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RACE AS A PROXY FOR DRUG RESPONSE: THE DANGERS AND CHALLENGES OF ETHNIC DRUGS

*Rene Bowser**

INTRODUCTION

Considerable debate exists concerning the use of race in medical research and in clinical practice. Race, according to some, is of little or no biological significance and, therefore, should be of little or no importance in making treatment decisions.¹ Others insist that a patient's race can, and should, influence the doctor's thinking about possible diagnoses and cures.²

Pharmacogenomics has fueled the controversy.³ Physicians have long known that individual patients respond differently to medications even at the standard dose. Thus, prescribing drugs is an iterative process in which physicians initially prescribe a standard dose or choice of medication and then adjust in response to observed toxic or therapeutic response. Having an a priori knowledge of a patient's drug response is clearly beneficial.

Well-meaning scientists now suggest that race may serve as a proxy for drug response. Numerous studies seem to indicate that patients of different racial and ethnic groups metabolize drugs differently due to differences in genetics.⁴ Other scientists suggest that the observed ra-

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1. See Jay S. Kaufman & Richard S. Cooper, *In Search of the Hypothesis*, 110 PUB. HEALTH REP. 662 (1995); Newton G. Osborne & Marvin D. Feit, *The Use of Race in Medical Research*, 267 JAMA 275 (1992); Robert S. Schwartz, *Racial Profiling in Medical Research*, 344 NEW ENG. J. MED. 1392 (2001).

2. See, e.g., SALLY L. SATEL, PC, M.D.: HOW POLITICAL CORRECTNESS IS CORRUPTING MEDICINE (2000). Current textbooks still say that knowing a patient's race helps the doctor make an accurate diagnosis.

3. Pharmacogenomics refers to the study of how inherited genetic variations affect an individual's ability to respond to a drug and the use of that knowledge in drug discovery and development. Race-specific drug therapy draws its rationale from the presumption that the frequencies of genetic variants influencing the efficacy of a drug are substantially different among races. Richard S. Cooper et al., *Race and Genomics*, 348 NEW ENG. J. MED. 1166 (2003).

4. See, e.g., Alastair J.J. Wood, *Racial Differences in the Response to Drugs—Pointers to Genetic Differences*, 344 NEW ENG. J. MED. 1393 (2001).

cial differences in drug metabolism are not sufficiently precise or significant to make them clinically useful in guiding the choice of drugs.⁵

Despite tremendous gaps in scientific knowledge, corporations are not waiting. The newest wave in pharmaceutical research and marketing is ethnic niche markets. BiDil, a heart drug for African Americans, is currently being tested on six hundred African Americans at over one hundred sites.⁶ The Food and Drug Administration (FDA) has stated that it will approve the marketing of BiDil to African Americans (and only to African Americans) if it confers a significant benefit in slowing down the development of congestive heart failure in study participants.⁷ Press reports have uncritically reported BiDil as a breakthrough in treating heart failure in African Americans.⁸ Other drug companies are racing to find other candidate ethnic drugs.

The current search for racial differences to increase corporate profit should give us pause. As Patricia King points out:

[A] significant aspect of the Tuskegee experiment's legacy is that in a racist society that incorporates beliefs about the inherent inferiority of African Americans in contrast with the superior status of whites, any attention to the question of differences that may exist is likely to be pursued in a manner that burdens rather than benefits African Americans.⁹

This Article suggests that African Americans are more likely to be harmed than helped by the commercialization of presumed genetic differences in drug response.

II. THE LIMITATIONS OF RACIAL AND ETHNIC DATA

Concepts of race and ethnicity have evolved over time but tend to be nebulous and poorly defined in scientific research.¹⁰ Typically, a study participant's race or ethnicity is assessed on a questionnaire with

5. See, e.g., Cooper et al., *supra* note 3, at 1166; Constance Holden, *Race and Medicine*, 302 *Sci.* 594 (2003).

6. Press Release, NitroMed, NitroMed Receives FDA Letter on BiDil NDA, a Treatment for Heart Failure in Blacks Patients (Mar. 8, 2001), available at <http://www.nitromed.com/new-sindex.html> (last visited Apr. 16, 2004).

7. *Id.*

8. See, e.g., Victoria Griffith, *FDA Backs Ethnically Targeted Drug*, *FIN. TIMES*, Mar. 9, 2001, at 13; Ellen Licking, *This Heart Drug Is Designed for African Americans*, *BUS. WK.*, Mar. 26, 2001, at 71.

9. Patricia A. King, *The Dangers of Difference*, 22 *HASTINGS CENTER REP.* 35 (1992).

10. Scarlett S. Lin & Jennifer L. Kelsey, *Use of Race and Ethnicity in Epidemiologic Research: Concepts, Methodological Issues, and Suggestions for Research*, 22 *EPIDEMIOLOGIC REV.* 187, 189 (2000). The most contemporary and evidence-based position on race is that "it has become clear that human populations are not unambiguous, clearly demarcated, biologically distinct groups." *Am. Anthropological Ass'n, American Anthropological Association Statement on "Race"* (May 17, 1998), at <http://www.aaanet.org/stmts/racepp.htm> (last visited Apr. 16, 2004).

one or two questions, such as “what race do you consider yourself?” or “where did your ancestors come from?” Self-reporting is often suggested as the optimal method of collecting racial and ethnic data.¹¹ However, questions have been raised about the validity and reliability of self-reported data.¹²

Frequently, race is assessed by the perceptions of an interviewer.¹³ Concerns about the validity and reliability of these assignments have also been raised.¹⁴ As a general matter, the race and ethnicity assignments are made according to the assumptions and biases of the observer. Nonbiological factors like skin color, hair texture, surname, language spoken, and neighborhood of residence are used to assign individuals to mutually exclusive categories from which scientific results are obtained.¹⁵

In the United States, slavery cemented the importance of skin color. The 1890 U.S. Census distinguished mulatto (half black and half white) from quadro (one-fourth black) from octoroon (one-eighth black). And there was the “one drop” rule. If you had one black ancestor, you were black. The 2000 Census allowed people for the first time to check one of six races including “some other race,” which produced sixty-three combinations. About 6.8 million individuals (2.4% of the U.S. population) consider themselves multiracial.¹⁶

The Census changes also resulted in 800,000 respondents who said that they were both black and white.¹⁷ Moreover, the Census Bureau estimates that 75% of those who currently identify themselves as

11. See, e.g., Jay S. Kaufman, *How Inconsistencies in Racial Classification Demystify the Race Construct in Public Health Statistics*, 10 EPIDEMIOLOGY 101 (1999).

12. In the clinical context, one’s self-report of race ethnicity is less important than the perception of the health care professional, whose perception frequently determines the diagnosis and treatment. Likewise, self-perception in clinical trials can either overstate or understate the effects of discrimination and racism, factors that confound the clinical response to treatment.

13. Judith B. Kaplan & Trude Bennett, *Use of Race and Ethnicity in Biomedical Publication*, 289 JAMA 2709, 2710 (2003).

14. *Id.* at 2710.

15. A 2002 study found a high rate of discord between race and ethnicity as self-perceived and as recorded in clinical records for a large number of Veteran Administration patients; 70% of those who selected American Indian or Alaska Native were inconsistently recorded in the database, as were 14.1% of those who chose Spanish, Hispanic, or Latino, 13% of those who chose Asian, 5% of those who chose black or African American, and 1.5% of those who chose white. Ulrike Boemer et al., *Self-Reported vs Administrative Race/Ethnicity Data and Study Results*, 92 AM. J. PUB. HEALTH 1471 (2002).

16. U.S. CENSUS BUREAU, U.S. DEP’T OF COMMERCE, CENSUS 2000 PROFILE: RACE, COMBINATIONS OF TWO RACES AND NOT HISPANIC OR LATINO: 2000, available at http://factfinder.census.gov/servlet/QTTable?_bm=y&-geo_id=01000US&-qr_name=DEC_2000_SF1_U_QTP4&-ds_name=DEC_2000_SF1_U&-_lang=EN&-_sse=ON (last visited Apr. 16, 2004).

17. *Id.*

black could also identify themselves as multiracial.¹⁸ Consider the situation of Elyse Frazier, one of the participants in the BiDil clinical trials. When asked if she would be interested in participating in the study for African Americans, she was puzzled. Frazier's mother is half black, half Cherokee Indian, while her father is half black, half Blackfoot Indian. She was informed that she was eligible for the study, despite her ambivalence.¹⁹

Racial and ethnic identification can be complex and contextual. The racial identification of American Indians illustrates how self-identification can change over time. The number of American Indians increased 255% in thirty years (552,000 in 1960 to 1,959,000 in 1990).²⁰ As Michael Omi points out, "[this] rate of increase is virtually impossible demographically, but much of the increase is explained by changes in racial self-identification. These changes are driven by shifts in attitudes toward American Indians, a romanticization of the past and tangible benefits tied to American Indian identification."²¹

Viewed as a static and typological concept, race is inherently unable to explain the complex and changing structure of human biological variation.²² As with the 2000 Census, individuals will fail to fit neatly into racial boxes. Moreover, as anthropologist Alan Goodman has noted, "the placement of an individual into a given box says little about his or her biology: the racial mean is meaningless."²³ Research efforts that rely on ill-defined and crude measures of race will by necessity provide compromised answers.

III. RACE AND PHARMACOGENOMICS

The fundamental question is whether racial differences in drug response do exist, and whether these differences can ever be useful for guiding treatment. As described below, the existing evidence suggests that race is a rather poor proxy for drug response.

First, race disappears when you look at the human genome. Studies of nuclear DNA sequences make clear that what is called race reflects just a few continuous traits determined by a tiny fraction of our

18. Lawrence Wright, *One Drop of Blood*, *NEW YORKER*, July 25, 1994, at 46, 48.

19. Ariana Eunjung Cha, *Race Plays Role in New Drug Trials: Treatment by Genetic Origin, Ethnicity Divides Medical Profession*, *WASH. POST*, July 28, 2003, at A1.

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

21. *Id.* at 15.

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

23. *Id.*

genes.²⁴ In other words, what people consider racial differences comprise only 0.01% of the body's estimated 35,000 genes. This tiny percentage gives no indication of variation at other parts of our genome.²⁵ Moreover, most geneticists concur that the bulk of genetic variation (90% to 95%) occurs within, not among, continental populations.²⁶ Thus, it is quite often the case that two persons from the same part of the world who look superficially alike are less related to each other genetically than two persons from other parts of the world who may look different.²⁷

Although it is obvious that many genetic diseases vary markedly among populations, those conditions are generally rare. Tay-Sachs disease, cystic fibrosis, and sickle cell trait, for example, are absent in many populations but present in others. For these conditions, racial groups are not the populations of interest. Persons of Jewish descent, not "whites," share a risk of Tay-Sachs disease; Americans of Northern European descent are more likely than other Americans to develop cystic fibrosis; and the sickle cell trait, thought to be an "African" trait, is found in many populations in which malaria was endemic, including the Mediterranean and Southern India.²⁸

Further, in any common disease such as heart failure or cancer, many genes are likely to be involved and each gene will have many

24. Svante Pääbo, *The Human Genome and Our View of Ourselves*, 291 SCI. 1219 (2001).

25. *Id.* at 1220.

26. Kelly Owens & Mary Clair King, *Genomic Views of Human History*, 286 SCI. 452 (1999). Genetic studies often use social labels such as "Chinese," "Nigerian," and "African American," that conceal a great deal of biological variation. Even a more specific ethnic label such as "Yoruba," which refers to a population of over ten million people distributed across a large multinational region of West Africa, can mask significant intragroup variation. See Richard Cooper et al., *Heritability of Angiotensin-Converting Enzyme and Angiotensinogen: A Comparison of US Blacks and Nigerians*, 35 HYPERTENSION 1141 (2000).

27. *Id.* Alan R. Templeton observes that human races are not distinct lineages, and this is not due to recent admixture; human races are not and never were pure. Instead, Templeton states "[h]uman evolution and population structure have been and are characterized by many locally differentiated populations coexisting at any time, but with sufficient genetic contact to make all of humanity a single lineage sharing a common evolutionary fate." Alan R. Templeton, *Human Races: A Genetic and Evolutionary Perspective*, 100 AM. ANTHROPOLOGIST 632-50 (1999).

28. See, e.g., Cooper et al., *supra* note 3, at 1167. See also Joseph L. Graves, *THE EMPEROR'S NEW CLOTHES: BIOLOGICAL THEORIES OF RACE AT THE MILLENNIUM* (2001). Several independent mutations in the (beta)-globin gene gave rise to different sickle hemoglobins in central and west Africa. These mutations spread through the population because they protected against malaria. They were dispersed in Greece, Saudi Arabia, Turkey, Iran, and elsewhere by migration and slavery. The frequency of the sickle cell trait (carrier status) among the African-American population is 8%. See Kangpu Xu et al., *First Unaffected Pregnancy Using Preimplantation Genetic Diagnosis for Sickle Cell Anemia*, 281 JAMA 1701 (1999). In the United States, nearly 10% of patients with various sickling disorders identify themselves as non-African Americans. See Darlene R. Powers, *Sickle Cell Disease in Non-Black Persons*, 271 JAMA 1885 (1994).

variants.²⁹ As Richard Cooper points out: “All the current data indicate that susceptibility alleles tend to be old, have moderate-to-small effects, and are shared among many populations.”³⁰

Drug response is also influenced by a host of factors, including overall health, lifestyle, support system, education, and socioeconomic status. All of these factors are difficult to control for and are likely to be affected, at least in the United States, by a person’s race.³¹

To confirm that it makes more biological sense to consider drug-metabolizing genes rather than skin color in drug choice, James Wilson, David Goldstein, and colleagues at University College London, compared twenty-three markers for such genes among 354 people representing eight classically defined races: white (Norwegian, Askenazi Jews, Armenians), black (Bantu, Ethiopian, and Afro-Caribbean), and Asian (Chinese and New Guinean).³² Using a technique called hierarchical cluster analysis, they found that the genetic markers form four natural groupings that do not correspond to any of the appearance-defined categories.³³ The results highlight what we already know: there exists substantial genetic diversity of individuals, which goes far beyond that which can be attributed to skin color or geographic origin.³⁴

Howard L. McCleod, a professor of medicine at the Washington School of Medicine in Missouri concludes: “There is no clear link between skin pigment and drug metabolism. Skin pigment is a lousy surrogate for drug metabolism status or most any aspect of human physiology.”³⁵

IV. RACIAL REPACKAGING—THE STORY OF BiDil

Even though race has not been shown to be a strong proxy for drug metabolism, a drug called BiDil is poised to become the first drug ever approved by the FDA to treat heart failure in African Americans, and only in African Americans. BiDil is a combination of two vasodilators, hydralazine and isosorbide dinitrate (H/I). Vasodilators dilate

29. Cooper et al., *supra* note 3, at 1168.

30. *Id.*

31. Editorial, *Genes, Drugs and Race*, 29 NATURE GENETICS 239, 240 (2001).

32. James F. Wilson et al., *Population Genetic Structure of Variable Drug Response*, 29 NATURE GENETICS 265 (2001).

33. *Id.* at 267.

34. In an editorial, the journal *Nature Genetics* advocated the use of the race-neutral approach proposed by Wilson and others because it moves us closer to the ultimate goal of “individualized therapy.” See *Genes, Drugs and Race*, *supra* note 31, at 240.

35. Howard L. McCleod, *Pharmacogenetics: More Than Skin Deep*, 29 NATURE GENETICS 247 (2001).

blood vessels and ease the strain put on the heart in pumping blood. BiDil is thought to have an added benefit of improving levels of nitric oxide in the blood, which is also thought to be of great benefit to individuals suffering from heart failure.³⁶

BiDil is an underused drug that has been around for decades; it certainly did not begin as an ethnic drug. This brief review of BiDil's origins demonstrates the centrality of commerce and the exploitation of racial categories in the repackaging of BiDil as a wonder drug for African Americans.³⁷

It all begins with the first Vasodilator Heart Failure Trial (V-HeFT I). In this medical trial, which lasted from 1980 to 1985, cardiologists found that the H/I (BiDil) combination appeared to have a beneficial impact in reducing mortality from heart disease.³⁸ The V-Heft I trial was soon followed by another trial, V-HeFT II, which lasted from 1986 to 1991. This trial compared the efficacy of the H/I (BiDil drugs) against the drug enalapril, an angiotensin-converting enzyme (ACE) inhibitor. The second trial found that enalapril had a more beneficial effect on mortality than the H/I combination.³⁹ The results of the second trial established ACE inhibitors as the front-line therapy for heart failure.⁴⁰ ACE inhibitors have not totally replaced H/I, however, because between 20% and 30% of congestive heart failure patients do not respond well to them. That is roughly 1.5 million patients annually (including members of all racial groups), and current guidelines still recommend the H/I combination for these patients.⁴¹

The V-HeFT investigators presented the H/I (BiDil drugs) as generally efficacious in the population at large, without regard to race. In 1987, Dr. Jay Cohn, one of the principal investigators in the V-HeFT studies applied for and received a patent on the H/I drugs.⁴² In the patent description, Cohn made no mention of race, asserting that H/I

36. Press Release, NitroMed, *supra* note 6.

37. For an excellent and comprehensive review of BiDil, see Jonathan Kahn, *How a Drug Becomes "Ethnic": Law, Commerce, and the Production of Racial Categories in Medicine*, 4 YALE J. HEALTH POL. L. & ETHICS 101 (2004).

38. 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 (1986).

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

40. *Id.*

41. 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/downloadable/heart/1013201138293HFGuidelineFinal.pdf> (last visited Apr. 14, 2004); C. Packer, *Consensus Recommendations for the Management of Chronic Heart Failure*, 83 AM. J. CARDIOLOGY 1A, 25A (1999).

42. U.S. Patent No. 4,868,179 (issued Sept. 19, 1989).

substantially and significantly reduces the incidence of mortality in congestive heart patients. Clearly, he believed the BiDil drugs would be used to treat all people suffering from heart failure.⁴³

The H/I drugs are generic drugs. Cohn and others combined them into a single pill for easy administration. By 1994, tests were conducted to make sure that the pill form was just as effective as the administration of the drugs separately. They were. Cohn and Medco, which had acquired the intellectual property rights from Cohn, were now ready to approach the FDA for the approval of BiDil for use in the general population.⁴⁴

In 1996, Medco submitted a new drug application (NDA) to the FDA. Jay Cohn optimistically asserted at the time that the BiDil formulation represented a very convenient dosage that, once approved by the FDA, would lead to an increased usage of this therapy in the general population.⁴⁵ An industry report estimated a potential market of up to sixty million dollars in annual sales for BiDil.⁴⁶

In an unanticipated move, however, the FDA voted nine to three against approving BiDil, even though extensive findings in peer reviewed journals supported Cohn's claim that the H/I combination substantially and significantly reduced the incidence of mortality in congestive heart failure patients.⁴⁷ The agency concluded that while the drug had clinical significance, it failed to meet the biostatistical criteria of probability and efficacy sufficient for the FDA to grant a NDA. In particular, the FDA noted that data from the V-Heft studies contained too many variables specified as endpoints for them to interpret the data with biostatistical certainty.⁴⁸ The next day, Medco's stock dropped by 25%.⁴⁹

To salvage the drug, the BiDil promoters repackaged it along racial lines. Jay Cohn went back one more time to the V-HeFT data, this time to analyze the differential effects of BiDil and enalapril by race.⁵⁰

43. See Kahn, *supra* note 37, at 113.

44. *Id.*

45. *Id.* at 114.

46. *Id.* at 113-14.

47. *Id.* at 114-15. 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. CTR. FOR DRUG EVALUATION & RES., FOOD & DRUG ADMIN., CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMM'N, 80TH MEETING (Feb. 27, 1997), available at <http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3264t2.pdf> (last visited Apr. 16, 2004).

48. See Kahn, *supra* note 37, at 114.

49. *Id.*

50. Although the V-HeFT investigators had been tracking data by race from the outset, they had never conceptualized BiDil as a race specific therapy. As pointed out by Professor Kahn,

In 1999, Cohn and others published a paper asserting that the H/I combinations worked better in blacks than ACE inhibitors.⁵¹ Specially, they concluded:

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 in the white population . . . [t]he 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*.⁵²

That same year Daniel Dries coauthored a study in the prestigious *New England Journal of Medicine* suggesting that racial differences exist in the natural progression of congestive heart failure.⁵³ The implicit conclusion is that heart disease is a *different* disease in blacks and whites and, therefore, it must be treated with different therapies.⁵⁴ This theory of biological difference is consistent with Jay Cohn's claim that the black/white disparity in death rates from heart failure is partly attributable to "a pathophysiology found in black patients that may involve Nitric Oxide (NO) insufficiency arising from either reduced NO production, enhanced NO inactivation or both."⁵⁵

In 1999, NitroMed Inc., a Boston area biotech firm specializing in the development and commercialization of nitric oxide enhanced medicines, acquired the intellectual property rights to BiDil.⁵⁶ NitroMed announced its plans to amend the NDA to seek approval for the use of BiDil to treat and prevent mortality associated with heart failure in African-American patients.⁵⁷ After a meeting in Washing-

Jay Cohn chose quite deliberately not to go into the racial data in his FDA presentation. *Id.* at 116.

51. 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).

52. *Id.* at 182.

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

54. The idea that blacks and whites have a different course and progression of disease is not new. Indeed, the scientific basis behind the infamous Tuskegee Syphilis Experiment was the unproven theory that syphilis affected blacks and whites differently. Numerous black men in Macon County, Alabama needlessly died and suffered as the United States Public Health Service subjected them to unethical experiments without their consent. Nothing of scientific importance was gained from the study. See, e.g., JAMES JONES, *BAD BLOOD* (1993).

55. Press Release, NitroMed, NitroMed Initiates Confirmatory BiDil Trial in African American Heart Failure Patients (Mar. 17, 2001), available at <http://www.nitromed.com/newsindex.html> (last visited Apr. 16, 2004).

56. Press Release, NitroMed, NitroMed Acquires BiDil New Drug Application for Treatment of Congestive Heart Failure (Sept. 10, 1999), available at <http://www.nitromed.com/newsindex.html> (last visited Apr. 16, 2004).

57. *Id.*

ton, the FDA approved the use of BiDil as a drug to treat heart failure in African Americans, pending the successful results of a confirmatory trial.⁵⁸ That trial, A-HeFT, the African American Heart Failure Trial, is currently underway.⁵⁹

The FDA's tentative approval represents a significant expansion of the potential BiDil market. NitroMed currently estimates that approximately 750,000 African Americans suffer from heart disease.⁶⁰ The implication is that all African Americans suffering from heart disease should be taking BiDil (because it is a different disease), not just those who cannot tolerate or do not respond well to ACE inhibitors. Without doubt, the huge commercial implications of the first ethnic niche market allowed NitroMed to raise over \$31.4 million from several private venture capital firms to support the confirmatory trials.⁶¹ Recently, pharmaceutical giant Merck & Co., Inc. formed a multi-year research collaboration with NitroMed, even though BiDil is the company's most advanced product to date.⁶²

V. A NEW THERAPY OR A NEW MARKET FOR AN UNDERUSED DRUG?

BiDil started as a drug for use in the general population but has emerged as a drug for use only in African Americans. A fundamental question is whether significant scientific evidence demonstrates that all African Americans with heart problems should take this drug, or are NitroMed's claims merely a scheme to expand and exploit a potentially lucrative market. As discussed below, substantial evidence raises serious questions about the underpinnings of NitroMed's claims.

First, the study authored by Peter Carson along with Jay Cohn, claiming that blacks respond better to H/I than to ACE inhibitors, retrospectively analyzed data from V-HeFT I and II.⁶³ It was not prospectively designed to study racial differences in response to treatment, rather, an existing and rather old data set was reanalyzed.

58. Press Release, NitroMed, *supra* note 6.

59. For a description of A-HeFT, see Clyde W. Yancy, *Does Race Matter in Heart Failure?*, 146 AM. HEART J. 203 (2003).

60. Kahn, *supra* note 37, at 107.

61. Press Release, NitroMed, NitroMed Completes \$31.4 Million in Private Financing (June 14, 2001), available at <http://www.nitromed.com/newsindex.html> (last visited Apr. 16, 2004).

62. Press Release, Rho Ventures, NitroMed and Merck Form Strategic Collaboration: Companies Enter Multi-Year Agreement to Research and Develop Nitric Oxide Based Medicines (Jan. 7, 2003), available at http://www.rho.com/rho_ventures/media_center/investment_archive/releases/nitromed_010703.html (last visited Apr. 16, 2004).

63. See Carson et al., *supra* note 51, at 178.

There are well documented statistical problems involving randomization and stratification by race in such retrospective studies.⁶⁴

Second, black participants had higher levels of comorbid factors such as diabetes and hypertension.⁶⁵ Essentially, the white and black populations were not the same. Few doctors would use monotherapy (a single drug) for cardiovascular disease in patients with concomitant diabetes and hypertension. Therefore, this study may simply confirm what we already know: use of a single ACE inhibitor at a standard dose is not effective for patients who also have diabetes and hypertension, but is effective for patients without these conditions.

Third, the study purports to consider relevant nongenetic environmental influences on the development and progression of heart failure, and includes two such factors—education and “financial distress (yes vs. no) during the past twelve months.”⁶⁶ While education and experience of financial distress are relevant factors to consider in examining nongenetic environmental influences, the implicit understanding is that they are exhaustive of all such relevant factors.

Vast medical and public health literature shows that a host of deleterious conditions accompany black status in the United States, including differential exposures to environmental toxins, discrimination, residential segregation, and differential political power, both in terms of individual level of control and the allocation of resources.⁶⁷ Indeed, a Harvard study shows that the stress of experiencing racism raises blood pressure.⁶⁸ It is now well established that physiological

64. See, e.g., M. Packer et al., *The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure*, 334 NEW ENG. J. MED 1349 (1996).

65. Carson et al., *supra* note 51, at 183.

66. Dries et al., *supra* note 53, at 612.

67. See Nancy Krieger et al., *Racism, Sexism, and Social Class: Implications for Studies of Health, Disease, and Well-Being*, 9 AM J. PREVENTIVE MED. 82 (Supp. 1993); Thomas A. LaVeist, *The Political Empowerment and Health Status of African Americans: Mapping a New Territory*, 97 AM. J. SOC. 1080 (1992) (finding a statistically significant inverse association between black political power and black post neonatal mortality); Theodore J. Joyce et al., *An Assessment of the Benefits of Air Pollution Control: The Case of Infant Health*, 25 J. URB. ECON. 32 (1989) (finding a link between environmental toxins and black infant mortality and morbidity).

68. Nancy Krieger & Stephen Sidney, *Racial Discrimination and Blood Pressure: The CARDIA Study of Young Black and White Adults*, 86 PUB. HEALTH REP. 1370 (1996). Krieger and coauthor Stephen Sidney asked 4,086 blacks and whites about their experiences with racial discrimination. Black/white differences in blood pressure were substantially reduced by taking into account reported experiences of racial discrimination and unfair treatment. Other studies lend support to Krieger's view that internalized responses to racial discrimination may be associated with elevated blood pressure. See, e.g., Veita L. Sanders Thompson, *Perceived Experiences of Racism as Stressful Life Events*, 32 COMMUNITY MENTAL HEALTH J. 223 (1996); Chery A. Armstead et al., *Relationship of Racial Stressors to Blood Pressure Responses and Anger Expression in Black College Students*, 8 HEALTH PSYCHOL. 541 (1989).

processes respond to psychosocial stress.⁶⁹ Therefore, the unmeasured variation in environmental exposures could account for the differential response in hospitalization and survival, not differences in drug metabolism.

Fourth, as fortune would have it, one of the strongest critiques has come from one of the coauthors of the original study, Dr. Daniel Dries. In 2002, Dries took issue with the earlier *New England Journal of Medicine* piece arguing that the ACE inhibitor, enalapril, worked equally well in blacks and whites:

Despite recent concerns that angiotensin-converting enzyme (ACE) inhibitors may be less efficacious in black patients with [heart failure], the present study demonstrates that enalapril significantly reduced the risk of development of [heart failure] in both blacks and whites The consistency of results in black and white subjects strengthens the argument that ACE inhibitor-therapy should continue to be used in black patients with [heart failure].⁷⁰

These findings are consistent with the recent African American Study of Kidney Disease and Hypertension that demonstrated a benefit of ACE inhibitor therapy in patients with renal disease.⁷¹

Finally, NitroMed has relied heavily on the claim that African Americans have twice the risk of dying from heart failure than whites.⁷² If this is true, then it is highly plausible that the difference is due to genetic rather than environmental factors. This two-to-one disparity has been floating around uncontested in the scientific literature for decades. Dr. Jonathan Kahn of the University of Minnesota has demonstrated conclusively that the NitroMed claim about the scope of black and white differences is simply untrue.⁷³ Dr. Kahn traced the citation sources back nearly two decades, and found that the difference between blacks and whites is actually 1.2 to 1.⁷⁴ While there is a difference, it is far less than the two-to-one ratio that would warrant

69. See, e.g., Bruce S. McEwen, *Protective and Damaging Effects of Stress Mediators*, 338 *NEW ENG. J. MED.* 171 (1998).

70. Daniel 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. C. CARDIOLOGY* 311, 314 (2002).

71. L.Y. Agoda, *Effect of Ramipril vs Amlodipine on Renal Outcomes in Hypertensive Nephrosclerosis: A Randomized Controlled Trial*, 285 *JAMA* 2719 (2001). Other studies have found the evidence too weak or inconclusive regarding the lack of ACE inhibitor benefit in blacks. See, e.g., J.S. Kalus et al., *Role of Race in Pharmacotherapy of Heart Failure*, 36 *ANNALS OF PHARMACOTHERAPY* 471 (2002); K.C. Ferdinand, *Contemporary Treatment of Heart Failure: Is There Adequate Evidence To Support a Unique Strategy for African Americans? Con Position*, 4 *CURRENT HYPERTENSION REP.* 311 (2002).

72. Press Release, NitroMed, *supra* note 6.

73. Kahn, *supra* note 37, at 121-22.

74. *Id.*

special trials for blacks. Thus, “substantial scaffolding of the BiDil clinical trials is based upon incorrect statistical data on racial disparities.”⁷⁵

VI. RACE, DRUGS, AND COMMERCE—A TROUBLING COMBINATION

Some doctors have already decided to no longer treat black patients suffering from heart failure with ACE inhibitors.⁷⁶ This highlights the potential harm to minority patients that will arise from the efforts to market drugs along racial lines. The best or front-line therapy will likely be replaced by a therapy that its promoters claim is more effective.

In the case of ACE inhibitors, the Joint National Committee on Prevention, Detection, Evaluation of High Blood Pressure (JNC VI) concludes that “differences in antihypertensive efficacy between ACE inhibitors and other agents can usually be overcome by higher doses” or “dietary sodium reduction and diuretics.”⁷⁷ As mentioned above, a primary reason that blacks did not respond as well to ACE inhibitors in Cohn’s study was because they were sicker and, therefore, needed a higher dosage. This strongly suggests that there is no clinical need for BiDil.

Substituting BiDil for ACE inhibitors will likely lead to substandard care. Recent findings show that ACE inhibitors have a significant protective effect against stroke, diabetes, heart failure, and end-stage kidney disease, independent of their blood pressure lowering properties.⁷⁸ The National Institutes of Health (NIH) stopped an ongoing clinical trial comparing calcium blockers to ACE inhibitors after it became clear that the ACE inhibitor significantly reduced mortality and the need for dialysis.⁷⁹ NitroMed has made no claim that BiDil can offer protection against organ damage or offer any secondary benefits.

75. Troy Duster, *Medicine and People of Color: Unlikely Mix—Race, Biology and Drugs*, S.F. CHRON., Mar. 17, 2003, at B7.

76. *Genes, Drugs and Race*, *supra* note 31, at 239.

77. Joint Nat’l Comm. on Prevention, Detection, Evaluation & Treatment of High Blood Pressure, *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure*, 157 ARCHIVES INTERNAL MED. 2413 (1997). The committee concluded that “ACE inhibition should be considered in all African-American patients with hypertension, unless contraindicated, and not dismissed simply because of race or ethnicity.” Kenneth A. Jamerson, *Rationale for Angiotensin II Receptor Blockers in Patients with Low-Renin Hypertension*, 36 AM. J. KIDNEY DISEASES 25 (2000 & Supp. 2000).

78. *See, e.g.*, Jamerson, *supra* note 77.

79. *NIH Modifies Trial as ACE Inhibitors Slow Renal Disease in African Americans*, 56 GERIATRICS, Jan. 2001, at 19.

Indeed, no one knows what the long-term negative effects of the drug will be.

African Americans are not a distinct genetic group and therefore do not require a different and inferior drug for heart failure. Richard Cooper, chairman of the preventive medicine and epidemiology department at Loyola University puts it this way: "I think it's bizarre, marketing a drug to people who are black. The scientific evidence supporting the notion that there's a differential response in race is weak or nonexistent."⁸⁰

Other BiDils are sure to surface. Medical researchers are mining through decades of old clinical trials data to find an overlooked differential racial response to drugs.⁸¹ American drug giant Pfizer, Inc. is particularly interested in hypertension-related genes in blacks.⁸²

The combination of race, drugs, and corporate profits is eerie. Fraud and genetic hucksterism are primary concerns.⁸³ Already, one pharmaceutical company has misrepresented its data to help a plunging stock. On February 24, 2003, the biotech company VaxGen, Inc. publicly announced the results of the first ever phase III efficacy trial of an HIV vaccine candidate.⁸⁴ The company reported the bad news that there was little difference in the HIV infection rate between the placebo group versus the participants who actually received the shots.⁸⁵ VaxGen shares sank almost 50%.⁸⁶

When VaxGen broke the data down into racial groups, the company proudly announced that the vaccine worked in blacks, causing infection rates to drop 78%.⁸⁷ According to a market analyst, if the vaccine were approved only to treat blacks in the United States, the potential market could be 7.6 million people and, assuming fifty dollars per dose, that could generate revenue of approximately \$2.3 billion over the next several years.⁸⁸ VaxGen CEO Lance Gordon

80. Cha, *supra* note 19.

81. Holden, *supra* note 5, at 594.

82. *Id.* at 596.

83. The conjecture that possessing a financial interest increases research bias is empirically testable. At least one study has demonstrated that clinical trials sponsored by pharmaceutical companies were more likely to favor new drugs, an outcome beneficial to the sponsoring companies, than studies without corporate support. See Sheldon Krimsky, *The Profit of Scientific Discovery and Its Normative Implications*, 75 CHI.-KENT L. REV. 15 (1999).

84. Press Release, VaxGen, VaxGen Announces Initial Results of Phase III AIDS Vaccine Trial (Feb. 24, 2003), available at <http://www.vaxgen.com/pressroom/index.html> (last visited Apr. 16, 2004).

85. *Id.*

86. See Bernadette Tansey, *Investors Drop VaxGen Stock: Brisbane Firm To Continue Work on AIDS Vaccine*, S.F. CHRON., Feb. 25, 2003, at B1.

87. Press Release, VaxGen, *supra* note 84.

88. Tansey, *supra* note 86.

described the data on blacks as a “marvelous result” and said the company would still push for FDA approval of the vaccine for use with high risk groups or populations in which the vaccine might be effective.⁸⁹

Several AIDS advocacy groups demanded VaxGen’s data and issued statements outlining their concerns that the racial numbers were wildly overstated, potentially as a deliberate face-saving and stock price-saving strategy.⁹⁰ VaxGen stood by its numbers.⁹¹ Prompted by advocacy groups, the NIH stepped in to resolve the issue.⁹² After reviewing the data, the NIH reported that the finding of effectiveness in blacks was “likely spurious.”⁹³

Most, if not all, announcements of differential responses will likely be spurious. While studies have identified a difference in the frequency of drug metabolizing polymorphisms among blacks, these studies are usually based on small sample sizes that make it impossible to extrapolate the results to all African Americans. For instance, a recent study claims that blacks metabolize nicotine at a slower rate than whites.⁹⁴ The study included only fifty-seven African Americans; they were substantially more likely to smoke menthol brands than whites.⁹⁵ The differences in metabolism were not impressive; there was only an 8% difference in the variable of interest.⁹⁶ The explicit message, however, is that all blacks metabolize nicotine slowly.

VII. CONCLUDING THOUGHTS

The promise of pharmacogenomics is a future in which all medicine is tailored to the individual. Drugs will be selected based not only on the person’s disease, but also on the likelihood to respond to the drug and the person’s chances of experiencing side effects. But selling drugs is about markets. As Troy Duster points out, “[t]hese markets are not about individual designer drugs, but about groups and popula-

89. *AIDS Group: Vaccine Claims Misleading* (Feb. 28, 2003), at <http://www.vaccinationnews.com/DailyNews/2003/February/AIDSGroup26.htm> (last visited Apr. 23, 2004).

90. *Id.*

91. Press Release, VaxGen, VaxGen Issues Statement on Clinical Trial Data Analysis (Feb. 27, 2003), available at <http://www.vaxgen.com/pressroom/index.html> (last visited Apr. 16, 2004).

92. See Richard Jefferys, *The Diabolic Science: VaxGen’s Claims of Vaccine Efficacy Evanesce in Autumn’s Last Light*, 10 TAGLINE 8 (2003), available at <http://thebody.com/tag/oct03/vaccine.html> (last visited Apr. 16, 2004).

93. *Id.*

94. Neal L. Benowitz et al., *Ethnic Differences in N-Glucuronidation of Nicotine and Cotinine*, 291 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 1196 (1999).

95. *Id.* at 1197. Blacks cleared nicotine through the cotinine pathway at 14.8 ml/min/kg compared to 17.7 ml/min/kg for whites. *Id.*

96. *Id.* at 1198.

tion aggregates that become the target market."⁹⁷ Racial and ethnic groups comprise large potential markets, and drug promoters are financially motivated to search for racial differences in drug response.

Scientific objectivity can often be clouded by financial conflicts of interest. In the mid-1980s, researchers found that clinical trials sponsored by pharmaceutical companies were much more likely to favor new drugs (an outcome beneficial to sponsoring companies) than studies not supported by companies.⁹⁸ Xigris is one example of how selective use of data can show a positive effect of a drug when one might not exist. Eli Lilly spent millions of dollars on this anti-sepsis drug; there is no effective treatment for sepsis and the approval of this drug would carry with it generous financial rewards. Halfway through the study, however, Eli Lilly found no significant difference between the placebo group and the group receiving the drug. After the researchers excluded several categories of people (and the corresponding data points), a significant positive result appeared.⁹⁹ This salient point was not mentioned in the initial publication of the results but surfaced during a meeting of an FDA approval committee that chastised the study sponsors for concealing this fact.¹⁰⁰

Our nation has a long and troubled history of mistreatment and oppression of racial groups in medicine based on incorrect theories and misunderstandings about biological difference.¹⁰¹ The results of clinical trials on drug effectiveness are complex, hard to interpret, and, therefore, prone to statistical sleight of hand. Our society must be vigilant in insuring that pharmaceutical companies will not reap large financial benefits from ethnic drugs at the expense of the health of racial and ethnic minorities.

97. Duster, *supra* note 75.

98. See Krinsky, *supra* note 83, at 34.

99. *Shares of Lilly Drop After Panel's Split on Sepsis Drug*, N.Y. TIMES, Oct. 18, 2001, at C4.

100. In a split vote, the FDA Advisory panel was unable to recommend approval for Xigris based on concerns that patient entry criteria changed halfway through the trial, which may have exaggerated Xigris's efficacy results. Xigris gained FDA approval in November 2001. See *Eli Lilly's Xigris: Struggling to Overcome its Problems in the Sepsis Market*, at http://www.bioportfolio.com/news/datamonitor_29.htm (lasted visited on Apr. 16, 2004).

101. See Rene Bowser, *Racial Profiling in Healthcare: An Institutional Analysis of Medical Treatment Disparities*, 7 MICH. J. RACE & L. 79 (2001).