

Bidil: recontextualizing the race debate

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Introduction

June 2007 marked the second anniversary of the Food and Drug Administration (FDA)'s approval of BiDil, the first drug to be licensed for a specific ethnic population, namely self-identified blacks. However, BiDil remains mired in controversy over race-based medicine. This controversy has played out mainly in the United States (US), but has important implications world wide for the trajectory of personalized medicine. There is compelling evidence of BiDil's efficacy. No other drug combination has been shown, under the same circumstances, to have such a large survival advantage, and improvement in time to first hospitalization and quality of life in African Americans with heart failure.¹ African Americans are a minority with a particularly high risk of heart failure. The American College of Cardiologists, the American Heart Association and others² (<http://circ.ahajournals.org/cgi/content/full/112/12/e154>) have accepted these findings and made recommendations in keeping with the evidence. Yet today, only a very small proportion³ of African-American

patients, who might benefit from it, are currently receiving it.

The series of prior scientific and clinical studies leading to the African-American Heart Failure Trial (A-HeFT) and the approval of BiDil are well known.^{1,4–9} They provide adequate scientific justification for a clinical trial to have recruited self-identified blacks exclusively. Following the eruption of the race-based medicine controversy, the FDA strongly defended its decision.¹⁰ There is little doubt it was acting within its mandate and primarily with a view to benefiting the African-American community of heart failure patients that had little other choice. To understand the BiDil case and by extension, potential opportunities and harms of marketing drugs targeted at specific populations, we interviewed 18 key informants including scientists, clinicians involved in the A-HeFT clinical trial, representatives of groups that supported or cosponsored the trial, including the Association of Black Cardiologists, regulators at the FDA, ethicists and the management team of NitroMed, the company that developed BiDil. The opinions expressed here are based on these interviews, on the published literature and on our own perspective of exploring emerging technologies to improve global health.^{11–13} We found that a very substantial part of the discourse did indeed focus on the risks and threats of race-based medicine. This subject has been

covered well in the literature,^{14–29} and we have summarized the concerns and recommendations from our data in Table 1. We found that this concern, in some instances, seems to be very narrowly conceived and overshadows the broader context in which the BiDil case exists. We conclude that to make race-based medicine the defining issue of BiDil overlooks other, more compelling perspectives.

A-HeFT has highlighted the importance of minority recruitment in clinical trials

Evidence-based medicine and empirically based observation are standards in clinical research. Thus stratifying clinical trials on the basis of critical variables and enriching clinical trials with patients from the subpopulation in which the treatment was observed as effective are considered reasonable approaches.^{10,29} Table 2 lists a selection of current trials registered with ClinicalTrials.gov that are enriched on the basis of race, gender or both. Both approaches are encouraged by the US FDA, who as part of s.2.14.50 of a New Drug Application, require an analysis by age, gender and race and the National Institute of Health whose 'Policy Statement on Inclusion of Race and Ethnicity in HHS Data Collection Activities' requires grant recipients to report their findings by age, gender and race.^{30,31} They also exist as part of a larger effort to uncover the causative agents behind the growing health disparity between racial and ethnic groups in the United States.²⁹ However, as we heard from Dr. Keith Ferdinand, Chief Scientific Officer for the Association of Black Cardiologists, 'Well, previous trials have not focused on minority groups. [...] There may be some nuances in exposure, complications, side effects, the medicines, which can't be predicted when you only have a very limited subgroup of the various racial group that's participated in the trial.' In this respect, A-HeFT is considered a landmark trial, which evidenced the importance of minority recruitment.

Table 1 Concerns associated with the use of race in medical research*Scientific basis and definition of race is disputed*

<i>Criticism</i>	<i>Response/recommendation</i>
Defining Race is controversial as there is not a standardized method and most find it to be arbitrary due to the influence of social construction and discrimination	Outward appearance is insufficient and should not be used given its inconsistency and lack of scientific basis, instead, self-reported race, geographical ancestry or Ancestral Informative Markers (AIMS) can provide better alternatives as it is clear that certain genetic variation, localized to regions or populations does exist
Inconsistent 'racial' categories cannot be extrapolated to a global context as they are influenced by national/local socio-political factors	Race/ethnic categories need to be standardized on a global scale; this can be achieved through a multidisciplinary dialogue on the use of race/ethnicity in pharmacogenomics
Genetics will be confused/conflated with race resulting in negative consequences such as discrimination as a result of genetic predeterminism	A multidisciplinary dialogue on the use of race/ethnicity in pharmacogenomics is required—the debate regarding the use of race and ethnicity is important and arguments against its use are important and should create dialogue on how to better describe populations

Self-reported versus assigning racial categories by AIMS or geographical ancestry

<i>Criticism</i>	<i>Response/recommendation</i>
Self-reported race is not an effective method for categorizing populations for clinical trials as it is not reliable, not standardized and should become obsolete	Self-reported race can provide a reasonable measure of ethnicity and act as a crude surrogate for various contributing factors to local health disparities
AIMS or geographical ancestry may serve as a more objective method for assigning 'racial' or 'ethnic' categories	AIMS may raise novel concerns, such as inclusion within a group, resulting in hesitation on the parts of Institutional Review Boards to approve their use in clinical studies
Self-reported 'race' and 'ethnicity' is confounded by admixture as most populations are not homogenous	Genomic controls can be implemented to standardize the data

Race is acting as a surrogate for health disparity

<i>Criticism</i>	<i>Response/recommendation</i>
Race can be conflated with health disparities with inequities being attributed to genetics instead of socio-economic and environmental factors	Race aligns with health disparities and as such the use of race and ethnicity to identify populations can provide an effective method for addressing health disparities

NitroMed believed that by focusing on African Americans, a traditionally underserved population in the US, they could contribute towards alleviating the health disparity. Indeed, we found that many of the ethical and social concerns raised post-A-HeFT came as a surprise for those whose work was meant to provide a solution to a seemingly intractable medical problem. Dr Anne Taylor, Chair of

the A-HeFT Steering Committee and lead author in the New England Medicine Journal paper, told us 'No controversy exists about studying Ashkenazi Jewish women with breast cancer suppressor genes. No controversy exists about studying African Americans with kidney disease related to hypertension. Not much controversy about studying diabetes in Native Americans.' So why the

controversy surrounding BiDil? She thought it was most likely related to the source of funding for A-HeFT: 'and the concern was that, because of this funding by industry, the industry would somehow or the other promote racism for profit.'

Profit motive should not be used as a hammer against risk-taking small and medium enterprises like NitroMed

According to NitroMed, they found a niche where they could develop a market and improve health. Mike Sabolinski, former Chief Medical Officer at NitroMed, stated, '...when I looked from the outside into what NitroMed had done—now there are roughly 5 million heart failure patients in the United States, and NitroMed, by virtue of their business model, decided to basically address 750 000 of these patients'. Mark Pavao, Senior VP of Marketing at NitroMed told us 'We have to remember we're selling for 1/10th of the US opportunity, not 100% of the US opportunity.'

Did NitroMed exploit race for profit? Although it has been argued that commercial opportunity drove the development of BiDil,²¹ others suggest this is merely a reflection of the fiscal reality of drug development.¹⁵ The pharmaceutical industry, more so than other industries, is dependent upon intellectual property protection.³² NitroMed was acting within this culture, while developing a life-saving drug combination for an often neglected population. One of the more immediate ways of applying personalized medicine is by 'resuscitating' drugs previously withdrawn from the market (or off-patent) to develop them both for populations who are either not predisposed to the adverse effects or, as in this case, for whom efficacy can be demonstrated to a greater extent. Without 'method of use' patents of the type licensed by NitroMed, it would be difficult to encourage the industry to participate in this arena. Jay Cohn, the scientist behind the original development of BiDil stated 'No for-profit corporation studies cheap drugs'.

Table 2 Currently recruiting clinical trials enriched for race, gender or both³⁶

<i>Trial</i>	<i>Sponsor</i>
Effect of Entecavir in Blacks/African Americans and Hispanics With Chronic Hepatitis B Virus (HBV) Infection	Bristol–Myers Squibb
Study of Pharmacokinetics in HIV-Infected Women	Women’s College Hospital Canadian Institutes of Health Research
MEDI-524 (Numax-TM) for the prevention of respiratory syncytial virus (RSV) disease among native American Indian infants in the southwestern United States	MedImmune Inc.
EARTH 413: An Open-Label Study to evaluate the effectiveness and safety of donepezil hydrochloride (Aricept) in hispanic patients with mild to moderate Alzheimer’s Disease (AD)	Eisai Inc.
Study of Asian patients with hypercholesterolemia in the UK—rosuvastatin 5 mg versus atorvastatin 10 mg: self-described Asian	AstraZeneca
Study evaluating the safety and efficacy of bazedoxifene in postmenopausal Asian women	Wyeth
HerpeVac Trial for women	National Institute of Allergy and Infectious Diseases
Survey of prostate cancer in Ghanians (Accra, Ghana)	National Cancer Institute and National Center on Minority Health and Health Disparities
Safety and efficacy of nebivolol in the treatment of hypertension in African Americans	Mylan Bertek Pharmaceutical

The race controversy is only one of the many issues which contributed to BiDil’s low sales

Although, the original sales forecasts for BiDil were extremely optimistic, as mentioned earlier, approximately 3%³ of African-American patients, who might benefit from it, are currently receiving it. In fact, BiDil’s failure to gain a foothold in the marketplace and to capture the attention of physicians may have been a result of several factors, including a self-limited market, high price points, the race controversy, the availability of generics, exclusion from formularies and poly-pharmacy in treatment of heart failure. Although NitroMed executives cite marketing issues as the main reason behind BiDil’s low sales, others

suggest that it is a combination of high price points and exclusion from formularies. BiDil is priced high at \$1.80 per pill with an average prescription of 3.4 pills per day and the average yearly cost ranges from \$1400 to \$2800 a year. NitroMed has been criticized for the high price point it set for BiDil. Perhaps as a result, managed care organizations have not included BiDil on their formularies, instead opting to reimburse patients for the cheaper generic components. In addition, until very recently BiDil was not widely available in important prescription plans for the elderly in the US, a situation which led some to consider this ‘so contrary to evidence-based medicine and so extraordinary that it arouses suspicions of institutional

racism.’³³ Both of these factors fuel the ethical dilemma that has been raised by many with respect to ensuring access of health products derived from pharmacogenomics. Appropriate policy guidelines on how to compensate for market segmentation represent a current gap that needs to be addressed to ensure equal access to population-based therapeutics and genome-based therapies.

The FDA regulatory process has been tested by BiDil: FDA has convincingly justified its actions, but regulatory gaps do exist

Instead of focusing narrowly on race, we need constructive ways in which to move forward the agenda of finding working solutions to the health problems of minorities. As genome sequencing and single nucleotide polymorphism scans (and now copy number variations and other large scale structural variations) become cheaper, we may actually achieve personalized medicine and the issue of race may become moot. In the meantime, regulatory gaps must be addressed to mitigate concerns raised in the context of BiDil. For example, how do we deal with individuals who do not fit the race/ethnic profile indicated on a drug label, yet respond to the therapy? Should we require companies, such as NitroMed, to pursue follow-up studies to determine the biological basis for drug response? Gregg Bloche suggests, ‘there’s a possibility that pharmaceutical companies that get drugs approved on the basis of race, could come together and say, okay we are committed to devote a certain percentage of our profit from the sale of these drugs to follow up research to determine what the biologic determinants of these racial differences, if any, may be. And when I say biological, I’m referring to environmental and to genetic.’ In this vein, it is encouraging that NitroMed is currently voluntarily financing an ongoing follow-up genetic study, investigating the potential genetic basis for the response to BiDil.³⁴ However, voluntary follow-up studies may only occur when incentives exist: Dr Howard McLeod, Director of the UNC Institute for Pharmacogenomics and

Individualized Therapy, states ‘if NitroMed identifies the genetic basis for response to BiDil, this should expand the market. This will make the drug available to more people and NitroMed might then make their money back.’ McLeod therefore suggests that the FDA, European Agency for the Evaluation of Medical Products and other regulatory bodies should create new regulatory requirements by creating ‘phase IV’ studies to identify biomarkers.

BiDil is a necessary stepping stone in the trajectory of personalized medicine

BiDil will not be the last therapeutic drug developed that makes use of enrichment for a particular population. Indeed it should not be, if we are to follow scientific and evidence-based approaches with the ethical principle of beneficence. As suggested by Bloche, ‘Well I think inevitably, since we do have different distributions of diseases in different populations, inevitably we’ll see more of this sort of thing’. There are now others. DeCODE Genetics is currently studying DG-031 (Veliflapon), which may prevent heart failure in African-American patients with a history of myocardial infarction.³⁵ Citing the need to reformulate DG-031 (Veliflapon), DeCODE Genetics has temporarily suspended the Phase III clinical trial in ‘self-reported’ African Americans with plans to resume the trial in the next year.^{36,37} Nevertheless, the finding that a variant of the gene which codes for leukotriene A4 hydrolase (*LTA4H*) confers a threefold greater risk of myocardial infarction in self-identified African Americans, in comparison to European and American Caucasian cohorts,^{38,39} affirms that racial or ethnic categorization (or, as we would prefer, geographical ancestry) continues to be useful and might lead to major breakthroughs. This is one way that we are seeing a progression towards a genomic approach to explain legitimate differences between populations, which will ultimately contribute to a mature understanding of human diversity and the abandonment of race as a concept.⁴⁰ This is echoed in a statement by Frederico Goodsaid, of

Table 3 Positive outcomes that have arisen from the events leading to the approval of BiDil

- There is a clear clinical benefit of using BiDil in African Americans—resulting in lives saved
- A-HeFT has highlighted the importance of minority recruitment in clinical trials
- FDA regulatory process has been probed in the context of BiDil, providing future clarification for drug development along similar lines
- The conflation of issues around race-based medicine has been raised in a concrete setting providing valuable debate
- The potential for ‘resuscitating’ drugs and drug combinations for use in specific subpopulations has been given a concrete example supported by strong clinical evidence
- The potential medical value of geographical ancestry has been highlighted, helping to frame the context of other studies
- NitroMed is currently voluntarily financing an ongoing follow-up genetic study, investigating the potential genetic basis for the response to BiDil (GRAHF Study).
- NitroMed has provided companies with valuable lessons regarding the process of development, approval and subsequent marketing of population-based therapeutics, thereby contributing to the understanding of the trajectory that personalized medicine is taking

the Centre for Drug Evaluation and Research, FDA, who told us: ‘Personalized medicine today may mean that you have classifications by ethnicity. Personalized medicine as you move ahead, and you know more and more what these markers are, should become incrementally independent of ethnicity. But we have to start with the knowledge about pharmacogenomic biomarkers we have today. And that’s why at this point ethnic classifications are still important.’

Conclusion

Pharmacogenomics is increasingly regarded as a way to improve health globally through application of the knowledge derived from human genomic variation. However, as of yet, individual genotyping is cost prohibitive and knowledge of biomarkers is limited; instead investigators rely on categorizations of race, ethnicity, gender and age to explain variation in both disease mechanisms and response to available therapeutics. As a result, population-based therapies, such as BiDil are an emerging trend in drug development. Two years after the approval of BiDil, opinions remain split: some perceive it as a huge breakthrough for African-American heart failure patients while others consider it a ‘scientific tragedy’. We agree with

the statement that ‘when racial labels are used in drug datasheets and health advisories, inferences should be based on robust evidence.’⁴¹ We have found that BiDil is a stepping stone in that direction. The next steps, already evident, are towards gathering such evidence. The evolution of BiDil highlights the many issues that we are and will continue to be confronted with as we move to adopt pharmacogenomics and personalized medicine. Further, BiDil highlights that emerging technologies are not always easily integrated within already existing frameworks. In the future, companies such as DeCODE, employing genomic variation data, will continue to challenge our notions of traditional drug development and healthcare. It is important that we not criticize industry on the basis of profit motives without ensuring that the necessary market incentives are in place for them. In addition, we need to recognize the concerns which were raised and where possible begin to proactively introduce new legislation to address the gaps. It is essential that as we move towards the adoption of pharmacogenomics, stakeholders move beyond the divisive debate about race and, instead, take stock of the positive outcomes associated with the development of BiDil (Table 3) to understand how we can use human

genomic variation and pharmacogenomics as tools to improve drug development and health care globally.

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Duality of Interest

The authors declare no competing financial interests.

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