

A-HeFT and BiDil

Topic & Clinical Relevance

- In 2005, BiDil, a combination pill of two standard therapies utilized in heart failure (hydralazine and isosorbide dinitrate), became the **first drug to receive approval from the US Food and Drug Administration (FDA) to treat a specific racial group.**
- The decision that gave the company NitroMed approval for its drug BiDil exclusively to a “racial group” represented a milestone in US drug policy. The decision ignited a debate that polarized the African American community, confounded proponents of personalized medicine, and dismayed groups opposed to reinscribing racial categories into science.
- On the basis of three clinical trials that showed the “dramatic effectiveness” of BiDil in Black patients alone, the FDA approved the drug as an adjunct to standard therapy for the treatment of heart failure in self-identified black patients with cardiac disease (the underlying trial being named “African American Heart Failure Trial, or “A-HeFT”).
- The idea behind BiDil has not been disputed—namely, that for some people with congestive heart failure who do not produce enough nitric oxide, vasodilators can be an effective adjunct therapy in reducing heart attacks. However, its **approval for a single racial group is scientifically unfounded, and furthermore raises questions of the place of racial designations in clinical practice.**

Historical Roots

- **The original clinical trials for this drug in the 1980s were not centered around racial groups.**
 - Only after results of a “multi-racial” trial (V-HeFT trial) showed insufficient evidence to obtain FDA approval did race become relevant as a means to revive the commercial prospects of BiDil. This stratified analysis showed significant racial differences in response to the drug, however contained data involving only 49 African American subjects. It was this analysis that allowed Cohn and Carson to obtain a race-specific methods patent to use hydralazine and isosorbide nitrate combination pill to treat “heart failure in the African-American patient”. Subsequently several researchers (9 out of the 11 authors) with direct financial ties to NitroMed conducted an additional clinical trial of Black *self-identifying* participants in order to gain FDA approval for BiDil.
- BiDil’s approval calls the definition of race into question. The concept of “race” in the USA grew out of slavery when state laws dictated racial identity by percentage admixture. In fact, in the landmark 1896 US Supreme Court decision Plessy v. Ferguson, the defendant Plessy who was escorted off of a train for whites only for being identified as black in fact self-identified as seven-eighths white. The problematic use of poorly-defined race groups is not a new concept in the US.

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Frequent Misconceptions

- **“Self-identified” race gets around the issue of using race as criteria for drug indications or guiding clinical care.**
 - Even self-identification is an unreliable marker. The reliability of self-identification as a proxy for racial or ethnic identity was called into question in the 1970s after the US Bureau of the Census did follow-up interviews to assess the consistency of self-reporting and found that 34% of respondents changed their ethnic or racial identity within 2 years. In the 2000 US Census, 7 million people identified themselves as more than one race and 800 000 respondents claimed to be black and white. Why should the drug’s approval for a differentiated group be based upon such quixotic criteria? Despite all the reasons why “race” has no role in science, it was a science-based agency that approved BiDil for a racial group.
 - Socially constructed nor self-identified concepts of “race” should not serve as a proxy for an unknown or ill-defined biological markers. Doing so is poor experimental design and should call the validity of a study into question.
- **BiDil, and other drugs which have a race-based indication, represent a step towards personalized medicine.**
 - Personalized medicine is built on the principles of genetics and physiology. Race, on the other hand, is a social construct. Krinsky puts this frankly as: “There are no racial genes, no clear genomic divide between any of society’s socially constructed racial categories, and no stable cluster of medically relevant genes that is necessarily linked with ancestry or skin color. BiDil’s success with self-identified black people could have been a statistical accident or there could be, as yet, some unknown factor that accounted for it.” (Krinsky, 2012)
 - Instead, BiDil is part of a trend that has been reinscribing racial taxonomy, either through geographical ancestry or indigenous populations, into science, but does this without credible genetics.

How BiDil Contributes to Health Inequity

- With no clear biological or scientific definition of “Black race” use in clinical trials, **prescribing BiDil exposes Black-identifying patients to a drug that may or may have proven benefit on an individual basis.** Apart from efficacy, the assessment of tolerability and safety, in light of poorly defined inclusion criteria, call into question the risk/benefit of prescribing BiDil.
- Although the fundamental mechanism of BiDil is well established, there is **currently no strong credible evidence that the drug is effective in generalized populations.** It is unclear which segments of the population truly show evidence-based benefit.
- BiDil was designed with commercial interests in mind, engineered to be more expensive and targeted specifically at Black patients. Furthermore, BiDil was tested and approved in doses that are not available for its generic components (hydralazine and isosorbide dinitrate), which was intentionally done by NitroMed to discourage doctors from easily devising ways for patients to get the same benefits from the

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long available, and much less expensive generics. **This race-based pricing and marketing strategy only serves to perpetuate racial inequity in this country.**

Possible Solutions

- Consider alternative, guideline-directed treatments for patients with heart failure who self-identify as Black. Keep in mind that BiDil is a combination drug composed of two vasodilators which are available in generic form and likely more accessible to patients of any insurance status.

Takeaway Points

- **The research that led to the FDA approval of BiDil has become a well known case of poorly designed, race-based research** with numerous methodological limitations and confounding factors - such as the use of self identified race, no unifying genetic markers of the study population, no comparison group - that make it more of a race marketing campaign than a study that promoted the wellbeing of marginalized patient populations.
- BiDil's success is one not of personalized medicine but of **exploiting race to gain commercial and regulatory advantage in the pharmaceutical marketplace.**
- **Guideline-directed alternatives to BiDil exist** (including separate prescription of its component drugs hydralazine and isosorbide dinitrate) and should be considered when treating Black patients with heart failure.

References

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