Mar. 17, 2001), http://www.nitromed.com/newsindex.html (last visited Dec. 7, 2003). The 2:1 ratio was reiterated by the principal investigator of the African American Heart Failure Trial (A-HeFT). *Id.*

significant role at the forefront of broader political and legal discussions of the legitimacy of identifying and acting upon perceived biological or genetic differences among the races. This is hardly surprising, given NitroMed's own emphasis on "ethnic differences in the underlying pathophysiology of heart failure."[7] More surprising, however, is the lack of attention paid to just how BiDil became ethnic. Claims couched in scientific rhetoric and supported by the imprimatur of peer-reviewed journals are frequently afforded deference, and BiDil is no exception. Both the general news media and a number of science and medical journals have covered BiDil extensively without any substantial effort to investigate the claims made in press releases and medical reports.[8] The story they tell is of the path-breaking development of a new therapy for heart failure to help an underserved racial population.

However, when one investigates the origins and development of BiDil, a different and far more complex story emerges. At the most basic level, it turns out that BiDil became an ethnic drug through the interventions of law and commerce as much as through medical understanding of biological differences that correlate with racial groups. This part of the story has been masked both by well-meaning concerns about perceived health disparities and by an imprudent reliance on erroneous or incomplete statistical data.

This Article is first a retrospective analysis of how law, commerce, science, and medicine interacted to produce a distinctive understanding of BiDil as an ethnic drug, shaping which questions were asked at critical junctures in its development and orienting how they were pursued. Second, it is a prospective consideration of how the science and medicine thus produced may come to affect legal and commercial understandings of the significance of race in relation to biology. All of this unfolds against the backdrop of ongoing struggles over the legal, political, and biomedical status of race as a category for mobilizing resources and making claims in society.

Part I of this Article presents the context of current debates over the relation of racial to biological categories, particularly in the context of identifying and addressing health disparities. Part II presents the case for BiDil as made by its promoters. Their claims are built around assertions of differential rates of heart failure among blacks and whites, observed differences in average levels of nitric oxide in blacks and whites, and hypothesized underlying genetic differences between blacks and whites

7. *Id.*

8. *See, e.g., infra* notes 17, 102 and accompany text.

that may account for such inter-race variation. These are the claims that framed NitroMed's approach to the FDA for approval of the race-based trial. Part III deconstructs the case for BiDil by going back to its origins in the late 1970s and early 1980s and exploring the story of how it became ethnic. BiDil was born in the early 1980s as a drug for everyone, with no ethnic marking. The primary forces driving the re-invention of BiDil as an ethnic drug, I argue, were legal and commercial, rather than biomedical. Part IV considers some of the implications of this story for the development of social policies to redress health disparities, and explores the broader legal and political ramifications it may hold for the status of racial groups in society. This last Part is animated by a concern that various interventions of the federal legal and regulatory apparatus in BiDil's journey toward ethnicity may be leading the federal government improperly to endorse the use of race as a biological category in classifying its citizenry. Finally Part V offers recommendations, including that the federal government must develop guidelines that will help its administrative agencies to distinguish the use of race as a socio-political category to redress historical inequities and social prejudice from the use of race as a purportedly biological category. These guidelines will be important for ensuring the appropriate development and marketing of new biomedical products and services.

I. RACE, BIOLOGY, AND HEALTH DISPARITIES

The medical literature is replete with examples of health disparities that correlate with social categories of race.[9] The federal government has devoted considerable resources to identifying and redressing health disparities that correlate with race and/or socio-economic status. In 1985, the U.S. Department of Health and Human Services created an Office of Minority Health (OMH) "to improve and protect the health of racial and ethnic populations through the development of effective health policies and programs that will eliminate disparities in health."[10] OMH also monitors efforts to achieve the goals of *Healthy People 2010*, a federal

9. *See, e.g.*, U.S. DEP'T OF HEALTH & HUMAN SERVS., HEALTHY PEOPLE 2010: UNDERSTANDING AND IMPROVING HEALTH (2d ed. 2000), *available at* http://www.healthypeople.gov/Document/tableofcontents.htm#under (last visited Dec. 27, 2003). Such disparities involve not only prevalence of disease, but also quality of care. *See, e.g.*, INST. OF MED., UNEQUAL TREATMENT: CONFRONTING RACIAL AND ETHNIC DISPARITIES IN HEALTH CARE (2002).

10. U.S. DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF MINORITY HEALTH, ABOUT OMH, *at* http://www.omhrc.gov/OMH/sidebar/aboutOMH.htm (last visited Dec. 19, 2003).

initiative that has a special focus on eliminating racial and ethnic disparities in health.[11]

The federal government has also played a primary role in driving the recent revolution in genomics through its multi-billion-dollar support of the Human Genome Project. One great hope of the project is to develop knowledge about gene structure and function that will "lead to revolutionary new ways to diagnose, treat, and someday prevent the thousands of disorders that affect us."[12] The encounter between new genetic knowledge and efforts to identify and redress health disparities has generated heated debates over whether and how to use social categories of race in biomedical research.[13]

Since Richard Lewontin's ground-breaking work on blood group polymorphisms in different groups and races in the 1970s,[14] scientists have understood that race will statistically explain only a small portion of genetic variations. As a recent editorial in *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.'"[15] Yet, current research bearing on the efficacy of BiDil casts heart failure in African Americans as a "different disease" that may have an underlying basis in genetic differences.[16] Popular accounts of the drug invariably mention the 2:1 mortality statistic and often echo the understanding that it reflects an underlying biological difference among the races.[17] Interestingly, press

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11. *See id.*; U.S. Dep't of Health & Human Servs., Healthy People 2010, *at* http://www.healthypeople.gov/ (last visited Dec. 27, 2003).

12. U.S. DEP'T OF ENERGY, HUMAN GENOME PROGRAM, ABOUT THE HUMAN GENOME PROJECT, *at* http://www.ornl.gov/hgmis/project/about.html (last visited Dec. 7, 2003).

13. The literature on this topic is immense. For a good overview, see Sandra S. Lee et al., *The Meanings of 'Race' in the New Genomics: Implications for Health Disparities Research*, 1 YALE J. HEALTH POL'Y L. & ETHICS 33.

14. Richard C. Lewontin, *The Apportionment of Human Diversity*, 6 EVOLUTIONARY BIOLOGY 381 (1972).

15. *Genes, Drugs and Race*, 29 NATURE GENETICS 239, 239 (2001).

16. *See* Clyde W. Yancy, *The Role of Race in Heart Failure Therapy*, 4 CURRENT CARDIOLOGY REP. 218 (2002) [hereinafter Yancy, *Role of Race*]; *see also* Clyde W. Yancy, *Heart Failure in Blacks: Etiological and Epidemiological Differences*, 3 CURRENT CARDIOLOGY REP. 191 (2001); Clyde W. Yancy, Editorial, *Heart Failure in African Americans: A Cardiovascular Enigma*, 6 J. CARDIAC FAILURE 183 (2000) [hereinafter Yancy, *Cardiovascular Enigma*].

17. Major media outlets reporting on BiDil include the *New York Times, Wall Street Journal, Financial Times, Business Week*, the BBC and ABC News. *See, e.g.*, Griffith, *supra* note 2; Sheryl Gay Stolberg, *Skin Deep: Shouldn't a Pill Be Colorblind?*, N.Y. TIMES, May 13, 2001, at

accounts targeted primarily at African American audiences tend to share this view. For example, *Black Issues in Higher Education* approvingly quotes Dr. Clyde Yancy, a cardiologist from the University of Texas, Southwestern Medical Center in Dallas and a co-investigator in BiDil's confirmatory trial, who refers to the likelihood that there is a genetic basis for differential rates of heart failure between blacks and whites.[18] Similarly, the *Chicago Defender*'s report on the "slight genetic differences" presumed to underlie such therapies as BiDil declares that "studies in this new century of astounding scientific advancement show that some diseases differ among races."[19]

On the one hand, the identification of health disparities with genetic variations may lead to the development of innovative new therapies of the

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4-1; Rachel Zimmerman, *Pair of Genes Is Said To Increase Risk of Heart Failure in Blacks*, WALL ST. J., Oct. 10, 2002, at D2; *This Heart Drug Is Designed for African Americans*, *supra* note 2; *Heart Drug Targets Black Patients*, BBC NEWS, Apr. 6, 2001, http://news.bbc.co.uk/1/hi/health/1262093.stm (last visited Nov. 5, 2003); Sealey, *supra* note 2. Many local and regional newspapers and television stations have also reported on the drug, as have numerous professional journals and newsletters. *See, e.g.*, Editorial Board, *Trial for 'Ethnic' Drug*, 291 SCIENCE 2547 (2001); *First Clinical Heart Failure Study Exclusively for Blacks Conducted*, L.A. SENTINEL, Apr. 11, 2001, at A12; Ricki Lewis, *Race and the Clinic: Good Science?*, THE SCIENTIST, Feb. 18, 2002, at 16; Jessica Pasley, *Heart Study Examines Ethnicity Factors To Treat Disease*, THE REPORTER, March 15, 2002, http://www.mc.vanderbilt.edu/reporter/?ID=1990 (last visited Jan. 5, 2004); Sharon Schmickle, *Under the Skin, We're All Alike - Except Medically, Science Says*, MINNEAPOLIS STAR-TRIBUNE, March 26, 2002, *available at* http://health.csuohio.edu/healthculture/news/fulltext/st3_26_02.txt (last visited Jan. 5, 2004); Press Release, University of Texas Southwestern Medical Center at Dallas, Disparities in Black Americans' Responses to Heart-Failure Therapies May Signal 'Different Disease' (May 13, 2002), http://irweb.swmed.edu/newspub/newsdetl.asp?story_id=409 (last visited Jan. 5, 2004); *Clinical Trial To Look at Effectiveness of Heart Failure Medication in African-Americans*, Methodist Health Care System, *at* http://www.methodisthealth.com/news/heart/april2001/index.htm (Apr. 2001); *Congestive Heart Failure*, Heart-Help.net, *at* http://www.heart-help.net/chfnew.html (last visited Jan. 5, 2004); Victoria Stagg Elliott, *FDA May Approve New Heart Drug for Blacks*, Amednews.com, *at* http://www.ama-assn.org/amednews/2001/03/26/hlsc0326.htm (March 26, 2001).

18. *Noteworthy News: Heart Failure in Blacks May Signal 'Different Disease'*, BLACK ISSUES HIGHER EDUC., June 20, 2002, at 26, *available at* http://www.findarticles.com/cf_dls/m0DXK/9_19/89077189/p1/article.jhtml (last visited Dec. 19, 2003).

19. *Slight Genetic Differences Justify Innovative Medical Treatment*, CHI. DEFENDER, May 1, 2001, at 9.

sort envisioned by the Human Genome Project and help to address significant health problems that disproportionately affect minority communities in the United States. On the other hand, linking genetic variation to racial groups may also contribute to what anthropologist Alan Goodman has noted as a "comeback" in "racialized notions of biology."[20] Given our nation's long and troubled history of mistreatment and oppression of racial groups based on (mis)understandings of biological difference—not least in the area of medical research[21]—such a "comeback" should give us pause. Additionally, as genetic explanations come to dominate discussions of health disparities, they could well lead to a reallocation of scare resources away from addressing the larger social, economic, and political causes of such disparities. The appeal of taking a predominantly biomedical approach to addressing health disparities is undeniable—instead of fixing social inequality you simply fix molecules.

II. THE CASE FOR BIDIL

Congestive heart failure[22] is a debilitating chronic disease that affects an estimated five million Americans, with approximately 400,000 to 700,000 new cases each year.[23] NitroMed currently estimates that there are approximately 750,000 African Americans who have been diagnosed with heart failure.[24] One recent estimate placed the direct health care costs of

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20. Alan H. Goodman, *Why Genes Don't Count (for Racial Differences in Health)*, 90 AM. J. PUB. HEALTH, 1699, 1699 (2000).

21. *See, e.g.*, TROY DUSTER, BACKDOOR TO EUGENICS (1990); JAMES H. JONES, BAD BLOOD: THE TUSKEGEE SYPHILIS EXPERIMENT – A TRAGEDY OF RACE AND MEDICINE (1981); DANIEL J. KEVLES, IN THE NAME OF EUGENICS (1995).

22. The terms "congestive heart failure" (CHF) and "heart failure" (HF) are often used interchangeably, although technically the former is a subset of the latter. Nonetheless, CHF mortality comprises the vast majority of all HF mortality. BiDil is specified for the treatment of CHF.

23. Mardi Gomberg-Maitland et al., *Treatment of Congestive Heart Failure*, 161 ARCHIVES INTERNAL MED. 342 (2001). The data on prevalence are drawn from the National Health and Nutrition Examination Survey (NHANES III), which was taken between 1988 and 1993. *See* NAT'L HEART, LUNG & BLOOD INST., DATA FACT SHEET: CONGESTIVE HEART FAILURE IN THE UNITED STATES: A NEW EPIDEMIC,
http://www.nhlbi.nih.gov/health/public/heart/other/CHF.htm (last visited Nov. 5, 2003).

24. NitroMed, Inc., SEC Filing, Form S-1/A, Registration No. 333-108104, at 2, (Oct. 2, 2003),
http://www.sec.gov/Archives/edgar/data/927829/000104746903032333/a2119126zs-1a.htm (last visited Dec. 7, 2003).

treating heart failure at between twenty and forty billion dollars annually.[25] It is a complex condition and sometimes difficult to diagnose. Symptoms can include fatigue, weight gain, swollen legs or ankles, difficulty breathing, and a hacking cough, but in some cases the condition is asymptomatic. Unlike a heart attack, heart failure does not involve an immediate cessation of heart function but rather occurs when the heart functions improperly due to weakening by disease or defect. It is a progressive and ultimately fatal condition, with one in five persons dying within five years of onset.[26] Current guidelines specify that "most patients with heart failure should be routinely managed with a combination of four types of drugs: an angiotensin-converting enzyme (ACE) inhibitor, a beta-adrenergic blocker, a diuretic, and (usually) digitalis."[27] Adjunctive therapies, namely angiotensin II receptor blockers and spironolactone, have extended the therapeutic options within this scheme.[28]

BiDil belongs to none of these categories. It is a combination of two potent vasodilators—hydralazine and isosorbide dinitrate (H/I). By dilating blood vessels, vasodilators ease the strain put on the heart in pumping blood. BiDil is also believed to increase levels of nitric oxide in the blood, which is generally thought to be beneficial for many individuals suffering from heart failure.[29]

Advocates of BiDil point to the widely cited statistic (featured so prominently in NitroMed's press releases) that African Americans die from heart failure at a rate twice that of white Americans.[30] They connect current

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25. Milton Packer & Jay N. Cohn, *Consensus Recommendations for the Management of Chronic Heart Failure*, AM. J. CARDIOLOGY, Jan. 21, 1999, at 1A.

26. NAT'L HEART, LUNG & BLOOD INST., *supra* note 23.

27. *See, e.g.*, AM. COLL. OF CARDIOLOGY & AM. HEART ASS'N, ACC/AHA GUIDELINES FOR THE EVALUATION AND MANAGEMENT OF CHRONIC HEART FAILURE IN THE ADULT (2001), *available at* http://www.americanheart.org/presenter.jhtml?identifier=11841 (last visited Nov. 5, 2003); Packer & Cohn, *supra* note 25. Digitalis is the traditional prototype of a class of drugs known as cardiac glycosides.

28. *See, e.g.*, AM. COLL. OF CARDIOLOGY & AM. HEART ASS'N., *supra* note 27; Packer & Cohn, *supra* note 25.

29. *See* Joseph A. Franciosa et al., *African-American Heart Failure Trial (A-HeFT): Rationale, Design, and Methodology*, 8 J. CARDIAC FAILURE 128, 129 (2002); *see also* NitroMed, BiDil® Backgrounder: Heart Failure, *at* http://www.nitromed.com/bildil/DOCS/heartfailure.html (last visited Dec. 31, 2003).

30. *See, e.g.*, Franciosa et al., *supra* note 29 (involving numerous cardiologists); *see also* Press Release, NitroMed, Inc., NitroMed and Merck Form Strategic Collaboration (Jan. 7, 2003), http://www.nitromed.com/newsindex.html (last visited Jan. 4, 2004); Press Release, NitroMed, Inc., *supra* note 7; Press Release, NitroMed, Inc., *supra* note 1.

research indicating the importance of nitric oxide in preventing heart failure to other research suggesting that blacks seems to have lower levels of nitric oxide in their blood.[31] They argue that the unique combination of drugs in BiDil may be particularly efficacious in black patients because one of BiDil's components, isosorbide dinitrate, is a nitric oxide "donor" and its other component, hydralazine, is an anti-oxidant which may enhance the efficacy of nitrates.[32]

Nitromed's race-based trial—known as A-HeFT, the African American Heart Failure Trial—is currently underway. It was originally expected to be completed sometime late in 2003 but subsequent estimates by investigators suggest that enrollment will not be completed until sometime in 2004,[33] and recent statements by NitroMed contemplate that A-HeFT will not be completed until early 2005.[34]

A-HeFT cardiologist Clyde Yancy has argued that heart failure in blacks is a "different disease."[35] Analyzing data published from the Studies of Left Ventricular Dysfunction (SOLVD) trials (examining racial differences in the natural history of left ventricular dysfunction), he asserted that socio-economic factors could not account for the difference in mortality rates between African Americans and white Americans.[36] According to Yancy, "all too frequently, there is an eagerness to impugn psychosocial factors, commonly known as socioeconomic status (SES), as the major explanation for any observed differences in cardiovascular disease seen in blacks."[37] As evidence he pointed to a retrospective multivariate analysis of the SOLVD data controlled for educational level and "a history of financial distress."[38] Even controlling for these socio-economic factors the data still show a higher mortality rate in blacks. Yancy concluded that this observation "seemingly supports the concept that physiologic explanations for disease expression might be present in this patient population."[39] This led Yancy to hypothesize that there is ultimately a basic genetic difference in blacks that accounts for the "unique

31. *See, e.g.*, Franciosa et al., *supra* note 29.

32. *See id.* at 129.

33. *See* Clyde W. Yancy, *Does Race Matter in Heart Failure?*, 146 AM. HEART J. 203, 205 (2003).

34. *See, e.g.*, NitroMed, Inc., SEC Filing, *supra* note 24, at 11.

35. *See, e.g.*, Yancy, *Role of Race, supra* note 16; Clyde W. Yancy, *Treatment of Heart Failure in African Americans: Clinical Update*, 12 ETHNICITY & DISEASE S19, S25 (2002).

36. Yancy, *Role of Race, supra* note 16, at 218.

37. *Id.*

38. *Id.*

39. *Id.*

epidemiology, worse prognosis, and potential variances in responses to pharmacological interventions in heart failure."[40] The focus on locating differences at the molecular level is logically connected to the related search for a treatment that appears to work differentially well in blacks at this same level—hence BiDil. Further driving the case for BiDil are arguments made by some cardiologists that ACE inhibitors are less efficacious in black patients than in whites. Most prominent among these is a study published in 2001 in the *New England Journal of Medicine* that compared how blacks and whites responded to ACE inhibitor therapy.[41] While making no claims as to mortality rates, the study found ACE inhibitor therapy to be associated with a significant reduction in risk of hospitalization for white patients, but not for black patients.[42] The authors argued that "on the basis of available physiological, pharmacologic, and clinical data, it seems appropriate to consider current therapeutic recommendations [concerning ACE inhibitors] as applying to white patients but not necessarily to black patients."[43]

Subsequent reporting on BiDil in major media—from the *Financial Times*[44] and *Business Week*[45] to ABC News[46] and the BBC[47]—has scrupulously noted the differential response to ACE therapy between blacks and whites. NitroMed's own website refers to such research, noting that the package insert for the ACE inhibitor enalapril states that "black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks."[48]

Dr. Jay Cohn, a cardiologist at the University of Minnesota and a co-

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40. *Id.* Yancy does provide a caveat that "race is an arbitrary social/political designation, and is pertinent as a crude marker of genetic variations only because of reproductive isolation within any given race." *Id.* at 224. Yet this comes only after an extensive discussion of what he characterizes as "an emerging database of potentially important genetic variations that may explain" differences between black and white patients in heart failure. *Id.* at 224.

41. Derek V. Exner et al., *Lesser Response to Angiotensin-Converting-Enzyme Inhibitor Therapy in Black as Compared with White Patients with Left Ventricular Dysfunction*, 344 NEW ENG. J. MED. 1351 (2001).

42. *Id.* at 1355.

43. *Id.* at 1357.

44. Griffith, *supra* note 2.

45. *This Heart Drug is Designed for African Americans*, *supra* note 2, at 71.

46. Sealey, *supra* note 2.

47. *Heart Drug Targets Black Patients*, *supra* note 17.

48. NitroMed, BiDil® and the African American Heart Failure Trial (A-HeFT), *at* http://www.nitromed.com/bildil/DOCS/background.html (last visited Dec. 7, 2003).

author of the ACE inhibitor study, has followed up by arguing for a "unique strategy" for treatment of heart failure in African Americans.[49] Cohn contrasts results from previous heart failure trials indicating that blacks do not respond as well as whites to ACE inhibitors with results for BiDil[50]—he argues BiDil actually provides a greater benefit to blacks than to whites.[51]

The dual message is clear: ACE inhibitors do not work as well in blacks; BiDil works better in blacks. The case for BiDil can thus be roughly summarized as follows: 1) blacks die from heart failure at a rate twice that of whites; 2) given this great disparity it seems that there must be some underlying biological or genetic (as opposed to "merely" social or environmental) factor accounting for the difference; 3) supporting this hypothesis are studies that control for socioeconomic factors and still show racial differentials in outcome; 4) moreover, additional studies indicate that blacks do not respond as well as whites to certain front line heart failure therapies; 5) therefore, a response is called for that addresses this different biology; 6) enter BiDil, a pharmaceutical response to the statistical disparity that appears to have a differentially beneficial effect on blacks at the molecular level.[52]

III. DECONSTRUCTING THE CASE FOR BIDIL

A. 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 circumstances that transformed the drug's identity.[53]

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49. Jay N. Cohn, *Contemporary Treatment of Heart Failure: Is there Adequate Evidence to Support a Unique Strategy for African-Americans? Pro Position*, 4 CURRENT HYPERTENSIONS REP. 307, 307 (2002). Cohn co-authored the study by Exner et al., *supra* note 41.

50. Cohn, *supra* note 49. Cohn notes that previous heart failure trails also show that blacks do not respond as well as whites to angiotensin II receptor blockers and to at least one beta blocker. *Id.*

51. *See* Peter Carson et al., *Racial Differences in Response to Therapy for Heart Failure: Analysis of the Vasodilator-Heart Failure Trials*, 5 J. CARDIAC FAILURE 178 (1999); *see also infra* Part III.B.

52. This logic is made quite clear in NitroMed's own statement on BiDil. *See* NitroMed, *supra* note 48.

53. To paraphrase Shakespeare, some drugs may be born ethnic, some may achieve ethnicity, but BiDil had ethnicity thrust upon it. *Cf.* WILLIAM SHAKESPEARE, TWELFTH NIGHT,

Over the past twenty years a revolution has occurred in heart failure treatment with the development of a wide array of pharmaceutical interventions that improve both the quality of life and the 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 and involved cardiologists from around the country working together with the U.S. Veterans Administration. It took patients who were already on a background regimen of digoxin and a diuretic and randomized them into three groups, one receiving a placebo, one receiving an alpha adrenergic blocker called prazosin, and one receiving a combination of hydralazine and isosorbide dinitrate (H/I)—the two drugs which comprise BiDil. The V-HeFT investigators found that prazosin proved no better than the placebo in reducing mortality. Their results indicated, however, that the H/I combination seemed to have a beneficial impact on mortality, though the difference was only of "borderline statistical significance."[54]

The V-HeFT I trial was soon followed by V-HeFT II, which lasted from 1986 to 1991. 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.[55] ACE inhibitors, however, have not totally supplanted H/I because not everyone responds well to them and some cannot tolerate the side effects. One news report estimated that twenty to thirty percent of congestive heart failure patients do not respond favorably to standard therapies of "diuretics,

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act 2, sc. 5 ("Some are born great; Some achieve greatness; And some have greatness thrust upon 'em.").

54. Jay N. Cohn et al., *Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure: Results of a Veterans Administration Cooperative Study*, 314 NEW ENG. J. MED. 1547, 1547 (1986).

At the time, it was believed that this beneficial impact was due to a distinctive hemodynamic effect produced by the H/I combination. However, since no other vasodilator regimen has had a similar effect, it is now believed that the combination may have a distinctive effect on levels of nitric oxide (NO) in the blood. NO is believed to help protect against damage to the heart that may result in heart failure. *See, e.g.*, AM. COLL. OF CARDIOLOGY & AM. HEART ASS'N, *supra* note 27; Packer & Cohn, *supra* note 25; W. J. Paulus et al., *Nitric Oxide and Cardiac Contractility in Human Heart Failure: Time for Reappraisal*, 104 CIRCULATION 2260 (2001).

55. Jay N. Cohn et al., *A Comparison of Enalapril with Hydralazine-Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure*, 325 NEW ENG. J. MED. 303 (1991).

digitalis or ACE inhibitors . . . particularly ACE inhibitors."[56] Given current estimates that nearly five million Americans suffer from heart failure, that group potentially represents 1.5 million patients annually. Current guidelines still recommend considering the use of H/I for these patients.[57]

The V-HeFT investigators did not build the trials around ethnicity. They enrolled both black and white patients, and in the published reports of the trials' successes they did not break down the data by race. Rather, they presented H/I—BiDil's components—as generally efficacious in the population at large, without regard to race.[58] In 1987, one year after the results of V-HeFT I were published, Dr. Jay Cohn, one of the trials' principal investigating cardiologists, applied for a patent on a "method of reducing mortality associated with congestive heart failure using hydralazine and isosorbide dinitrate."[59] The U.S. Patent and Trademark Office issued the patent to Cohn in 1989.[60] Referring to V-HeFT I and II in the patent description, Cohn asserted that is had been "surprisingly and unexpectedly discovered that . . . a combination of hydralazine hydrochloride and isosorbide dinitrate has been [found] to substantially and significantly reduce the incidence of mortality in [congestive heart failure] patients."[61] Cohn's patent application did not mention race. He clearly conceived of this as a method to treat all people suffering from heart failure.

Hydralazine and isosorbide dinitrate are generic drugs. Cohn and others later combined them into a single pill for easier administration. In 1992, a trademark application was filed for this new pill as BiDil®. The mark was formally registered in 1995 to Medco Research, Inc.,[62] a biotech

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56. *Boehringer Mannheim Pharmaceuticals Corporation to Market New Medco Heart Drug*, PR NEWSWIRE, Nov. 9, 1993.

57. *See, e.g.*, AM. COLL. OF CARDIOLOGY & AM. HEART ASS'N, *supra* note 27; Packer & Cohn, *supra* note 25.

58. The reports were numerous, bearing on a variety of characteristics measured in the trials. It appears that none of these reports disaggregated the data by race until 1999 with the publication of Peter Carson et al., *supra* note 51.

59. U.S. Patent No. 4,868,179 (issued Sept. 19, 1989), http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=4,868,179.WKU.&OS=PN/4,868,179&RS=PN/4,868,179 (last visited Dec. 13, 2003).

60. *Id.*

61. *Id.*

62. U.S. Trademark Registration No. 1896747 (registered May 30, 1995), http://tess2.uspto.gov/bin/showfield?f=doc&state=an6u36.2.1 (last visited Dec. 13, 2003).

corporation in North Carolina's Research Triangle, which had earlier acquired the intellectual property rights to BiDil from Cohn. One report from 1997 estimated a potential market of up to sixty million dollars in annual sales for BiDil.[63]

By 1994, Medco had begun clinical testing of BiDil to establish its bioavailability and bioequivalence to the coadministration of the two H/I drugs separately—a critical precursor to approaching the Food and Drug Administration with a New Drug Application (NDA) to get approval for marketing BiDil.[64] By 1996, the completed study found BiDil to be bioequivalent, and Medco prepared to approach the FDA with its NDA. Jay Cohn noted at the time that "the BiDil® formulation represents a very convenient dosage form that, once approved [by the FDA], should lead to increased usage of this effective therapy."[65] Later that year, Medco submitted an NDA to the FDA.[66] The following February, the Cardiovascular and Renal Drugs Advisory Committee of the FDA's Center for Drug Evaluation and Research held a meeting to consider Medco's BiDil application. Medco sent Cohn and three other representatives to the meeting to make the case for BiDil.

Cohn recommended approval of BiDil for congestive heart failure "on the basis of a survival benefit in V-HeFT I and trends for increased exercise tolerance and long-term ejection fraction in both trials."[67] Ultimately, however, the Advisory Committee voted against approving BiDil.[68] The next day, Medco's stock plunged by twenty-five percent.[69]

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63. *Should've Asked for a Second Opinion (Medco Research Inc.'s Research on Drug BiDil Rejected by FDA)*, BUS. N.C., July 1997, at 14; *see also FDA Panel Rejects Medco's CHF Drug on Mortality Stats*, MED. INDUSTRY TODAY, Feb. 28, 1997 (noting an estimated total "cardiovascular market" at four billion dollars and a total market for BiDil at between twenty-five and sixty million dollars).

64. *Medco's New BiDil® Heart Failure Drug Formulation Begins Human Bioequivalence Testing*, PR NEWSWIRE, Nov. 7, 1994.

65. *Medco Research Finds BiDil® Bioequivalent and Re-Acquires Rights from Boehringer-Mannheim Pharmaceuticals Plans to Submit NDA*, PR NEWSWIRE, Apr. 2, 1996.

66. *Medco Research Files NDA for BiDil®*, PR NEWSWIRE, July 3, 1996.

67. CTR. FOR DRUG EVALUATION & RESEARCH, CARDIOVASCULAR & RENAL DRUGS ADVISORY COMM., MINUTES FROM THE 80TH MEETING OF THE FOOD AND DRUG ADMIN. 2 (Feb. 27-28, 1997), http://www.fda.gov/cder/foi/adcomm/97/cardac_022797_summin_agen_quest.pdf (last visited Oct. 11, 2003) [hereinafter MINUTES].

68. *Id.* at 3. Among other findings against BiDil, the Advisory Committee recommended unanimously that "there was no statistically significant effect on mortality for V-HeFT I." *Id.* at 2.

69. *Medco Drug Hits FDA Wall*, TRIANGLE BUS. J., Feb. 27, 1997, *available at*

The Advisory Committee's recommendation appeared to fly in the face of the extensive findings published in highly respected peer-reviewed journals that seemed to support Cohn's confident patent application claim that the H/I combination "substantially and significantly reduced the incidence of mortality"[70] in congestive heart failure patients. Moreover, as Cohn emphasized before the committee, the American Heart Association, the American College of Cardiology, and the World Health Organization had all included H/I as a recommended therapy for patients who did not tolerate ACE inhibitors.[71]

Why was the extensive data from V-HeFT I and II inadequate? Cohn himself provided part of the answer, urging the committee to recall the age and the context of the study.

> [K]eep in mind that this is a study designed 20 years ago. This was a VA cooperative study. This was not designed really as a regulatory study so that careful selection of criteria for endpoint were not as precise as one would see in a protocol designed today with the goal to come to this committee and ask for approval. So, one has to look at this a little differently than one might at a more recently organized mega-trial in which p values are clearly defined as the goals for the trial.[72]

The Advisory Committee agreed with Cohn as to the shortcomings of the dated study, but did not follow his suggestion that they look at its data "a little differently." Instead, the committee followed the recommendations of their biostatisticians who found that "there were too many variables specified in the protocols as primary endpoints" for them to interpret the V-HeFT data "with any degree of certainty."[73] Therefore, the Advisory Committee voted nine to three against recommending that BiDil be approved for use in congestive heart failure.[74] Following the FDA's rejection, Medco got out of the BiDil business and let the intellectual

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http://triangle.bizjournals.com/triangle/stories/1997/02/24/daily12.html (last visited Dec. 18, 2003).

70. U.S. Patent No. 4,868,179, *supra* note 59.

71. CTR. FOR DRUG EVALUATION & RESEARCH, CARDIOVASCULAR & RENAL DRUGS ADVISORY COMM., TRANSCRIPT FROM THE 80TH MEETING OF THE FOOD AND DRUG ADMIN. 53 (Feb. 27, 1997), http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3264t1.pdf (last visited Aug. 5, 2002) [hereinafter TRANSCRIPT].

72. *Id.* at 61-62.

73. MINUTES, *supra* note 67, at 2.

74. *Id.* at 3. Once again, it is worth noting that the NDA and its rejection by the Advisory Committee were both grounded on an analysis of BiDil as a general drug applicable to all heart failure patients regardless of race or ethnicity.

property rights revert to Cohn.

B. BiDil's Ethnic Rebirth

At this point, BiDil appeared to be dead in the water. However, in the transcript of the FDA meeting itself, there is a hint of BiDil's road to resurrection. Early on in his presentation before the Advisory Committee, Cohn noted:

> The majority of the patients [in both V-Heft I and II] were Caucasian. That is, about seventy percent of them in both trials, but there was a fairly sizeable number of African Americans in the trial. We won't go into that, but we have much data comparing the Caucasian and African-American responses.[75]

The V-HeFT investigators had been tracking data by race from the outset. They had not, however, conceptualized BiDil as a racially specific therapy. To the contrary, Cohn chose quite deliberately not to "go into that" before the FDA.[76] It was only after the Advisory Committee recommended against approving BiDil for use in a general population that the V-HeFT investigators went back one more time to their data—data that Cohn himself reminded the Advisory Committee had been generated by a trial designed nearly twenty years earlier—and produced the first published studies analyzing the differential effects of H/I and enalapril by race.[77]

These race-based studies were completed in a broader context of rising

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75. TRANSCRIPT, *supra* note 71, at 20-21.

76. *Id.* at 21.

77. Of course, the investigators could have broken down the data into any one of a large number of other possible sub-groups: The V-HeFT I and II reports listed at least twenty-two baseline characteristics that could each have provided an alternative basis for retrospective analysis of efficacy, independent of race. *See, e.g.*, Susan Ziesche et al., *Hydralazine and Isosorbide Dinitrate Combination Improves Exercise Tolerance in Heart Failure: Results from V-HeFT I and V-HeFT II*, 87 CIRCULATION VI-56 (Supp. 1993). In fact, a 1993 article by Cohn suggested a number of variables that might impact therapeutic responses but did not include race. He identified such issues as: "Do women respond the same as men? Do individuals with coronary disease respond differently than those with cardiomyopathy? Does ventricular geometry influence response to therapy? Are there biochemical or hormonal markers that will affect the response to specific intervention?" Jay N. Cohn, *The Vasodilator-Heart Failure Trials (V-HeFT): Mechanistic data from the VA Cooperative Studies*, 87 CIRCULATION VI-1, VI-2 (Supp. 1993). Each of Cohn's questions marked a potential sub-group for analysis, but interestingly, none of his questions concerned race.

political attention to the importance of addressing race and gender disparities in health policy and administration. In 1997, the federal government passed the Food and Drug Administration Modernization Act, which, among other things, required the Secretary of Health and Human Services "in consultation with the Director of the National Institutes of Health and the representatives of the drug manufacturing industry, [to] review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials."[78] That same year, President Clinton delivered a much publicized apology for the federal government's role in the notorious Tuskegee Syphilis Study, which exploited black men for decades in the name of medical research.[79] The BiDil investigators, then, were not the only ones closely considering race in medicine.

Against this backdrop, Cohn, together with Peter Carson, M.D., Susan Zeische, R.N., and Gary Johnson, M.S., published a paper in September 1999 titled *Racial Differences in Response to Therapy for Heart Failure: Analysis of the Vasodilator-Heart Failure Trials.*[80] The retrospective analysis of data from V-HeFT I and II compared a total of 395 black patients with 1024 white patients with similar baseline variables and characteristics (including age, history of coronary heart disease, hypertension, blood pressure, heart rate, etc.). It found that "the H-I combination appears to be particularly effective in prolonging survival in black patients and is as effective as enalapril in this subgroup. In contrast, enalapril shows its more favorable effect on survival, particularly in the white population."[81] Following a caveat about the limits of its data, the paper concluded that "the consistency of observations of a racial difference in response in V-HeFT I and V-HeFT II . . . lend credence to the suggestion that therapy for heart failure might appropriately be *racially tailored.*"[82]

The paper argued that H/I (the BiDil drugs) appeared to work better in blacks than in whites.[83] More importantly, though not explicitly stated in the paper, the statistics on H/I's impact on black mortality might be sufficiently powerful to meet the FDA's threshold criteria for regulatory significance. That same month, NitroMed, a Boston-area biotech firm

78. Food and Drug Administration Modernization Act of 1997, Pub. L. 105-115, § 115, 111 Stat. 2296, 2313.

79. President William J. Clinton, Remarks in Apology for Study Done in Tuskegee (May 16, 1997), *at* http://www.cmh.pitt.edu/presremarks.html (last visited Dec. 17, 2003).

80. Peter Carson et al., *supra* note 51.

81. *Id.* at 182.

82. *Id.* at 186 (emphasis added).

83. *Id.* at 183, 186.

specializing in the development and commercialization of nitric oxide enhanced medicines, announced it had acquired the NDA for BiDil and related intellectual property rights from Jay Cohn.[84] The announcement also disclosed NitroMed's plans to amend the NDA to seek an indication specifically for African American patients. Shortly thereafter, Jay Cohn and Peter Carson, the lead author of the article on racial differences in the V-HeFT data, applied for a patent on "methods for treating and preventing mortality associated with heart failure in an African American patient" with hydralazine and isosorbide dinitrate or mononitrate. They then assigned the patent rights to NitroMed.[85] Thus was BiDil reborn as an "ethnic" drug.

C. Statistical Mischief in Race-Based Mortality Rates[86]

With its race-specific patent on file, the next step for NitroMed was to lay the groundwork to submit its amended NDA to the FDA. At this point the statistic that blacks die from heart failure at a rate twice that of whites began to play a significant role in the development of BiDil. Earlier that year, in February 1999, Peter Carson had co-authored a study by Dries et al. entitled *Racial Differences in the Outcome of Left Ventricular Dysfunction*—a prime indication of congestive heart failure.[87] Based on retrospective analysis of data from the SOLVD prevention and treatment trials, the article suggested that "there may be differences in the natural history of . . . left ventricular dysfunction between black and white patients."[88] Significantly, the study purported to control for socioeconomic factors by analyzing "[b]ase-line data on educational level and the percentage of participants reporting 'major financial distress' (yes vs. no)" during the

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84. *NitroMed To Seek Heart Failure Indication for BiDil*, J. MED. INDUSTRY TODAY, Sept. 13, 1999, at 71; Press Release, NitroMed, Inc., NitroMed Acquires BiDil™ New Drug Application for Treatment of Congestive Heart Failure (Sept. 10, 1999), http://www.nitromed.com/newsindex.html (last visited Dec. 7, 2003).

85. U.S. Patent No. 6,465,463 (issued Oct. 15, 2002), http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,465,463.WKU.&OS=PN/6,465,463&RS=PN/6,465,463 (last visited Dec. 13, 2003).

86. For a more complete analysis of this issue, see Jonathan Kahn, *Getting the Numbers Right: Statistical Mischief and Racial Profiling in Heart Failure Research*, 46 PERSP. BIOLOGY & MED. 473 (2003).

87. Daniel L. Dries et al., *Racial Differences in the Outcome of Left Ventricular Dysfunction*, 340 NEW ENG. J. MED. 609 (1999).

88. *Id.* at 616.

previous twelve months.[89] Framing the entire report was the assertion in the opening paragraph that "[t]he population-based mortality rate from congestive heart failure is 1.8 times as high for black men as for white men and 2.4 times as high for black women as for white women"—an overall black to white ratio of heart failure mortality of approximately 2:1.[90]

The logic behind the study is clear: There is a 2:1 disparity in mortality rates between blacks and whites; it seems unlikely that socioeconomic status (SES) alone can account for such a large difference; therefore, conduct retrospective analysis of heart failure data that purports to control for SES, and see if there is any remaining disparity that can be attributed to biology. The 2:1 statistic thus shapes which questions get asked and how they are pursued. However, although the logic is consistent there are two major problems with the study's premise. First, the study's conception of relevant socioeconomic influences on health is very thin. Second, the 2:1 statistic itself is not correct.

With regard to socioeconomic influences, the level of education and experience of financial distress certainly are relevant factors to consider in examining non-genetic environmental influences on the development and progression of heart failure. However, the implicit understanding that they are exhaustive of such relevant factors is puzzling, to say the least. As one letter in response to the article noted:

> Obviously, it is impossible to control perfectly for the complex and somewhat nebulous concept of socioeconomic status in any study, and Dries et al. appropriately advise caution in the interpretation of their results. By focusing, however, on biological factors as the fallback explanation for their findings, the authors pay inadequate attention to the environmental, psychosocial, and economic factors that are just as likely, if not more likely, explanations of racial differences in health.[91]

Dr. Clyde Yancy, an advocate of identifying genetic factors underlying supposed racial disparities in heart failure mortality, has noted "a striking [sic] disproportionate incidence of hypertension as a plausible cause of heart failure."[92] There is a vast array of medical and public health literature connecting racial differences in hypertension to social factors such as diet,

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89. *Id.* at 612.

90. *Id.* at 609.

91. Somnath Saha, *Letter to the Editor*, 341 NEW ENG. J. MED. 87 (1999) (citing N. Krieger et al., *Measuring Social Class in US Public Health Research: Concepts, Methodologies, and Guidelines*, 18 ANN. REV. PUB. HEALTH 341 (1997)).

92. Yancy, *Cardiovascular Enigma*, *supra* note 16, at 183.

environment, exercise, and stress.[93] Many of these social factors correlate strongly with social categories of race. For example, one study has shown that the stress of experiencing racism seems to elevate blood pressure.[94] The study by Dries et al. captures none of these variables.[95] Strangely, after noting the centrality of hypertension as a plausible cause of heart failure, Yancy goes on to cite the data from the Dries et al. study on socioeconomic factors as support for his hypothesis that heart failure is a "different disease" in African Americans with a genetic difference likely underlying the difference.[96] Yancy and Dries et al.'s thin conception of socioeconomic factors seems to indicate an underlying assumption that because hypertension is a biological condition, any disparities associated with its prevalence must similarly be biological.

As a source for the 2:1 mortality statistic, Dries et al. cited a 1987 editorial in the *American Heart Journal* written by Richard Gillum, M.D., from the Office of Analysis and Epidemiology Program at the National Center for Health Statistics. However, Gillum's version of the statistic was outdated and differed in several important ways. First, Gillum's statistic relies upon mortality rates from 1981—that is, eighteen years before the publication of Dries et al.'s article in 1999. By 1999, far more current data on mortality rates was readily available and indicated a substantial narrowing of the gap between blacks and whites between 1980 and 1995.[97]

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93. *See, e.g.*, William W. Dressler, *Lifestyle, Stress and Blood Pressure in a Southern Black Community*, 52 PSYCHOSOMATIC MED. 182 (1990); Michael J. Klag et al., *The Association of Skin Color with Blood Pressure in US Blacks with Low Socioeconomic Status*, 265 JAMA 599 (1991); D.R. Williams, *Black-White Differences in Blood Pressure: The Role of Social Factors*, 2 ETHNICITY & DISEASE 126 (1992).

94. Nancy Krieger & Stephen Sidney, *Racial Discrimination and Blood Pressure: The CARDIA Study of Young Black and White Adults*, 86 AM. J. PUB. HEALTH 1370 (1996); *see also* E. Harburg et al., *Socio-Ecological Stress, Suppressed Hostility, Skin Color, and Black-White Male Blood Pressure: Detroit*, 35 PSYCHOSOMATIC MED. 276 (1973); Williams, *supra* note 93.

95. As mentioned earlier, this study controlled only for education and a singular metric of financial history. *See supra* note 87, 89 and accompanying text.

96. Yancy, *Cardiovascular Enigma*, *supra* note 16.

97. Prior to the Dries et al. publication, the CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) noted that between 1980 and 1995 there was a steady narrowing in the gap between blacks and whites for mortality from heart failure. Indeed, looking at mortality rates for individuals age sixty-five and older (among whom approximately ninety-four percent of heart failure deaths occurred in 1994) the *MMWR* observed, "Because of greater declines in death rates for heart failure among black adults, from 1980 to 1995 the black:white ratio for men narrowed from 1.3:1 to 1.1:1 and for women from 1.4:1 to 1.1:1." CTRS. FOR DISEASE CONTROL & PREVENTION, *Changes in Mortality from Heart Failure—United States, 1980-1995*, 47 MORBIDITY & MORTALITY WEEKLY REP. 633 (1998),

The failure of Dries et al. to find the more current data can only be described as reckless given both the controversial nature of claims connecting race with biology and the relative ease with which a knowledgeable researcher could obtain current data.

Second, Gillum specified that "for persons *aged 35 to 74 years*, the ratio of age adjusted rates for blacks and whites was 1.8 for men and 2.4 for women."[98] Dries et al.'s article failed to include Gillum's age specific qualification of the data. This is not a minor oversight. Rather it drastically alters both the meaning of the data presented and the overall framework within which the study is being presented. Gillum also noted that "the ratio of black-to-white rates [of mortality] was highest under age sixty-five, approaching 1 [i.e., 1:1] in persons seventy-five years of age and over."[99] Finally, by the numbers presented in Gillum's own table of statistics, the age group of thirty-five to seventy-four contained approximately sixty-nine percent of black heart failure mortality but only twenty-nine percent of white heart failure mortality.[100] Thus, seventy-one percent of whites who die from heart failure die after age seventy-four and are not captured in the age thirty-four to seventy-four statistic. By these statistics blacks may have *earlier* onset and *earlier* mortality from heart failure, but this is not the same thing as a *higher* mortality rate. In fact, the most current data available from the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics place the age-adjusted ratio of black to white mortality from heart failure at something under 1.1:1 for 1999.[101]

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http://www.cdc.gov/mmwr/preview/mmwrhtml/00054249.htm (last visited Dec. 3, 2003). Moreover, the 1999 CDC Wonder data set provides an overall age-adjusted mortality rate ratio for blacks to whites of 1.08:1. *See* discussion *infra* note 101.

98. Richard F. Gillum, *Heart Failure in the United States, 1970-1985*, 113 AM. HEART J. 1043, 1043 (1986) (emphasis added).

99. *Id.*

100. *Id.* at 1044.

101. To obtain the current statistic, I went to the CDC Wonder mortality tables, typed in an information request for the most recent year available (1999) for the category of Heart Failure (ICD-10 I50.0) and asked for age-adjusted compressed mortality rates by race measured by the closest fiscal year standard population (FY2000). The results were an age-adjusted death rate for all blacks of 20.5 per million and all whites of 18.9 per million. Thus, the black to white ratio is approximately 1.08:1. The source of the Wonder Mortality Data Set is the CDC's Office of Analysis and Epidemiology at the National Center for Health Statistics. Seeking longer-term numbers, the compressed mortality from the years 1979 to 1998 using a FY2000 standard population leads to a ratio of roughly 1.14:1. If you use a FY1970 standard population the ratio rises to 1.27:1. This higher number over the longer term fits with data released in the CDC's *Morbidity and Mortality Weekly Report* (MMWR). *See*

Unfortunately, the 2:1 statistic has not been widely challenged, and it has since taken on a life of its own, appearing throughout both the popular media and in peer-reviewed medical and scientific journals.[102] Almost every reference to BiDil now appears in the company of the 2:1 statistic. Its wide circulation throughout discussions of race-based approaches to treating heart failure has been further aided by the federal government's own inept handling of statistics. For example, the website maintained by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH), contains three different web pages that variously report the black to white mortality ratio from heart failure as 2:1,[103] 1.4:1,[104] and "slightly higher in blacks than in whites."[105]

A companion to the 2:1 statistic has been the assertion that ACE inhibitors work less well in black than in whites.[106] As noted above, Cohn and others made the assertion in an article published by the *New England Journal of Medicine* in May 2001[107]—a mere two months after NitroMed's announcement of the commencement of A-HeFT, the African American Heart Failure Trial. This assertion, when combined with findings that BiDil works better in blacks,[108] may be understood to imply that perhaps *all* African American heart failure patients should be taking BiDil—not merely those who cannot tolerate ACE inhibitors—a significant expansion of the potential market. Significantly, the entry for the ACE inhibitor

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discussion *supra* note 97.

102. *See supra* note 17 and accompanying text (discussing mention of the 2:1 statistic in popular media); *see, e.g.*, Dries et al., *supra* note 87 (employing outdated mortality rate ratios); Yancy, *Cardiovascular Enigma*, *supra* note 16.

103. NAT'L HEART, LUNG, & BLOOD INST., FACTS ABOUT HEART FAILURE, http://www.nhlbi.nih.gov/health/public/heart/other/hrtfail.htm (last visited Dec. 18, 2003).

104. NAT'L HEART, LUNG, & BLOOD INST., *supra* note 23.

105. NAT'L HEART, LUNG, & BLOOD INST., MORBIDITY AND MORTALITY: 2002 CHARTBOOK ON CARDIOVASCULAR, LUNG, AND BLOOD DISEASES 39, *available at* http://www.nhlbi.nih.gov/resources/docs/02_chtbk.pdf (last visited Dec. 7, 2003).

106. Cohn linked this assertion quite explicitly to the 2:1 statistic: "Because black people are twice as likely to suffer from heart failure and twice as likely to die from heart failure, the unique needs of this particular population must be addressed. . . . The results of the SOLVD trials provide statistically significant data on how disparate the outcomes for white and black patients truly are." Press Release, Univ. of Minn., Racial Disparity in Efficacy of Common Heart Failure Treatment (May 3, 2001), *at* http://www.newswise.com/articles/2001/5/HEART.UMN.html (last visited Nov. 7, 2003).

107. Exner et al., *supra* note 41.

108. *Id.*; *see also* Cohn, *supra* note 49.

Vasotec (enalapril) in the current edition of the *Physicians' Desk Reference* (*PDR*), in apparent—but not explicit—reference to the Exner et al. article, states in the section on "Indications and Usage" that "in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks."[109]

Unlike the 2:1 statistic, the findings on ACE inhibitors have not gone unchallenged. Surprisingly, one of the strongest critiques has come from one of the co-authors of the original study, Dr. Daniel Dries. Dries published a paper in 2002 in which he took issue with the earlier *New England Journal of Medicine* piece and argued that "enalapril appears to be equally efficacious in black and white patients."[110] Another article found the retrospective analysis of the SOLVD data was too weak to provide any conclusions regarding the lack of benefit ACE inhibitors offer black patients.[111] Yet another article argues that the data on ACE inhibitors are insufficient to support a "unique strategy" for treating African American heart failure patients.[112] Finally, a recent meta-analysis of major clinical trials found no evidence of racial differences in responses to ACE inhibitors.[113] Yet, the *PDR* retains the reference to racial difference.

Nonetheless, the combined retrospective analyses of the V-HeFT and SOLVD data, framed by the fallacious 2:1 mortality statistic, have propelled the emergence of BiDil as an apparent means to redress a health disparity in an underserved population. Hence it seems reasonable that by 2001, NitroMed had garnered the support of the Association of Black Cardiologists (ABC) and the Congressional Black Caucus in its bid for approval of the ethnically repositioned BiDil. NitroMed approached the FDA, and in March 2001 came the announcements that BiDil was expected to be approved by the FDA pending the successful completion of A-

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109. *Vasotec I.V. Injection*, *in* PHYSICIANS' DESK REFERENCE 2105 (2003), *available at* http://www.biomed.lib.umn.edu/mdxcgi (last visited Nov. 7, 2003).

110. Daniel L. Dries et al., *Efficacy of Angiotensin-Converting Enzyme Inhibition in Reducing Progression from Asymptomatic Left Ventricular Dysfunction to Symptomatic Heart Failure in Black and White Patients*, 40 J. AM. COLL. CARDIOLOGY 311, 311 (2002).

111. J.S. Kalus & J.M. Nappi, *Role of Race in Pharmacotherapy of Heart Failure*, 36 ANNALS PHARMACOTHERAPY 471, 471 (2002).

112. K.C. Ferdinand et al., *Contemporary Treatment of Heart Failure: Is There Adequate Evidence To Support a Unique Strategy for African-Americans? Con Position*, 4 CURRENT HYPERTENSIONS REP. 311 (2002).

113. Paul G. Shekelle et al., *Efficacy of Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers in the Management of Left Ventricular Systolic Dysfunction According to Race, Gender, and Diabetic Status*, 41 J. AM. COLL. CARDIOLOGY 1529 (2003).

HeFT.[114] When NitroMed announced the initiation of A-HeFT at the annual meeting of the ABC, CEO Michael Loberg emphasized, "NitroMed looks forward to working closely with the ABC and other clinical thought leaders in the completion of this important trial."[115] Explaining the ABC's sponsorship of A-HeFT, B. Waine Kong, CEO of the ABC, declared, "It is in the name of science that we participate."[116]

D. Surrogate Markers and Surrogate Marketing

The reinvention of BiDil as an ethnic drug enabled NitroMed to garner support beyond the ABC and the Congressional Black Caucus. On June 14, 2001, NitroMed announced the completion of a private financing round raising $31.4 million from several venture capital firms to support the A-HeFT trials.[117] NitroMed's ability to raise such substantial funding in the aftermath of the "dot com" collapse in the stock market is testament to the business appeal of developing a drug at the forefront of biological niche marketing. Where drugs such as Viagra may target one sex or another, BiDil promises to lead the way in ethnic niche marketing of pharmaceuticals. On November 6, 2003, in the latest round of fundraising to support the development and marketing of BiDil, NitroMed went public. The initial public offering was managed by Deutsche Bank Securities and J.P. Morgan. NitroMed offered six million common shares at a target price of eleven dollars per share with a proposed market cap of $305 million.[118] In the emerging field of pharmacogenomics, where drug

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114. Press Release, NitroMed, Inc., *supra* note 1.

115. Press Release, NitroMed, Inc., *supra* note 7.

116. Stolberg, *supra* note 17. To further aid in recruiting patients for the trial, NitroMed has enlisted Feinstein Kean Healthcare, a subsidiary of Oglivy PR Worldwide, one of the world's largest public relations firms. See Press Release, Humana, Inc., Humana and NitroMed Form Program to Expand Clinical Trial Access to Minorities (Aug. 8, 2002), http://www.humana.com/corporatecomm/newsroom/releases/PR-News-20020808-150024-NR.html (last visited Jan. 15, 2004).

117. Press Release, NitroMed, Inc., NitroMed Completes $31.4 Million Private Financing (June 14, 2001), http://www.nitromed.com/newsindex.html (last visited Dec. 7, 2003).

118. *See, e.g.*, NitroMed, Inc., SEC Filing, *supra* note 3; *NitroMed To Sell 6 Mln IPO Shares for $11-$13 Each*, REUTERS, Oct. 2, 2003, http://biz.yahoo.com/rf/031002/health_nitromed_ipo_2.html (last visited Dec. 7, 2003); Press Release, NitroMed, Inc., NitroMed, Inc, Announces Its Initial Public Offering (Nov. 5, 2003), http://www.nitromed.com/newsindex.html (last visited Dec. 7, 2003); *Developer NitroMed Plans To Raise $72 Million in IPO*, IPOHOME, Oct. 2, 2003, *at* http://www.ipohome.com/marketwatch/iponews2.asp?article=3163 (last visited Dec. 7, 2003).

companies are hoping to tailor therapies ever more closely to the genetic profile of individuals or groups of consumers, identifying racial/ethnic correlations with disease is becoming big business. As one announcement for a 2004 conference on *Multicultural Pharmaceutical Marketing and PR* put it:

> Major U.S. Drug [sic] manufacturers are making it a high priority area to cultivate relationships with ethnic consumers, physician groups, community networks and other key stakeholder groups to uncover new market growth. Disproportionately high incidence of diabetes, obesity, heart disease, cancer, HIV/AIDS, asthma and other health conditions among these segments require many strategic and tactical moves in pharmaceutical marketing and PR.[119]

To a significant degree, NitroMed's development of BiDil can be viewed as one such strategic or tactical move.

In the context of pharmacogenomics the purportedly benign racialization of the BiDil becomes more problematic. In their analysis of potential impacts of the use of race in pharmacogenomics, Lee et al. observed:

> Although the idea of individually tailored therapy is the goal, it appears likely that products will actually be targeted according to race. One can only speculate on the cultural impact of the commercialization of drugs for racialized populations and the decision by pharmaceutical companies to bring to market therapeutics created for a certain group of consumers.[120]

They concluded with the admonishment that "[c]areful policy guidelines on the marketing of medicines . . . to racially defined groups are needed."[121] The cultural impact of BiDil is already becoming evident in the widespread coverage in the media lending support to the idea that race may be used as a biological category.

Ironically, many of the BiDil researchers are among the first to caution that they are merely using race as a surrogate marker to identify underlying genetic variation that accounts for the differential response to

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119. STRATEGIC RESEARCH INST., 5TH ANNUAL MULTICULTURAL PHARMACEUTICAL MARKETING & PR CONFERENCE, http://www.srinstitute.com/ApplicationFiles/web/webFrame.cfm?web_id=205 (last visited Dec. 15, 2003).

120. Lee et al., *supra* note 13, at 57.

121. *Id.*

BiDil. Cohn himself has noted that "skin color is only a crude indication of underlying genetics differences."[122] Similarly, the article he co-authored on racially differential responses to ACE inhibitor therapy cautions that "[i]t must be recognized that racial categorization is only a surrogate marker for genetic or other factors responsible for individual responses to therapy. Indeed, racial intermixing makes genetic distinctions problematic, and any identified differences will certainly not apply to all the members of each stratified group."[123]

Yet, race remains a primary category around which these researchers organize their efforts. They present race as instrumental—a means to a larger end of more precisely tailored drug therapy, therapy that will be able to overlook race all together. Dr. Sally Satel, a psychiatrist and author of a *New York Times Sunday Magazine* article called *I Am a Racially Profiling Doctor*,[124] has characterized the work on BiDil this way:

> The ultimate purpose of work like Cohn's and other biological realists is to identify factors that may be genetic in origin. First, researchers hope that identifying particular genetic markers with certain ethnic groups will yield insight into the genetic basis of disease and reveal why certain conditions are more prevalent in some groups. Second, the ultimate goal is to understand differences between *individuals*, not between races or ethnic groups.[125]

Satel here lays out an idealized progression of medical research and, by implication, of marketing, toward truly individualized pharmacogenomic approaches to therapy that focus on genetic variation independent of racial categories. On the road to this ideal, however, Satel and others identify race as a useful category of medical analysis. For example, Cohn has explained that "[i]t seems to [him] absolutely ludicrous to suggest that this prominent characteristic [i.e., race] that we all recognize when we look at people should not be looked at."[126]

Satel, Cohn and others who embrace such "racial profiling" in medicine move from social group to biological group to individual

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122. Griffith, *supra* note 4 (quoting Dr. Cohn).

123. Exner et al., *supra* note 42, at 1357.

124. Sally Satel, *I Am a Racially Profiling Doctor*, N.Y. TIMES MAG., May 5, 2002, at 56.

125. Sally Satel, *Medicine's Race Problem*, 110 POL'Y REV. 49, 55 (2001), *available at* http://www.policyreview.org/DEC01/satel.html (last visited Dec. 17, 2003).

126. Jon Entine, *The Straw Man of Race*, 16 WORLD & I 294, *available at* http://www.jonentine.com/reviews/straw_man_of_race.htm (last visited Dec. 27, 2002) (quoting Dr. Cohn).

genome. They begin with the assumption that it is useful and legitimate to use social categories of race as "crude markers" to get at biological groups of people who share a common genetic predisposition to a particular disease.[127] After a group is identified, the goal is to proceed to the level of the individual genome to explain disease. Once it is possible to scan individual genomes for genetic variations the need to refer to the biological group fades away. Without the biological group, the initial surrogate social group—in this case a racial group—is erased as irrelevant to understanding the disease. Here race is understood as epiphenomenal. True difference is cast at the material level of the molecule.

In his recent article *Does Race Matter in Heart Failure?*, Clyde Yancy captured this logical progression.[128] Answering his title's question in the affirmative, Yancy goes on to assert that

> a group of patients do exist that appear to be at a particular risk for less good outcomes. Currently this group shares the same racial designation, a grouping that is overtly crude and completely arbitrary. What will hopefully emerge, however, are the exact clinical and *genetic descriptors of race* that will supercede something as nebulous as skin color and address the more compelling and appropriate physiological traits that put all persons at risk for heart failure.[129]

Yancy's use of the term "genetic descriptors of race" alongside his recognition of racial groupings as crude and arbitrary markers attests to how biomedical researchers may at once acknowledge concerns about the use of race as a biomedical category, while in practice affirming race as an objective genetic classification. Furthermore, his reduction of race to "skin color" evidences a strikingly simplistic conception of the term given social scientists' longstanding critique of it as unstable, historically contingent and generally hard to define in a concrete way.[130]

There are two additional problems with the model emerging from the work of Cohn, Satel, and Yancy et al. First, most diseases have powerful environmental and social components—many of which correlate with social categories of race. For example, a recent report from the Institute of Medicine found that racial and ethnic minorities tend to receive lower-quality health care than do whites, even when insurance status, income,

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127. *See, e.g.*, Yancy, *supra* note 2, at 205.

128. *Id.*

129. *Id.* (emphasis added).

130. *See e.g.*, MICHAEL OMI & HOWARD WINANT, RACIAL FORMATION IN THE UNITED STATES: FROM THE 1960S TO THE 1990S 54-55 (1994).

age, and severity of conditions are comparable.[131] An over-emphasis on the molecular basis of disease can undermine support for broad-based social policy approaches to redressing such health disparities. This need not be an either/or situation, but in a time of economic hardship, a genetically deterministic approach to disease could likely direct scarce resources away from more public health oriented social approaches to managing disease.

Second, the promise of fully individualized genomic medicine is decades away and in the "gap" between current practice and the full realization of pharmacogenomic medicine there is room for much potential harm. Consider that a widely available, affordable, and rapid technology for scanning individual genomes is years, perhaps decades off. In the meantime, researchers are working to correlate certain genetic variations with particular racial groups. When a drug such as BiDil gets produced, researchers understand that it works at the molecular level, affecting, for example, levels of nitric oxide in the blood. Nonetheless, a drug company cannot effectively market BiDil to the biological group of individuals who have a particular genetic polymorphism that may lead to lower levels of nitric oxide. Rather, NitroMed will market BiDil to the social group known as African Americans, because at this point we simply lack the resources or technology to scan every individual's genetic profile. Furthermore, although many individuals identifying with non-African American racial groups will have this variation, on average, a higher proportion of African Americans are hypothesized to have it. Hence, it is far easier to target African Americans than to identify a market of particular individuals who happen to respond well to BiDil because of their genetic makeup regardless of race. The corporation uses the fact of an identified biological difference to create a market based on a social group. Medical researchers may use race as a surrogate to get at biology in drug development, but corporations are using biology as a surrogate to get at race in drug marketing.

E. The Role of Law in Race-ing BiDil

The role of law as player in the emergence of BiDil as an ethnic drug began in 1980, more or less coincidentally with the initiation of V-HeFT I. That year, President Carter signed into law two pieces of legislation that would transform relations between industry and academic researchers.[132]

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131. INST. OF MED., *supra* note 13, at 1-2.

132. *See, e.g.*, Sheldon Krimsky, *The Profit of Scientific Discovery and Its Normative Implications*, 75 CHICAGO-KENT L. REV. 15 (1999). Krimsky notes, "The new federal initiatives on technology transfer and academic-industry-government collaborations were responsible for

The first, the Stevenson-Wydler Technology Transfer Act,[133] encouraged interaction and cooperation among government laboratories, universities, big industries and small businesses. The second, the Bayh-Dole Patent and Trademark Laws Amendment,[134] 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 U.S. Veterans Administration, could be commercialized through patent and trademark law. Thus Jay Cohn and Peter Carson were able to obtain intellectual property rights in BiDil-related patents and enter into deals with the likes of Medco and NitroMed to commercialize the discoveries made through the V-HeFT trials.

The first intervention of patent law in the development of BiDil, however, was negative and restrictive rather than productive. Following the successful completion of V-HeFT II in 1989, the next logical step would have been to conduct a trial that explored the combined effects of ACE inhibitors with H/I. Cohn himself pushed for such a trial and openly bemoaned the lack of corporate support to enable him and other cardiologists to go forward.[135] The key reason, as Cohn later noted, was because hydralazine and isosorbide dinitrate were both generic drugs. In the absence of intellectual property rights to the therapeutic compound, corporate support for further tests involving the components of BiDil would not be forthcoming.[136] Thus, years before BiDil was ever presented

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a marked rise in university patents. In 1980, American university patents represented one percent of all U.S. origin patents. By 1990, the figure rose to 2.4%. Within that decade, the number of applications for patents on NIH-sponsored inventions increased by nearly 300%." *Id.* at 22.

133. 15 U.S.C. § 3701 (1994). In particular, the Act encourages the transfer of technology developed in federal laboratories to the private sector for further development through Cooperative Research and Development Agreements. In some instances, this involves the transfer of legal rights, such as the assignment of patent title to a contractor or the licensing of a government-owned patent to a private firm. In other cases, the transfer endeavor involves the informal movement of information, knowledge, or skills through person-to-person interaction.

134. 35 U.S.C. §§ 200-212 (1994).

135. Jay N. Cohn, *Lessons from V-HeFT: Questions for V-HeFT II and the Future Therapy of Heart Failure*, 16 HERTZ 267, 270 (1991).

136. Reviewing the course of the V-HeFT trials, Cohn noted:

> The natural evolution of V-HeFT would have mandated that the vasodilator regimen [to be combined with enalapril in V-HeFT III] would be the combination of the hydralazine and isosorbide dinitrate, which has been so effective in V-HeFT I and V-HeFT II. Unfortunately, the need for financial

to the FDA, the lack of relevant intellectual property value seemed likely to condemn hydralazine and isosorbide dinitrate to obscurity as treatments for heart failure. Not only did further trials of H/I in combination with other drugs seem unlikely, but there would be no money to push publicity and marketing of the H/I therapy as it was then understood.

Cohn revived the commercial prospects for BiDil in by patenting the method of combining hydralazine and isosorbide dinitrate to treat congestive heart failure,[137] and then by developing 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 dispense and to use the H/I combination but was not itself a new therapy. With BiDil, a doctor only had to write one prescription and the patient only had to take a total of six pills (two pills three times a day) instead of sixteen (four pills four times a day).[138]

Yet, the measure of convenience to BiDil alone was insufficient to drive its development. A consultant to the FDA panel that ultimately rejected BiDil's NDA in 1997 noted that the two generic component drugs of BiDil are available for anyone to use for heart failure. The FDA's denial of the BiDil NDA would not change that. Rather, he observed that "the practical impact of the FDA not approving this combination today is that there won't be an economic incentive for the sponsor to get out and provide educational material for a lot of doctors to know how to use the drugs best."[139]

> support has made it necessary that the vasodilator be an agent with potential commercial interest. Thus, a calcium antagonist has been substituted in V-HeFT III for the hydralazine nitrate combination, and it will be felodipine – a calcium antagonist with considerable vasoselectivity.

Jay N. Cohn, *supra* note 78, at VI-2 to VI-3; *see also* Jay N. Cohn, Invited Editorial, *Treatment of Infarct Related Heart Failure: Vasodilators Other Than ACE Inhibitors*, 8 CARDIOVASCULAR DRUGS & THERAPY 119, 120 (1994) ("One of the problems with advocating non-ACE vasodilators in treatment of the post-infarct period relates to the inadequacy of the database on these drugs. Since hydralazine and isosorbide dinitrate are generic agents, there has been no effort on the part of a pharmaceutical company to mount large-scale trials or to develop an NDA for drug approval. In contrast, the ACE inhibitors have been heavily marketed and their use for infarct related heart failure appears to be growing rapidly.")

137. U.S. Patent No. 4,868,179, *supra* note 60.

138. Interview with Dr. Anne Taylor, Principle Investigator and Chairperson: A-HeFT, in Minneapolis, Minn. (Nov. 11, 2002). Of course, six pills a day is still considered a lot. Indeed, doctors generally do not expect to see a great improvement in patient compliance with a drug regimen until the dosage is down to two times per day. *Id.*

139. TRANSCRIPT, *supra* note 72, at 210.

The true breakthrough for BiDil, therefore, was not simply the combination of two generic drugs into one; it was the development of new intellectual property rights. With patent protection in hand, it would become advantageous for a drug company to develop and market BiDil aggressively to doctors and patients. For this reason, Medco acquired the rights to BiDil in the early 1990s and started investing time and money in conducting trials and developing marketing strategies in preparation for submitting its NDA to the FDA. Patent law, and to a lesser extent trademark law which allowed for added brand name value in the marking of BiDil®, thus provided a critical impetus toward the creation of BiDil. On the one hand, this comports well with the classic justification of patent law as providing a spur to invention. On the other hand it indicates how patent law may also distort a market, potentially obscuring less expensive generic alternatives that have the same therapeutic value.

However, Medco's efforts came to naught in February 1997, with the FDA Advisory Committee's rejection of its NDA for BiDil. Following the rejection, the value of the intellectual property rights plummeted along with Medco's stock; the rights reverted to Cohn, and Medco exited the story of BiDil's development.

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 led the BiDil researchers to reconceptualize their drug along racial lines in order to get a "second bite" at the apple of FDA approval. By 1999, 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 because of the reanalysis of the old V-HeFT data along racial lines.

NitroMed acquired the intellectual property rights to BiDil in November 1999—a mere two months after the paper by Carson et al. identified purported racial differences in response to the H/I combination administered in V-HeFT I and II. In the hands of its new corporate handlers and their public relations consultants, BiDil soon was reborn as an ethnic drug. The subsequent spate of publicity attending the inauguration of A-HeFT demonstrated 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 2000 patent appears much the same as Cohn's original 1989 patent.[140] 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."[141]

The issuance of the new patent is commercially important because the original patent is set to expire in 2007. The new race-based patent will not expire until 2020. Significantly, in issuing the second patent, the United States Patent and Trademore Office (PTO) found that Cohn's first method-of-use patent for BiDil did not constitute "prior art" with respect to the new patent application. Rather, it found the application's race-specific method of treatment to be a "non-obvious" extension of the earlier concept and hence patentable.[142] A search of the U.S. PTO database for similar race-specific claims in a patent revealed this to be the only patent for such a race-specific drug treatment. Patent law is supposed to promote the invention of new and useful products. In the case of BiDil, patent law did not spur the invention of a new drug, but rather the recharacterization of an existing therapy for a particular segment of society—in short, the repackaging of the drug as ethnic.

With the issuance of the patent on October 15, 2002, race entered the world of patent law in a new and explicit way. The scope of patent protection is typically referred to in terms of "metes and bounds." The metaphors of physical property are quite deliberate. Cohn's and Carson's new patent racializes the "metes and bounds" of their intellectual property claims. As scholars such as Cheryl Harris[143] and Richard Thomson Ford[144] have noted, American law has a long tradition of characterizing property and physical spaces in racial terms—often to devastating effect. Whether in the most egregious and obvious form of race-based slavery or in subtler identifications of neighborhoods or even names[145] with race making it

140. U.S. Patent No. 6,465,463 (issued Oct. 15, 2002), http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,465,463.WKU.&OS=PN/6,465,463&RS=PN/6,465,463 (last visited Dec. 13, 2003).

141. *Id.* (emphasis added).

142. NitroMed, Inc., *supra* note 3, at 12.

143. Cheryl I. Harris, *Whiteness as Property,* 106 HARV. L. REV. 1707 (1993).

144. Richard Thomson Ford, *The Boundaries of Race: Political Geography in Legal Analysis,* 107 HARV. L. REV. 1841 (1994).

145. *See, e.g.,* Alan B. Krueger, *Sticks and Stones Can Break Bones, but the Wrong Name Can*

more difficult to obtain mortgages or jobs, the nature and value of property has long been profoundly influenced in and through its association with race.

Previous associations of race and property have generally involved a devaluing of associations with racial minorities. Certain more recent legal classifications of race, as in affirmative action, have the potential to offer challenges to exclusionary conceptions of racialized property rights.[146] The racialization of BiDil's patent appears to be more in line with such assertedly "benign" uses of racial categories and has actually added value to the drug, hence the readiness of such groups as the Association of Black Cardiologists and the Congressional Black Caucus to support A-HeFT. In this regard, BiDil gains cultural capital by being characterized as a means to redress an important health disparity in a historically underserved population.

IV. LEGAL AND POLICY IMPLICATIONS OF RACE AS BIOLOGY IN THE WAKE OF BIDIL

There are dangers attending even purportedly benign uses of racial categories in the context of biomedicine that distinguish them from uses such as affirmative action. Specifically, in connecting race to biology, the advocates of BiDil run the risk of reviving long discredited notions of race *as* biology. This risk is less relevant to policies such as affirmative action that are often designed to redress specific past social or political inequities.[147] The role of the federal legal and regulatory system in producing BiDil as an ethnic drug is especially important because it lends the imprimatur of the state to the use of race as a biological category. Between the FDA's letter commenting on the ultimate approvability of BiDil as a race-specific drug and the U.S. PTO's recent issuance of the patent for using H/I in African American patients, powerful federal agencies have acknowledged the legitimacy of using race as a marker for biological difference. In this context, we see the federal government indirectly fueling the "comeback" in "racialized notions of biology" against which Alan Goodman cautioned.[148]

There are real health disparities in society that correlate with certain

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Make a Job Hard to Find, N.Y. TIMES, Dec. 12, 2002, at C2.

146. *See, e.g.*, Harris, *supra* note 143, at 1768-91.

147. *Cf.* City of Richmond v. J. A. Croson Co., 488 U.S. 469 (1989).

148. Alan H. Goodman, *Why Genes Don't Count (for Racial Differences in Health)*, 90 AM. J. PUB. HEALTH 1669, 1699 (2000).

racial groups. As sociologist Troy Duster has noted, "We can and should refer to race when we consider it as part of a complex interaction of social forces and biological feedback loops."[149] Duster cautions, however, that "it is also a mistake to uncritically accept old racial classifications when we study medical treatments. The task is to determine how the social meaning of race can affect biological outcomes."[150] The story of BiDil is a story of the failure of a wide variety of actors—from medical researchers to federal regulators to drug company executives—to heed Duster's warning.

Some doctors and scientists are clearly concerned. One news report on BiDil quoted Craig Venter, who was CEO of Celera Genomics when it completed its rough draft of the human genome in 2001, as saying, "It is disturbing to see reputable scientists and physicians even categorizing things in terms of race.... There is no basis in the genetic code for race."[151] Dr. Charles Curry, a cardiologist at Howard University Hospital cautioned, "[I]f NitroMed starts bombarding blacks with ads, those patients and their doctors could ignore other potentially effective treatments.... Patients don't respond to medications in the same way, so marketing drugs by race can be misleading."[152] Mark Pfeffer of Harvard's Brigham and Women's Hospital expressed skepticism about A-HeFT's approach because it substituted skin color for genetic analysis.[153] Finally, Joseph Graves, an evolutionary biologist at Arizona State University, argued that "linking illness—or any other trait, like intelligence or athletic skill—to appearance is a fundamental scientific error."[154] He expressed the further concern that "scientists are often too quick to look for genetic explanations for disparities in health, when lifestyle may be the answer."[155]

Proponents of the race-based approach to BiDil try to define the individual by reference to a biological group (i.e., individuals who respond well to BiDil)—not a social group (i.e., African Americans). They assert that the biological group merely "correlates" with race. Hence, the proponents of BiDil acknowledge that they are using race merely as a

149. Troy Duster, *Buried Alive: The Concept of Race in Science*, CHRON. HIGHER EDUC., Sept. 14, 2001, at B12.

150. *Id.*

151. Stolberg, *supra* note 21. Venter, however, here goes to the extreme of denying the significance of race altogether. The logic of his argument compels us to overlook the significance of health disparities such as varying rates of certain types of cancer or hypertension that do strongly correlate with certain *social* categories of race.

152. Sealey, *supra* note 4.

153. Editorial Board, *supra* note 21.

154. Stolberg, *supra* note 21 (quoting Dr. Graves).

155. *Id.*

surrogate marker to get at a distinctive underlying biology of response to heart failure therapy. Yancy, like Cohn, has argued that race "is pertinent [only] as a crude marker of genetic variation," and that "the only reason to have this discourse regarding racial differences in the natural history of cardiovascular disease is not to learn more about race per se, but rather to uncover new mechanisms of disease."[156]

However, in practice something different is happening. Hydralazine and isosorbide dinitrate do not address the social causes of heart failure, only the individualized biological ones. Such a therapy is administered based on understandings of biology. Cohn's and Carson's patent is not for a method of treatment that merely correlates with a social group—it specifies a chemical therapy for "African Americans." That is, it specifies African Americans as a biological group, and it has received the approval of the federal government for this classification. Now, NitroMed is similarly seeking regulatory approval for BiDil as a drug to treat African Americans, conflating social with biological categories. What sociologist Michael Omi observes with respect to the use of racial categories in the social sciences might well apply here: "[M]uch of sociological research, though firmly committed to a social as opposed to biological interpretation of race, nevertheless slips into a kind of objectivism about racial identity and racial meaning.... Although abstractly acknowledged to be a sociohistorical construct, race in practice is often treated as an objective fact."[157] The scholarly studies, press reports, and marketing copy for BiDil all contain brief caveats about race as a social category or as a crude marker for particular biological conditions. The caveats, however, are usually buried deep in the text, or else they are superceded by subsequent assertions or practices of treating race as, in effect, a genetic category (as with Yancy's hope to identify some "genetic descriptors of race"). The headlines always place in the foreground the identification of race with biology.

The drive to reduce disease to the level of the individual genome reflects a prototypically American emphasis on the autonomous, unencumbered individual as the primary subject of political and social concern.[158] This may appear to fly in the face of calls for "racial profiling" in medicine, but in fact there is an underlying and highly problematic logic at work here. In the context of the drive toward BiDil, those who

156. Yancy, *Role of Race, supra* note 20, at 224.

157. Michael Omi, *Racial Identity and the State: The Dilemmas of Classification*, 15 LAW & INEQ. J. 7, 21 (1997).

158. *See, e.g.*, Michael Sandel, *The Procedural Republic and the Unencumbered Self*, 12 POL. THEORY 81 (1984).

argue for racial profiling in medicine assert that it is permissible to use social categories of race as surrogates for biological characteristics that are understood to be "real" or "natural." Conversely, social, economic, and political differences that correlate with social categories of race have been undervalued as important determinants of health. The implicit message here is that the purportedly biological differences identified by BiDil researchers deserve priority over the social differences identified by studies such as that conducted by the Institute of Medicine. Such prioritization promises to affect the allocation of scarce health care resources away from addressing the social bases of disease and toward what may be an excessive concentration on disease on the molecular level.

To the extent that such logic is extended into the realm of racial classifications in law it has some additional troubling implications. First, in a general way it may support certain efforts to undermine affirmative action. Affirmative action programs use race as a social classification to redress past and present social, economic, and political injustice. As race becomes re-imagined primarily in terms of biology (genetics in particular), such programs may increasingly come to be seen as based in "ephemeral" or insubstantial differences that are not the basis of legitimate classifications. In contrast, legal classifications based on so-called "real" differences based in biology may be put forth as sufficiently substantial to withstand heightened or strict scrutiny.

For example, it would be legal to discriminate against blind people when looking to hire a school bus driver. While the group "blind people" might be understood to constitute a "discrete and insular minority" that has historically experienced a measure of unjust discrimination, having sight would pass legal muster as a bona fide occupational qualification closely related to the compelling state interest of insuring the safety of both school children on the bus and pedestrians. The case for discrimination could become more complicated in the case of barring epileptics from being school bus drivers. Certainly, one would not want a school bus driver to have seizure while on the road. But whereas the probability that a blind person cannot see the road is one hundred percent, the probability that a person with epilepsy with have a seizure while driving is something far less than one hundred percent. Nonetheless, the probability of such a seizure is also far higher than it would be for someone who did not have epilepsy. As a result, even though anyone can potentially have a seizure while driving, the greater probability that a person with epilepsy would have a seizure would probably justify discrimination in this context as sufficiently narrowly tailored to serve the compelling interest of protecting the lives of school children. However,

what happens when we add to the equation the fact that many types of epilepsy can be effectively controlled through medication? For such cases the probability of seizure goes down even further—at what point does the probability cease to justify discrimination?

To the extent that the federal government marks race as a "natural" biological category it may open the door to new forms of race-based discrimination. Already, for example, employers are permitted under law to discriminate based on certain health conditions where such discrimination is mandated as a "business necessity,"[159] or in other situations where the health condition interferes with a "bona fide occupational qualification."[160] Hence, the Supreme Court recently held it permissible under the Americans with Disabilities Act (ADA) for Chevron to refuse to hire Mario Echazabal to work in a refinery because his Hepatitis C would likely be aggravated by exposure to toxins at the refinery.[161] The ruling interpreted a section of the ADA that allowed employers to discriminate against workers whose condition posed a direct threat[162] to others in the workplace. At issue was whether the Act also covered conditions that only posed a direct threat to the workers themselves. The Court found that it did.[163] Thus, it legitimized Chevron's discrimination against Echazabel on the basis of its assertion that his Hepatitis C would likely pose a direct threat to him in the distinctive

159. *See, e.g.*, Chevron v. Echazabal, 537 U.S. 73, 80 (2002) (discussing, inter alia, § 12113(a) of the Americans with Disabilities Act, which allows employers to discriminate under a qualification standard shown to be job related and consistent with business necessity).

160. *See generally* Americans with Disabilities Act of 1990, Pub. L. No. 101-336, 104 Stat. 327 (1990) (codified at 42 U.S.C. §§ 12101-12213 (2000)). *See also, e.g.*, Albertsons v. Kirkingburg, 527 U.S. 555 (1999) (finding that an employer's refusal to hire for a commercial interstate truck driving job an individual on the grounds that he did not possess binocular vision correctable to a specified degree as mandated under a federal regulation did not constitute a violation of the ADA because the legislative history of the subject regulation demonstrated the regulation was based on considerations of the general public's safety); Automobile Workers v. Johnson Controls, Inc. 499 U.S. 187 (1990) (finding a policy barring all women of child-bearing age from jobs involving lead exposure as violative of Title VII of the Civil Rights Act because the policy did not involve the ability to perform the relevant jobs).

161. *Chevron*, 537 U.S. 73.

162. The ADA defines a "direct threat" as "a significant risk to the health and safety of others that cannot be eliminated by reasonable accommodation." Americans with Disabilities Act of 1990, 42 U.S.C. § 12111 (2000).

163. *Chevron*, 537 U.S. at 86.

setting of a refinery. The ruling required an individualized medical assessment, yet it also recognized the legitimacy of discriminating against an individual based on a biological medical condition.[164] Justice Souter's opinion reflected a general understanding that a work-related biological condition may provide a legal basis for discrimination. There is cause for concern, however, when one considers the implications of applying the logic of Souter's opinion to a situation where racial categories have become biological. To the extent that legal institutions such at the U.S. PTO or the FDA come to mark certain biological conditions as "racial," race may become a surrogate not only for medical research but also for a wide array of legally sanctioned discrimination. Specifically, it deserves noting that while Echazabel was legally entitled to receive an individualized medical assessment of his health status—i.e., having Hepatitis C—the determination of whether that condition posed a direct threat to him under the ADA was still determined by reference to probabilistic correlations between that condition and certain expected health outcomes in the presence of certain potentially aggravating factors in the environment. As race becomes correlated with various biological conditions, it takes only one further step to correlate race with a health threat.

In the not too distant past we have clear examples of discrimination based on a particular genetic condition being justified by only the most tenuous of probabilistic links to potential harm. Sickle cell trait has been the basis for differential genetic screening of populations and the outright exclusion from certain forms of employment. Is coincidence that this sickle cell trait is among the most powerfully racially identified conditions in our culture? As sociologist Troy Duster notes, "In the United States, approximately one in twelve blacks are carriers [of the sickle cell trait]. Because of this, sickle cell is popularly thought to be a 'black person's disease,' and this image penetrates the consciousness of those who are even partially informed about these matters." [165] Sickle cell anemia is a condition that impairs a person's red blood cells from carrying oxygen. It can cause mild or severe pain in organs, joints or muscles, and in extreme cases even death. A "carrier" of the sickle cell "trait" has one copy of the sickle cell gene (in the language of biology, they are "heterozygous"); individuals with the actual disease have two copies of the gene, one from each parent (known as "homozygous"). People with the trait (i.e., one gene) but not the actual disease do not manifest any ill health effects.

164. *Id.*

165. DUSTER, *supra* note 21, at 45.

Indeed it is thought that having one gene may enhance a carrier's resistance to malaria. While the prevalence of the sickle cell trait is higher in populations identified as African American than in populations identified as Caucasian American, the trait most emphatically is not exclusive to blacks or Africans. Rather, it is currently understood by the medical and scientific community as an artifact of populations descended from regions of the world with a high incidence of malaria such as West Africa. For example, the trait is also found among many Mediterranean populations, including especially Greeks and Sicilians, as well as certain Arab and Asian Indian populations, whereas it is rare in South African blacks.[166]

None of this mattered in the late 1960s when four black men died over an eleven month period while going through basic combat training at a U.S. Army camp at the relatively high altitude of 4,060 feet.[167] Autopsies revealed that all four had severe sickling of the red blood cells—although this could have been a consequence rather than a cause of their deaths. Nonetheless, a report of the deaths was published in the *New England Journal of Medicine* in 1970 and was followed up by a study conducted by the National Academy of Sciences (NAS). The NAS report found that the data were inadequate to support any specific conclusions but recommended that carriers of the sickle cell trait be excluded inter alia from copiloting an airplane. The U.S. Air Force Academy seized upon the NAS report to justify a new policy of excluding all blacks with the sickle cell trait. The policy continued until 1981 when a lawsuit finally prompted the Academy to end its policy.[168] Commercial air carriers adopted a similar policy that continued into the 1980s.[169]In this regard, it is instructive to reflect back upon the case of Echazabel. Just as the earlier Air Force Academy discrimination against blacks was done under the paternalistic guise of protecting them,[170] so too was the decision upholding Chevron's discrimination against Echazabel ultimately justified in the name of protecting him from danger. The ADA's concern for health risks or "direct

166. *See id.*; JONATHAN MARKS, HUMAN BIODIVERSITY: GENES, RACE, AND HISTORY (1995). For a powerful history of the politics of sickle cell anemia in the United States, see KEITH WAILOO, DYING IN THE CITY OF THE BLUES (2001).

167. The following story is drawn largely from DUSTER, *supra* note 21, at 24-27; KEVLES, *supra* note 21, at 277-79; and Raymond R. Coletta, *Biotechnology and the Law: Biotechnology and the Creation of Ethics*, 32 MCGEORGE L. REV. 89, 97 (2000).

168. *See* DUSTER, *supra* note 21, at 25-26.

169. *See id.*; Coletta, *supra* note 167, at 97.

170. *See* Janet L. Dolgin, *Personhood, Discrimination, and the New Genetics*, 66 BROOK. L. REV. 755, 818 (2000).

threats"[171] introduces calculations of probabilistic correlation between biological condition and danger that draw upon claims put forth by biomedical researchers who assert correlations among race, genetics, and the risk of disease. This is not to say that these correlations are per se unreasonable, but it should alert us to be careful to prevent such correlations from becoming overly attenuated, especially when they are used in relation to race.

More recently, in the 1998 case of *Norman-Bloodsaw v. Lawrence Berkeley Laboratory,*[172] employees at Lawrence Berkeley Laboratory (LBL), a research institution jointly operated by the federal government and the University of California, brought suit when they discovered that LBL, without their knowledge or consent, had tested blood and urine from mandatory physical exams for syphilis, sickle cell trait, and pregnancy. The court ultimately found a cause of action to lie under Title VII of the Civil Rights Act of 1964 and under state and federal privacy claims.[173] The screening, for sickle cell in particular, was differentially administered based on race: Blacks were singled out for testing. While all the tests were offensive at a number of levels, of particular interest for our purposes is the fact that LBL, a major scientific research institution administered by one of the country's preeminent public universities, was, in practice, treating African Americans as a biological group to be screened for the sickle cell trait. LBL's practices demonstrated no appreciation either of the fact that sickle cell trait is not limited to African Americans or of the fact that merely having the trait does not predispose a carrier to any adverse health conditions. Rather, the social and cultural identification of sickle cell trait as "black" pervaded and warped the employment practices of a supposedly sophisticated scientific research institution as recently as the 1990s.

As more biological conditions become correllated with race, differential screening of individuals for those conditions and perhaps even outright group-based exclusions from employment, insurance or other benefits may result. The mistreatment of African Americans with sickle cell trait is instructive here. It should be understood not as anomalous but as paradigmatic of problems that may develop as genetic knowledge and technologies continue to advance.

In this regard, it is important to note that most efforts to address genetic discrimination focus on the production, circulation, and potential misuse of a particular individual's genetic information. Statutes covering

171. Americans with Disabilities Act of 1990, 42 U.S.C. § 12111 (2000).

172. Norman-Bloodsaw v. Lawrence Berkeley Lab., 135 F.3d 1260, 1261 (9th Cir. 1998).

173. *Id.* at 1264.

these problems tend to cover issues of privacy, information control, and the evaluation of individualized medical conditions.[174]Identifying certain biological conditions, especially genetic conditions, with racial groups presents challenges of a different order. Instead of implicating new forms of discrimination based on specific individualized genetic conditions—what Susan Wolf has terms "geneticism"[175]—the re-biologization of race promises to entangle existing groups that have historically been subject to various forms of discriminatory treatment, such as African Americans, with new biological categories that are being produced through advances in the new genetics. The U.S. Air Force Academy and LBL did not single out blacks for screening based on access to private individual genetic information, but rather because of the identification of the social group "African American" with the biological group "sickle cell carrier."

As Lee et al. note, "Research utilizing race serves to 'naturalize' the boundaries dividing human populations, making it appear that the differences found reflect laws of nature. In fact, the use of race and ethnicity in biomedical research is problematic because it is caught in a tautology, both informed by, and reproducing, 'racialized truths.'"[176] Such a dynamic portends the potential reinvigoration of legally sanctioned race-based discrimination by recasting particular aspects of race in terms of biological difference. Such discrimination is unlikely to appear in the familiar forms of the past. We should not expect to see direct segregation or exclusion of entire racial groups from rights and benefits based on their identification with genetic difference. Rather, subtler forms of differential treatment may arise based on tenuous correlations between genetic difference and racial groups; these correlations may lead to selective discrimination within those groups that is justified by reference to underlying "real" genetic distinctions. Harm may come not from deliberate animus toward a particular group, but from which questions get asked, by whom, and to what ends. Such harm occurred in the past when the U.S. Air Force Academy acted on incomplete information and inadequate studies to differentially screen and exclude blacks, and such harms may occur in the future. For example, from the conception of heart failure as a

174. *See, e.g.*, Nancy Kass, *The Implications of Genetic Testing for Health and Life Insurance, in* GENETIC SECRETS 299-316 (Mark Rothstein ed., 1997); Mark Rothstein, *The Law of Medical and Genetic Privacy in the Workplace, in* GENETIC SECRETS 281-298 (Mark Rothstein ed., 1997). *See generally* LORI ANDREWS ET AL., GENETICS: ETHICS LAW AND POLICY 592-734 (2002).

175. Susan Wolf, *Beyond Genetic Discrimination: Toward the Broader Harm of Geneticism*, 23 AM. J.L. & MED. 345, 350 (1995).

176. Lee et al., *supra* note 13, at 55 (citations omitted).

"different disease" in blacks there is the potential for misallocation of resources away from traditional population health measures directed at ameliorating health disparities and toward the development of race-specific drugs such as BiDil.

V. SOME PRELIMINARY RECOMMENDATIONS

In many respects, the story of BiDil is a cautionary tale about what Martha Minow has called the "dilemma of difference": "[W]hen does treating people differently emphasize their differences and stigmatize or hinder them on that basis? And when does treating people the same become insensitive to their difference and likely to stigmatize or hinder them on *that* basis?"[177] In the case of biomedical research aimed at addressing race-based health disparities, however, this dilemma takes on a particular twist where treating people differently can both help and hinder them simultaneously. As noted above, treating sickle cell anemia as a "black" disease has led to serious instances of unjust discrimination. It has also, however, enabled the political mobilization of elements of the African American community to campaign for increased funding for sickle cell research and other related health programs which propelled the creation of the Office of Minority Health and the implementation of the *Healthy People 2000* and *2010* initiatives.[178]

Race is a social category but it has biological consequences. The two are not easily disentangled. Ignoring the relation between them can be as harmful as seeing them as essentially identical. The task becomes even harder when, as in the case of BiDil, the imperatives of commerce and of the federal regulatory system combine to influence understandings of the nature and status of race as a category in biomedical research. In the case of BiDil, we see that the power of the state, as manifested by regulatory agencies such as the PTO and the FDA, may be reinforcing and legitimizing ill-conceived understandings of racial difference as genetic. This has implications both for biomedical research and for broader social understandings of race.

To clarify our thinking, we must take to heart Duster's admonition to use and understand racial categories as part of a "complex interaction of

177. MARTHA MINOW, MAKING ALL THE DIFFERENCE: INCLUSION AND EXCLUSION IN AMERICAN LAW 20 (1990).

178. For example, current 2002 fiscal year CDC appropriations for "minority health" total $747,472,000. CTRS. FOR DISEASE CONTROL & PREVENTION, MINORITY HEALTH FUNDING, *at* http://www.cdc.gov/washington/funding/minorhea.htm (last visited Dec. 15, 2003).

social forces and biological feedback loops."[179] At a minimum, this should entail that any federal agency or institution conducting research with federal funds that reviews, approves, or itself uses race as a biological category or as a surrogate for a biological category be required to offer a clarification of their terms of analysis and a justification for using them in such a manner. In this regard, it is instructive to consider that the PTO already has provisions directing patent examiners to reject applications for design patents which disclose subject matter "which could be deemed offensive to any race, religion, sex, ethnic group, or nationality."[180] The provisions also assert that "[t]here is a further basis for objection in that the inclusion of such proscribed language in a Federal Government publication would not be in the public interest."[181] The PTO here seems to be acknowledging the significance of preventing the state from lending its imprimatur to improper uses of racial language. The basis is here laid for extending that concern from overtly offensive language to perhaps well-meaning but ill-conceived language that could promote a newly biologized understanding of racial difference.

Several prominent medical and scientific journals have recently adopted editorial policies that reflect a similar concern. The statement from the editors of *Nature Genetics* might well serve as a model for a regulatory admonition to such agencies as the FDA or the PTO when they are asked to review applications such as those submitted by the developers of BiDil:

> The laudable objective to find means to improve the health conditions for all or for specific populations must not be compromised by the use of race or ethnicity as pseudo-biological variables. From now on *Nature Genetics* will therefore require that authors explain why they make use of particular ethnic groups or populations, and how classification was achieved. We will ask reviewers to consider these parameters when judging the merits of a manuscript – we hope that this will raise awareness and inspire more rigorous design of genetic and epidemiological studies.[182]

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179. Duster, *supra* note 149, at B12.

180. U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE, § 1504.01(e), http://www.uspto.gov/web/offices/pac/mpep/documents/1500_1504_01_e.htm#sect1504.01e (last visited May 20, 2003).

181. *Id.* at § 608, http://www.uspto.gov/web/offices/pac/mpep/documents/0600_608.htm#sec608.

182. *Census, Race and Science, supra* note 2, at 99.

If the FDA or the PTO had been following such guidelines, the story of BiDil would likely have unfolded quite differently. Requiring federal agencies to take a closer look at filings and applications that use race as a biological category could force applicants to provide more rigorous justification for their use of such terminology. Just as under equal protection jurisprudence, where strict scrutiny by the courts exposes invidious motives behind legal distinction based on suspect classifications,[183] so too a harder administrative look at race when used as a biological category might reveal instances of its improper use.

The objective here is not to forbid the use of race as a category in federal policy, law, or regulation. Rather, it is to begin to articulate an institutional mechanism of guidelines whereby relevant administrative actors would be required to distinguish between uses of race as a socio-political category from uses of race as a biological and/or explicitly genetic category. The former can be used to track and/or redress historical inequities and current social prejudices. The latter, perhaps as a consequence of seeking relevant regulatory approvals for patents, products, and/or services, involves federal recognition of the use of race as a biological category. Therefore, whenever an applicant uses race in relation to biology before an agent of the state a justification for the use should be required. This justification should involve, first, an assertion that it serves a compelling interest and, second, a showing that the application uses race as biology in a way that is narrowly tailored to serving that interest. The second prong is necessary to force a distinction between observed correlations between certain biomedical conditions and certain socially identified racial groups, and racially specific genetic causation purported to underlie such correlations. Here that would mean providing compelling scientific evidence to support an assertion of race-specific genetic difference underlying any observed correlations. To date, no such differences have been identified by biomedical science. In the case of BiDil the first criterion would probably be met. Providing an effective therapy for heart failure in African Americans would likely be a compelling interest, although the actually efficacy of BiDil in this regard is yet to be established. However, even if we assume that the first prong were met, the story of BiDil shows that this particular use of race in relation to biology was *not* narrowly tailored to serve that interest. Rather, given the history of BiDil and the peculiar nature of its distinctive transformation into an ethnic drug, it is evident that it was initially developed without reference to

183. For the most recent Supreme Court pronouncement on this, see Grutter v. Bollinger, 123 S.Ct. 2325, 2337-38 (2003).

race and ultimately became racialized not because of clearly identified race-based biological differences but because of considerations of law and commerce.

In addition to these regulatory considerations of how and what the PTO and FDA should agree to sanction, there are myriad arenas where the identification of particular racial groups with specific genetic conditions could have possible legal ramifications. For example, racially correlated disease information raises issues of employment or insurance discrimination already touched upon in the story of sickle cell trait. In the realm of toxic torts, as gene-environment interactions become more fully understood, claims could be both organized and defended against by reference to racial categories.[184] It is also conceivable that a doctor might be sued for taking or failing to take race into account in making a diagnosis or prescribing treatment. How might this affect medical practice and the doctor patient relationship—especially as drugs increasingly are being marketed directly to consumers? In the case of BiDil, what is a doctor to make of the fact that, if approved, the FDA labeling specifies the drug for use only in African Americans, whereas guidelines from the American Heart Association specify the same H/I combination as a generally legitimate therapy for anyone who is intolerant of ACE inhibitors?[185]

Just how law and policy may become implicated in such diverse areas over time is impossible to foresee fully. What is foreseeable, however, is that as new genomics information becomes available, a range of actors will continue to seek correlations between racial and biological groups. Such correlations will not and should not be ignored. However, it is imperative that they not be invoked casually or without sufficient consideration of the complex relations between race and biology. Demanding a clear and full articulation of the basis and justification for developing and employing such correlations should be considered an essential starting point for confronting the challenges to come.

CONCLUSION

In the end, the story of BiDil is much more than an individualized account of how a particular drug became focused on a single, ethnic segment of the population. The story is also part of a broader contest over

184. *See, e.g.*, Morris Foster & Richard Sharp, *Race, Ethnicity, and Genomics: Social Classifications as Proxies for Biological Heterogeneity*, 12 GENOME RES. 844 (2002).

185. *See, e.g.*, AM. COLL. OF CARDIOLOGY & AM. HEART ASS'N, *supra* note 27.

classifications systems and context—which variables matter, as well as how and when. BiDil's development has depended upon the strategic appropriation of the social category of race to justify patenting and regulatory approval of a drug that purports to act on a "true" biological basis of heart failure. In the story of BiDil, race plays the role of a valuable surrogate—i.e., it is presented as having no medical value in its own right but takes on significance to the extent that researchers can tie it to a "real" biological group through statistical correlations (hence the centrality of the statistic that blacks die from heart failure at a rate twice that of whites). The unrelenting urge to establish such race-based correlations has led to an egregious failure to interrogate what turns out to be an inaccurate statistic. Moreover, even as BiDil's proponents acknowledge race to be merely a crude marker for biology, they have invoked race as biology to establish intellectual property rights, obtain regulatory approval, raise venture capital, and develop marketing campaigns. Regardless of the particular fate of BiDil as a drug to treat heart failure, its peculiar history on the road to the market presents a wide array of troubling and important issues concerning the future status of race as a category for constructing and understanding health disparities in American society.

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