The art of medicine

The short life of a race drug

The headlines back in June, 2005, read "FDA approves a heart drug for African Americans". 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 polarised the African American community, confounded proponents of personalised medicine, and dismayed groups opposed to reinscribing racial categories into science. Ever since Ashley Montagu published *Man's Most Dangerous Myth: The Fallacy of Race* in 1964, scientists have reached a broad consensus that "race" applied to human populations has no standing in science.

The story behind the approval of the so-called "race drug" has been well documented. In brief, BiDil is a combination drug consisting of two vasodilators, hydralazine hydrochloride and isosorbide dinitrate, that was patented by cardiologists Jay Cohn and Peter Carson in 1989 for congestive heart failure. The US Food and Drug Administration (FDA) rejected BiDil for a new drug application in 1997 when the clinical trial data failed to show sufficient statistical power of the drug's efficacy for a multiracial population with heart disease. On the recommendation of members of FDA's advisory committee, NitroMed re-examined the clinical trial data along racial lines and then ran a new clinical trial that enrolled 1050 men and women who self-identified as African Americans. The results showed a 43% decrease in mortality and a 39% reduction in risk of first hospitalisation against placebo. 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.

Some scientists viewed this decision as a step in the direction of personalised medicine, namely, developing drugs for more differentiated patient groups. The BiDil story played out against the backdrop of developments in building genomic databases, such as the International Human Haplotype Map (HapMap) and the Human Genome Diversity Project, in which population-specific patterns of genetic variation were correlated with geographical ancestry, which mapped onto historically based racial taxonomies. All of these efforts seem to be converging on drug treatment that is driven by genetic knowledge of patient groups and eventually of individuals, otherwise known as pharmacogenetics. 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.

If ancestral genomic identification, as a proxy for race, predicts disease clusters in a population, why shouldn't the public health and medical professionals use that knowledge to target effective drug therapies? Disease rates are often reported by race, health-care disparities are reported by race and class, and, more to the point, the FDA requests industry to collect race and ethnicity data on clinical trials. Let us suppose reliable evidence indicates that a drug is particularly effective for treating a medical condition among patients with *MC1R* recessive genes on chromosome 16. The alleles of these recessive genes are known for producing red hair. Without any mechanistic knowledge about how the drug works, would it be wrong to use a drug that was shown in a clinical trial to be effective for treating redheads? After all, physicians use a lot of trial and error in prescribing treatments and if they had some solid evidence that a "redhead drug" works for a medical condition, why not take advantage of it? Moreover, if a specialised drug is acceptable for redheads, why not a drug for black people?

Perhaps initially persuasive, the analogy between a "redhead drug" and a "race drug" breaks down. First, there are specific genes associated with red hair so there is a clearly identifiable genetic marker that can be used to develop a mechanistic model for why the drug works for this population group. In the case of BiDil, no genetic markers were used to obtain a population sample in the clinical trial. Second, 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 colour. 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.

While many commentators who supported the approval of BiDil for black patients state that "race" is not a scientifically precise term for identifying relevant genomic or physiological characteristics that differentiate population groups, nevertheless, they argue that "self-identified race" is a useful proxy for those characteristics. However, what is the evidence that the proxy "self-identified race" is a reliable surrogate? The best evidence derives from the fact that genetic variation conferring disease susceptibility is not equally distributed among ancestral populations. For example, sickle cell anaemia is more prevalent in populations whose ancestry can be traced to sub-Saharan Africa. However, "self-identified race" is a subjective term, influenced by cultural factors, and not even grounded in the ancestral genomics of, for example, the International HapMap Project. For the purpose of the clinical trials, "self-identified race" is interpreted as a dichotomous variable (black or non-black). If race were used as a proxy for ancestral African genomics it should be a continuous function (10%, 30%, 70%, etc). It makes no scientific sense to map a continuous function onto a dichotomous variable.

Many of the criticisms launched at BiDil were about the use of "race" as a proxy for genotype in the clinical trial or as variable in a scientific study. Since "race" is ill-defined

and "self-identified" racial identity is neither standardised nor reliable, then any science that derives from it cannot be reliable. Indeed, people's racial self-identity can change with circumstances. 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.

In a historical context too, the use of such racial classification is shown to be a subjective process. The concept of "race" in the USA grew out of slavery when state laws dictated racial identity by percentage admixture. A person who self-identifies as African American could have one great-grandfather (or about one-eighth of his or her genome) as the exclusive source of that identity. Homer Plessy was the plaintiff in an 1896 US Supreme Court decision (Plessy *v.* Ferguson) that established the "separate but equal" foundations of segregation in the USA. Plessy, who was escorted off a train for whites only, was considered black based on the infamous "one drop rule", even though he considered himself seven-eighths white. By contrast, Jean Toomer, author of the 1923 book *Cane*, which chronicled the lives of black Americans, sometimes identified himself as black and sometimes as white. Thus, two individuals, both with one-eighth African ancestry, might either be defined by others as black or self-identify as white or black. 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.

So what has happened to the first "race drug" approved by the FDA? At the time BiDil was approved, there was an estimated market of 750 000 black Americans out of a total of 5 million people with heart disease who might benefit from a pill. Wall Street analysts predicted annual sales of US$500 million, even $1 billion by 2010. According to the 2009 Securities and Exchange Commission 10K report filed by NitroMed, the company's sales from BiDil were $12·1, $15·3, and $14·9 million in 2006, 2007, and 2008, respectively. NitroMed began developing an extended release formulation of its drug, which it called BiDil XR, hoping it would capture a larger market. Between Jan 1, 2006, and March 1, 2009, stock shares in NitroMed fluctuated dramatically between a low of $0·15 to a high of $14·90 a share. Many physicians were sceptical about the "race drug". A focus group study of 90 primary care physicians' attitudes toward race-based therapies reported that the physicians expressed a wariness of using such therapies. Geneticists also voiced their opposition to approving and marketing a drug based on outmoded racial categories. In the wake of poor revenues and rising deficits, NitroMed offered itself for sale. In April, 2009, the health-care investment company Deerfield Management acquired NitroMed and paid its stockholders $0·80 per share, or about $36 million. NitroMed removed its stock listing on NASDAQ. In its 2009 10K report, NitroMed declared that the company had never been profitable and expected its future revenues from BiDil to fall significantly based on declining prescriptions, unwillingness of third party payers to provide reimbursement, and a reduction in their sales force and promotional efforts. In that same month the French company NicOx S.A. had announced that it agreed to purchase NitroMed's unlicensed patents covering nitric oxide-donating compounds, a field of continuing research activity.

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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. But who can benefit? Neither socially constructed nor self-identified concepts of "race" can serve as a proxy for an unknown or ill-defined biological marker that provides a causal connection to or strong association with a drug's effectiveness. Personalised medicine requires nothing less. If a drug works it is because of the genetics and physiology of the patient. Nothing I have reported about BiDil or concluded about the limitations of "self-identified race" as a clinical marker diminishes the progress and expected value of personalised medicine. At its best, personalised medicine promises to reduce adverse drug reactions through the discovery of genomic-based drug-interaction mechanisms that could reduce the guesswork associated with drug therapies. BiDil has underscored the importance of that approach. Racial blood lines are a thing of the past. Thus far, the short life of BiDil shows us that racial pharmacokinetics has nothing to offer in its place.

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Further reading

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