

## HEALTHCARE DISPARITIES

In our July meeting we had a great discussion about the socio-economic problems associated with healthcare disparities. For our next meeting we will ask the question about the validity of “race based medicine.” Central to this discussion will be the recent controversy surrounding the use of BiDil to lower blood pressure in African Americans (1-paper, 2-abstract, 3-abstract). We will next ask questions about whether genetic differences between races that can or should be exploited to relieve human suffering (abstracts 4 & 5). Finally we will look at one study that purports to detect difference in clinical tests between races and ask whether or not this is a valid line of research (abstract 6).

Please read the short paper by Powe, the Washington Post article and the accompanying abstracts and come prepared for good food and a lively discussion on July 26 in 243 Wolf Hall.

*1. Prescribing BiDil: is it black and white? Susanne B. Haga, PHD, Geoffrey S. Ginsburg, MD, PHD. J Am Coll Cardiol 48:12-4 (July 2006)*

The approval of BiDil as an adjunct treatment in self-identified blacks with heart failure raises questions regarding the underlying etiology of drug response in this target population and the ability to accurately identify patients who are most likely to benefit. Preliminary data have indicated that differences in nitric oxide synthesis between groups may account for differences in response to BiDil and genetic studies have begun to elucidate the mechanism of these differences. Until more accurate selection criteria are developed to identify patients who are most likely to benefit, both clinicians and the general public will need to consider the unique issues raised by BiDil.

*2. Genetic influences on health: does race matter? JAMA. 2006 Jan 25;295(4):384-5; author reply 385-6.*

Race is frequently used by clinicians and biomedical researchers to make inferences about an individual's ancestry and to predict whether an individual carries specific genetic risk factors that influence health. The extent to which race is useful for making such predictions depends on how well race corresponds with genetic inferences of ancestry, how frequently common diseases in different racial groups are influenced by the same vs different gene variants, and whether such variants have the same effects in different racial groups. New studies of human genetic variation show that while genetic ancestry is highly correlated with geographic ancestry, its correlation with race is modest. Therefore, while data on the correspondence of race, ancestry, and health-related traits are still limited, particularly in minority populations, geographic ancestry and explicit genetic information are alternatives to race that appear to be more accurate predictors of genetic risk factors that influence health. Making accurate ancestry inferences is crucial because common diseases and drug responses are sometimes influenced by gene variants that vary in frequency or differ altogether among racial groups. Thus, operationalizing alternatives to race for clinicians will be an important step toward providing more personalized health care.

*3. Prescription for Change: Why Race-Based Medicine is a Bad Idea. Adriane Fugh-Berman, M.D. Newsletter #89–December 2005/January 2006*

The FDA recently approved BiDil for treatment of congestive heart failure in African-Americans, making it the first therapy approved for a specific racial group. There are a lot of things wrong with this decision, which has implications beyond racial profiling in medicine.

First, a bit of background. BilDil is a combination of two older, generic drugs: hydralazine, a high blood pressure medicine; and isosorbide nitrate, which relaxes arteries' muscular walls, allowing more blood flow through arteries narrowed by heart disease. Until the 1990s, the combination was commonly used to treat congestive heart failure (heart muscle weakness that can follow a heart attack). A trial published in 1986, the Vasodilator Heart Failure Trial (VHeFT1), found hydral-azine/isosorbide nitrate (H/IN) therapy was barely superior to placebo; another drug called prazosin, however, was no better than placebo. In 1991, another trial (VHeFT2) compared H/IN to enalapril, a drug in the class called ACE inhibitors. Enalapril was superior to the isosorbide nitrate/hydralazine combination for prolonging survival, and ACE inhibitors subsequently became the primary treatment for heart failure. Some patients, however, cannot tolerate ACE inhibitors and are treated with H/IN.

One of the VHeFT investigators, Dr. Jay Cohn, patented a fixed combination of H/IN, now known as BilDil (the individual drugs that comprise BilDil were available generically, but it's possible to patent a combination of older drugs in a new dosage form). A new drug application was filed with the FDA, but the FDA rejected BilDil as a treatment for congestive heart failure in 1997, because the application depended on the results from VHeFT 1, a decade-old trial with problematic outcomes. Drug patents are only good for 20 years after being filed, so rejection for drug approval, even if the drug is eventually approved, cuts years off its profit potential. The company that sponsored BilDil gave up on it. NitroMed, a biotechnology company, obtained intellectual property rights for BilDil from Cohn, and got a new patent specifically on the use of BilDil in African-Americans. Getting a new patent reset the patent clock.

Commentary in the *New England Journal of Medicine* notes that: 'This patent, the first ever granted to a preexisting drug for a new, race-specific use, pushes back potential market entry by generic sellers of the fixed-dose combination from 2007 to 2020. Less than a month later, NitroMed went public, raising \$66 million (even though isosorbide dinitrate and hydral-azine are available separately in generic formulations, making it possible to closely approximate NitroMed's combination at a cost of about 44 cents per dose).'

BilDil was repackaged as an ethnic treatment based on a reanalysis of VHeFT2, in which 27% of the original group was African-American. Analyzing the subgroup separately indicated that some African-Americans did better on BilDil than enalapril. A new trial, the African-American Heart Failure Trial (A-HeFT), published in 2004, found that adding I/HN to standard therapy in African-American patients with heart failure substantially reduced deaths, reduced hospitalizations, and improved quality of life. It is not known whether adding I/HN to standard therapy would improve outcomes in other populations, as this hasn't been tested. In 2005, BilDil was approved for the treatment of CHF in African-Americans. NitroMed plans to charge \$1.80 a pill, about four times as much as taking the generic pills. Perhaps to deflect criticism, NitroMed will offer a discount program for those who can't afford it.

This approval creates a bad precedent, and does not improve patient care. There is no biological basis for race. 'Race', whether self-identified or inferred by skin color, is only the roughest of surrogate measures for genetic differences. Some diseases and conditions are more common in one or another ethnic group, but there are no diseases or conditions that always include (or

exclude) all members of any ethnic group. There is more variability in genetic differences within any population than there is among racial/ethnic populations.

Identification of a therapy as a African-American drug may cause doctors to automatically prescribe the drug to African-American patients—and withhold it from other patients—without taking into account the patient’s individual needs and responses. The only trial to date designed to look at outcomes in African-American patients found that BilDil was beneficial as an added treatment in those who were already on standard therapy for congestive heart failure.

Although it is often stated that ACE inhibitors don’t work as well in African Americans, a meta-analysis prepared for the Agency for Health Care Research and Quality examined the three placebo-controlled trials of ACE inhibitors stratified by race and concluded there was no mortality difference in the use of ACE inhibitors between African-Americans and Caucasians. There is no reliable evidence that BilDil as a single therapy is better than an ACE inhibitor in African-American patients, but promotion of BilDil may cause docs to prescribe BilDil alone.

BilDil’s approval is bad precedent. We can now expect drug companies scrambling to analyze both old and new clinical trials for subgroup benefit that can give new life to failed drugs. It has been said that if you torture data enough, they will tell you anything. Can it be long until a drug is approved for use in nonsmoking female poodle-owners between the ages of 27 and 33? - Adriane Fugh-Berman, M.D., is an associate professor in the department of physiology at Georgetown University School of Medicine, and a former chair of the National Women’s

#### *4. A common Fanconi anemia mutation in black populations of sub-Saharan Africa. Blood 105:3542-4 (2005)*

Fanconi anemia (FA) is a genetically heterogeneous chromosomal instability syndrome associated with multiple congenital abnormalities, aplastic anemia, and cancer. We report that a deletion mutation in the FANCG gene (c.637\_643delTACCGCC) was present in 82% of FA patients in the black populations of Southern Africa. These patients originated from South Africa, Swaziland, Mozambique, and Malawi. The mutation was found on the same haplotype and was present in 1% of controls from the black South African population. These data indicate that the birth incidence of FA in this population is higher than 1 in 40 000, which is much higher than previously supposed, and suggest that the FANCG deletion is an ancient founder mutation in Bantu-speaking populations of sub-Saharan Africa. Diagnostic screening is now possible by means of a simple DNA test.

#### *5. Genetic epidemiology of health disparities in allergy and clinical immunology. J Allergy Clin Immunol. 117:243-54 (2006).*

The striking racial and ethnic disparities in disease prevalence for common disorders, such as allergic asthma, cannot be explained entirely by environmental, social, cultural, or economic factors, and genetic factors should not be ignored. Unfortunately, genetic studies in underserved minorities are hampered by disagreements over the biologic construct of race and logistic issues, including admixture of different races and ethnicities. Current observations suggest that the frequency of high-risk variants in candidate genes can differ between African Americans, Puerto Ricans, and Mexican Americans, and this might contribute to the differences in disease prevalence. Maintenance of certain allelic variants in the population over time might reflect

selective pressures in previous generations. For example, significant associations between markers in certain candidate genes (eg, STAT6, ADRB2, and IFNGR1) for traits such as high total IgE levels observed in resistance to extracellular parasitic disease in one population and atopic asthma in another supports the common disease/common variant model for disease. Herein is a discussion of how genetic variants might explain, at least in part, the marked disparities observed in risk to allergic asthma.

*6. Racial variation in prostate specific antigen in a large cohort of men without prostate cancer. J La State Med Soc. 2001 Apr;153(4):184-9.*

Several studies have reported racial variation in serum prostate specific antigen (PSA) levels. Many of these studies, however, have included a significant number of men without a documented digital rectal examination (DRE) result or without prostate biopsies if abnormalities in PSA or DRE were detected. Thus, it is not clear that men with prostate cancer have been excluded in these analyses. In this report, data from 9,162 men (3,786 African-American men and 5,376 white men) are reviewed. All men had both serum PSA and DRE testing. Every man in this study had either a documented normal DRE and PSA (< 4 ng/mL) (3,422 African-American men and 4,795 white men) or a negative prostate biopsy (364 African-American men and 581 white men). Data were analyzed in age-matched decades. African-American men and white men had no difference in serum PSA levels between 30 and 39 years of age. At 40-49, 50-59, 60-69 and 70-79 years of age, African-American men had a statistically higher serum PSA level than white men. From these data, we conclude that racial variation in serum PSA is present in all decades above 40 years of age. Our data are unique in that this cohort included a substantial number of men between 30 and 39 years of age. In this group of young men, no racial differences in serum PSA were detected. These studies indicate, for the first time, that the onset of racial variation in PSA occurs after the fourth decade of life.