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BiDil: Personalized Medicine or Market Exclusivity?

"I see the ethical issues intertwined with the scientific issues. ... race makes the assumption that everyone in a group is the same. Based on what we know about human genome variation, a drug will not work for everyone in a particular group and there are people in other groups for whom it might work."

– Charmaine Royal, Ph.D., director of the GenEthics Unit,
National Human Genome Center

Congestive heart failure (CHF), or heart failure, is defined as a condition in which the heart fails to pump enough blood to the body's other organs. It can result from narrowed arteries that supply blood to the heart muscle, formation of scar tissue from myocardial infarctions, high blood pressure, cardiomyopathy – a condition where the heart muscle becomes inflamed, congenital heart defects, and infection of the heart valves ("Congestive Heart Failure"). In 2004, heart failure was the number one cause of death in the nation with a reported 5.2 million cases. In that same year, there were 7.9 million heart attacks and 550,000 new cases. In 2006, the total cost of treating heart failure was at an astounding \$29.6 billion ("National Healthcare Disparities Report"). This disease currently affects 4.8 million Americans, and has 400,000 new cases annually ("Congestive Heart Failure"). Although heart failure presents a substantial "public health and clinical management problem" for the general population, it presents an even worse problem for African Americans - affecting them at a disproportionately higher rate. According to American Heart Journal, there is a 33% higher rate of heart failure hospitalization in African American men than in white men and a 50% higher rate for African American women than for

white women ("Congestive Heart Failure in California"). These astounding numbers have promoted pharmacies and medical companies around the nation to search for a treatment.

Creation, Invention, Treatment

The 1980s saw the beginning of a revolution in the invention of treatments. The Veterans Administration, now known as the Department of Veterans Affairs, administered two cooperative studies. The first study, the Vasodilator Heart Failure Trail (V-HeFT I) found that a combination of two generic vasodilators – hydralazine hydrochloride and isosorbide dinitrate(H/I) – seemed to have a beneficial effect in treating heart failure. The second study – Vasodilator Heart Failure Trail (V-HeFT II) – occurred in the late 1980s and discovered that an angiotensin-converting enzyme (ACE) inhibitor was more effective in treating heart failure. As a result, ACE inhibitors became the primary means for treating heart failure (Pamela and Kahn, 2005). The current recommended hospital care for heart failure for the general population includes evaluation of the left ventricular ejection fraction, and receipt of ACE inhibitor for left ventricular systolic dysfunction ("National Healthcare Disparities Report"). July of that same year, race entered the picture in the form of BiDil (formerly known as H/I) – a medicine that can only be prescribed to African American patients ("BiDil").

Significance of the V-HeFTs

During the course of V-HeFT II, Jay Cohn – lead cardiologist on the V-HeFT studies – submitted a “methods” patent for using hydralazine and isosorbide dinitrate (H/I) combination to treat heart failure. Cohn had to settle for methods patent since he could not secure a “combination of matter patent,” which required the combination of these two generic drugs to produce a different result in comparison to the results obtained from using each generic drug separately. While a “methods” patent would have given Cohn monopoly on marketing the combination H/I for treating heart failure until the year 2007, it would not have given him the

power to prevent generic manufacturers from producing and selling the individual drugs at a much cheaper price. This “methods” patent would have expired last year if it were not for Cohn licensing the patent to Medco, a pharmaceutical company in North Carolina. Medco conducted bioequivalence studies on BiDil and submitted a new drug application (NDA) to the FDA in order to get approval for marketing BiDil as a method to treat heart failure. It is important to note that both Cohn’s methods patent and Medco’s NDA for BiDil were not race-specific (Pamela and Kahn, 2005).

In 1997, FDA’s Cardiovascular and Renal Drug Advisory Committee rejected Medco’s NDA for BiDil. This decision was due to the fact that Medco’s statistics were in “too much of a muddle” to meet the FDA’s standard for new drug approval (Pamela and Kahn, 2005). Although BiDil was considered to be efficacious by several committee members, the V-HeFT trials did not “produce the type of statistical information” that was required by the FDA in order to approve an NDA. Despite FDA’s rejection, Cohn was persistent (Pamela and Kahn, 2005). He went back to the now fifteen-year-old V-HeFT I data and analyzed it by race. As a result, he used a data that only had forty-nine African American subjects that were placed on H/I in order to show the significant racial difference in response to the drug. That same year, Cohn relicensed BiDil to NitroMed – a biotechnology company specializing in nitric oxide-based therapy. In 2000, Cohn applied for a race-specific methods patent in order to use H/I, or BiDil, to treat heart failure in African American patients only. In 2001, FDA agreed to approve BiDil as a race-specific drug once a confirmatory trial had been completed in African American subjects. This confirmatory trial, known as the African American Heart Failure Trial (A-HeFT) was the first time in the nation’s history that a preexisting drug was patented for a “new, race-specific use,” and thus

preventing generic sellers from entering the market scene until the year 2020 (Pamela and Kahn, 2005).

A-HeFT Design

A-HeFT was a randomized, double-blind, placebo-controlled study that enrolled over 1,000 self-identified African American subjects who had New York Heart Association (NYHA) class III or IV heart failure. According to NYHA Classification, class III patients had marked limitation of activity and Class IV patients were confined to beds or chairs. Subjects were required to remain on their current heart medication while they were randomized to receive either a placebo or BiDil. A-HeFT subjects were evaluated every three months in order to assess both clinical and self reported functional status. No patients were lost during this study. Results showed that with a 43% additional reduction in mortality when added to current standard therapies, BiDil had a significant improvement over placebo. BiDil also had an additional 39% risk reduction in first hospitalization for heart failure. As a result, the Data Safety Monitoring Board (DSMB) suspended the study in 2004, 8 month earlier than anticipated, since it would have been unethical to leave subjects on placebo when the benefits were so significant for BiDil. In 2005, FDA confirmed that there are no generic or therapeutic equivalents for BiDil – making it the first race-specific medicine in the U.S. ("Heart Failure in African Americans"). Ironically, NitroMed admits that BiDil might also work in individuals who are not African American since there has not been any research conducted in other racial groups other than self-identified blacks (Pamela and Kahn, 2005).

Personalized Medicine or Market Exclusivity?

The specific mechanism of BiDil has not yet been established. Independently, isosorbide dinitrate has vasodilatory effects on both the arteries and veins by releasing nitric oxide, which activates guanylyl cyclase and thus relaxes arterial smooth muscle. Hydralazine also relaxes

arterial smooth muscle in addition to providing synergistic activity with isosorbide by mitigating tolerance to nitrate ("Drugs Approved by the FDA"). It still remains unknown whether these two drugs in combination with an ACE inhibitor improve survival rates for the general population or just for specific racial groups ("Gene Expression: Patent for Race Specific Drug"). An even greater problem is that the study did not compare blacks to whites. It only enrolled blacks and used the data obtained to convince FDA. The study only proved that black subjects given BiDil in addition to their standard heart medication did better than black patients given a placebo in addition to their standard heart medication. This result neither shows nor proves anything since it only enrolled blacks and used the data obtained to convince FDA (Pamela and Kahn, 2005). In order to validate the results, a similar study should be conducted with BiDil in a racially diverse population. The lack of such research has prompted individuals to doubt the validity of BiDil.

Critics and Supporters

Critics of BiDil accuse the drug of reinforcing the idea that biological differences underlie the social concept of race. They say that "there is no biological basis for 'race'" and that there is more variation between two individuals within the same societal grouping of 'race' ("Nature Genetics"). BiDil would also prompt physicians and health professionals to depend on their patients to self-identify as 'black,' placing unnecessary stock on race. There was a case where researchers found that ACE inhibitors did not work on 800 patients who self identified as 'black.' As a result, doctors stopped prescribing the drug to patients that he/she perceived to be 'black.' This created an environment in which physicians and health professionals preferentially treated patients that were non-black in order to avoid the whole risky situation of using 'race' as a biological determinant. The same thing could happen with BiDil. Yet another group of critics state that it would be very difficult to control only for 'race' when there are other criteria for an

individual's response to a drug such as their overall health, lifestyle, support system, education, and socioeconomic status ("Nature Genetics"). And finally, critics argue that race is a crude marker to use since it is ill-defined. The fact that A-HeFT used subjects who self-identified as black not only limits 'black' to a social and cultural definition, but it also provides a poor connection to the underlying population genetics ("Gene Expression: Patent for Race Specific Drug").

Aside from ethical issues, the second major problem is that of market exclusivity. Generic manufacturers will be able to sell hydralazine and isosorbide dinitrate separately, but they will not be able to market them as treatments for heart failure. This market limit imposed by patent grants the inventors "market exclusivity" over BiDil (Pamela and Khan, 2005). This is an enormous economic reward for the patent holder – NitroMed – because it provides them with a monopoly over the market for this invention for the next 20-years. As a result, BiDil would sell for \$1.80 per pill, while generic drugs would sell for 30 cents a pill. BiDil also presents a threat to consumers by creating a trend in pharmaceutical industries that would change other cost-effective generic drugs into patented, expensive drugs (Pamela and Khan, 2005). On the other hand, supporters of BiDil argue that race-specific drugs would not only provide invaluable medical information about the molecular determinants of an individual's response to a drug, but it would also open more doors for other personalized medicines ("Nature Genetics").

Supporters of BiDil argue that personalized medicine is already in practice by physicians who recognize that patients respond differently to treatments, and that physicians have been choosing specific treatment options and drug dosages for their patients based on diagnostic test results, patient's family medical history, commorbidities, and lifestyle factors. For BiDil physicians would just have to add race to their list. With the growing technology in science, physicians have begun to understand the differences at the molecular or genetic level between

patients, which have enabled them to tailor treatment even more effectively than before. For example, knowledge of genetic variations is being used to help physicians better manage dosing of blood thinning drugs ("The Age of Personalized Medicine"). The only problem is the fact that these supporters are making the big assumption that genetic or molecular variation can be equated with race, and that race can be used to prescribe medications.

So now the question becomes if we can use race in treating patients. Should race be recognized and accepted as one of the factors taken into account for the growing world of personalized medicine? Would BiDil be classified as personalized medicine for African Americans or NitroMed's idea of market exclusivity?

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