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Race-specific drugs: regulatory trends and public policy

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Numerous articles and commentaries in the health literature recently have questioned the emergence of race as an increasingly powerful organizing principle in clinical medicine and pharmaceutical development [1,2]. Yet proposals for regulatory reform remain thin. Debate over race-based medicine crystallized around the FDA's June 2005 approval of BiDil, a drug approved to treat African-Americans with heart failure. Some saw BiDil as a dangerous example of marketing trumping science [3], whereas others heralded BiDil as a step towards eliminating racial disparities in health care [4]. One thing is clear: the BiDil debate has left major questions about how clinical trial design and drug regulation should engage this trend [5].

The need for new regulatory approaches to medicines with race-specific indications is growing more acute. A new trend towards designing and conducting clinical trials for race-specific medicines [6] carries serious implications for equitable access to pharmaceutical innovations. Under current policies FDA-approved racial indications might prevent certain groups from accessing certain drugs, even when there is little evidence to warrant such exclusion. Given the stakes of such exclusions for public health, new regulatory approaches are needed to ensure that the benefits of race-specific drug indications outweigh their potential harms and that marketing does not trump good pharmaceutical science. Reviewing this controversy within science and policy, we propose a relatively simple approach: race-specific indications should be rejected unless clinical trials can demonstrate convincingly that the drugs are both better than existing treatments for a specified group and no better than existing treatments for non-specified groups. This approach would substantially advance public health by preventing undue limitations on access to drugs and clinical trials while mitigating market incentives to overstate race's therapeutic significance.

The contested racial pharmacy

Cited by some as a breakthrough in 'personalized medicine', BiDil became the first drug to receive FDA approval for treating a specific racial group, namely African-Americans with heart failure. When BiDil failed to receive FDA approval as a race-neutral treatment largely because the original trials were not adequately designed [3], its approval as a race-specific medicine was propelled by a subsequent clinical trial (A-HeFT) that only included patients that self-identified as 'Black'. Improved efficacy

in this narrower trial ostensibly showed that BiDil significantly improved mortality rates and quality of life solely within this population [7]. Proponents of this race-specific indication conceded that race is an imprecise, if not crude, marker for understanding genetic or other biological mechanisms explaining this population's differential response yet ultimately found race to be a useful proxy to define the group most likely to benefit [4]. Critics of a race-specific approval argued that because BiDil's component parts – isosorbide dinitrate and hydralazine hydrochloride – are available generically and have been used for years to treat heart failure in all people, BiDil's race-specific approval ran the risk of preventing non-African-Americans from having access to the drug. It turns out that BiDil's manufacturer, Nitromed Inc., holds a patent for these drugs' combined use in African-Americans, which created an economic incentive to look narrowly at the African-American population to the exclusion of a broader study [3].

When the FDA ratified BiDil's racially exclusive clinical trial design, it might actually have undermined the broader goal of increasing racial minorities' participation in clinical trials. For instance, the very same logic suggests that the special efficacy of a drug in Whites – the largest and most lucrative segment of the U.S. market – could be used to justify the exclusion of non-Whites from clinical trials. This seems precisely to be what happened in 2006 when Schering-Plough decided to exclude African-Americans from the Phase 2 trial of SCH 503034, an investigational hepatitis C protease inhibitor [Community HIV/AIDS Mobilization Project (CHAMP) *et al.* (2006) Excluded African-American participants: open letter protests Schering-Plough's exclusionary study design (<http://www.aidsinfonyc.org/tag/coinf/birnkrantltr.html>)]. Even though African-Americans have the highest hepatitis C prevalence of any racial group in the United States, the company excluded this population not for any safety rationale but to boost efficacy numbers [8].

Race-based indications also raise important questions even when their use is fully warranted by clinical data [9]. Such indications encourage the reification of race as an immutable source of physical difference, whereby effects attributable to social forces and human choices – such as disparities in health outcomes – are given undue biological explanation. In addition to impacting other areas of social life, this false attribution can deflect attention from known causes of racial disparities in health outcomes linked to economic class, environmental conditions and other sociological considerations [9]. Yet the biomedical industry increasingly frames racial disparities in health as a

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function of genetic variations unique to certain racial populations, positing racially targeted medications as the most promising remedy. In these early days of personalized medicine, just what kinds of data will satisfy regulators when considering race-specific applications remains an open and difficult policy question [5].

Concerned about the emergent use of racial classification by government agencies in pharmaceutical indications, some legal commentators have considered whether this use might violate the prohibitions against racial discrimination within the United States Constitution – in particular, the 14th Amendment's Equal Protection Clause [10]. The long-standing doctrine of strict scrutiny requires that when the state uses racial classifications they must be 'narrowly tailored to further compelling government interests'. Strict scrutiny does not hold that all racial classifications are impermissible *per se*, only that they are worthy of our suspicion: its purpose is to ensure that government 'pursue[s] a goal important enough to warrant use of a highly suspect tool' [11]. Other commentators disagree that racial indications are constitutionally barred but have used the idea of strict scrutiny to propose best practices in how racial data are reported [12]. In one proposal, Kahn recommends that biomedical researchers demonstrate their 'narrowly tailored' use of race by requiring a tight fit between population categories, genetic categories and the disease or health issue under analysis [13].

These proposals are useful in that they use strict scrutiny's longstanding legal commitments to ensuring racial equality in education, employment and other areas of social life to inform how biomedicine can use race effectively and responsibly. Yet the existing proposals fall short of leveraging strict scrutiny's broad mandate to rethink a regulatory approach with specificity and precision. Minority health disparities are too large to rule out potential biomedical remedies but they also are too important to allow marketing to trump good science. In short the FDA needs sharper tools to review new drug applications that seek race-specific indications – tools that allow race specificity only when evidence is clear and compelling.

A higher evidentiary standard

A robust method for taking a strict scrutiny approach would address the kinds of evidence regulatory bodies might require before labeling medicines for specific races. In particular the FDA should deploy a heightened standard of efficacy when approving race-specific indications, particularly because U.S. law allows such claims to be marketed to doctors and consumers. In addition to traditional efficacy thresholds, evidence of race specificity should, at a bare minimum, require that clinical trials supporting race-specific indications show that a particular drug is not only better than existing treatments for the specified racial group but also no better than existing treatments for non-indicated groups.

How would such a rule operate? Numerous policies aimed at increasing ethnic and gender diversity in clinical trials have led biomedical researchers to adopt historically contingent U.S. census categories when reporting trial results for various populations [8]. As a result, the groups

likely to be specified for future race-specific new drug applications will be African-Americans, Whites, Asians and Latinos/Hispanics. Evidence that a proposed drug is no better than existing treatment in at least two of the three non-indicated groups would be persuasive. As mentioned above, indications for one race implicitly exclude (and restrict access to) other races. This new approach would help ensure that these exclusions are as narrowly tailored as possible to 'the compelling state interest' of promoting public health. The policy also would not deny racial minorities that needed treatments, as a drug could be offered without race-specific indications but with – if appropriate – information on race-correlated efficacy in the general label language.

BiDil's race-specific indication, for one, very well might not have passed muster under this standard. Clinical research prior to the racially exclusive A-HeFT trial did suggest that White patients would not benefit as much as African-American patients from the combination therapy [5], but the finding of a non-effect in Whites was far from definitive; two out of nine members of the FDA's Cardiovascular and Renal Drugs Advisory Committee voted for general approval, a result that many commentators found far preferable [14]. FDA officials have suggested that requiring a trial testing the African-American-only claim across multiple populations would have placed too large a financial burden on NitroMed [5]. We argue that should manufacturers want the race-specific approval that allows them to market such a claim, they should bear these costs. Otherwise, these drugs should be made available without racially restrictive indications provided that they fulfill all other FDA requirements. The medical community's poor history with racial minorities [15] as well as governments' troublesome usage of racial categories warrant this more careful approach.

This proposal becomes increasingly important as race comes to play a larger role in how drug companies are framing personalized medicine. We suggest this new approach as a minimum standard that can inspire greater confidence in both patients and medical professionals that these particular uses of race are driven by compelling biomedical reasoning and evidence. The proposed evidentiary standard is important to ensure broad patient access to new medications. Further, by screening out race-specific indications that might be more about creative marketing than pharmaceutical science, it furthers the public interest by protecting against the 'spill over effects' of race's reification in biomedicine.

Conclusion

In sum this proposal is offered as a way to ensure race's narrow tailoring to a coherent concept of scientific relevance in biomedical research. To the extent that race-specific medicines also might help to close health disparities, this heightened evidentiary standard has an additional benefit: it will assist policymakers in achieving the broadly accepted goal of meeting health needs across diverse populations while demanding substantive evidence for racial exclusions. Race can be used as a proxy for the group most likely to benefit from a drug as long as the effect is not to deny others valid treatments. Strict

scrutiny as a policy model along with testing efficacy across multiple racial groups as a methodological approach can help ensure scientific validity and that the benefits outweigh the harms.

The late Constitutional Law scholar Gerald Gunther noted that strict scrutiny is often 'strict in theory and fatal in fact', arguing that this approach often amounts to a back door attempt to prohibit government's use of racial categories entirely [16]. This is not our proposal's purpose. Rather, we aim to promote public health and the societal interest in approving race-specific indications, but only when they are used cautiously and are supported by robust scientific evidence. Pharmaceutical science and biomedicine most certainly should not be colorblind. But they also must not be 'color-struck'. The battles waged to afford racial minorities 'equal protection of the laws' in the United States can be useful guideposts for regulators when considering race-specific drug applications.

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