
Race, Money and Medicines

M. Gregg Bloche

Taking notice of race is both risky and inevitable, in medicine no less than in other endeavors. The literature on race as a classifying tool in clinical research poses this core dilemma: On the one hand, race can be a useful stand-in for unstudied genetic and environmental factors that yield differences in disease expression and therapeutic response. On the other hand, racial distinctions have social meanings that are often pejorative or worse, especially when these distinctions are cast as culturally or biologically fixed. Our country's troubled past in this regard and the persistence of race-related disadvantage should keep us on notice about this hazard. Yet paying attention to race in order to ameliorate past wrongs sometimes supports the quest for social justice, as Dorothy Roberts points out in this issue.¹ And at times, as Jay Cohn² and Raj Bhopal³ note, attention to race can make a therapeutic difference, to the point of saving lives.

Thus the challenge when medical researchers use racial categories is one of risk management. My aim in this commentary is to offer some guidelines for risk management by academic institutions, corporate and public funders, journal editors, regulators, and investigators themselves. I start with the proposition that past racial injustice is an important factor in assessing risk: what *has* happened is evidence of what *might* happen.⁴ As critical race theorists point out, biological understandings of race have repeatedly lent support to beliefs in racial hierarchy and inferiority. Supposed biological differences have had a central role in the "scientific" stories about race told by apartheid theorists, American white supremacists, anti-Semites, and assorted other theorists of bigotry. So it is not mere political correctness to caution that race-based physiological distinctions could feed negative attitudes toward groups portrayed as biologically less well-equipped.

Beyond this risk, there is the question of subjective fear – fear sustained by memory of past episodes of biologically rationalized repression. Should fear and anxiety of this sort "count," for risk management purposes, even when those who don't share it see no risk that use of racial categories will rekindle racist beliefs and behavior? Today's debate over the role of racial grouping in medical research is driven mostly by differences over how to answer this question. Those who worry a great deal about the rekindling of biological racism

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believe, of course, that their worries are well-founded. Meanwhile, many who worry less, or not at all, about this prospect see such fears as inflated and unworthy of a role in the calculus of risks and benefits that arise from use of racial categories.

These worries should “count,” I submit, since there is no firm basis for determining whether they are exaggerated, and since the wounded feelings (and trust) of people affected matter greatly. Indeed, it is part of our legacy of race-related indignity that hidden suf-

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fering of this sort has often gone neglected. Race, for this reason, should always be a “suspect” class in clinical research, not in the strong sense implied by equal protection law (which requires a “compelling” case for race-based distinctions⁵), but in the literal sense that using race should raise doubt. Avoidance of racial categories unless there is good scientific reason for using them would be a wise starting premise.

But we should set this presumption aside when scientific and clinical opportunity supports doing so; we shouldn't sacrifice lives or health merely to avoid classifying patients by race. The BiDil affair spotlights the awkward choices we must make along these lines, under real-world circumstances. As Jonathan Kahn has shown in his authoritative account, BiDil's emergence as a treatment for African-Americans with heart failure was a product of regulatory incentives as much as scientific opportunity.⁶ Race-based prescribing offered a pathway to extended patent protection for a combination therapy made up of two decades-old generics (hydralazine and isosorbide dinitrate). Kahn and others object to these incentives and to race-based clinical decision-making more generally. But the clinical trial that resulted in BiDil's approval produced a stunning result: compared to conventional therapies alone, the BiDil combination (administered with conventional treatment) improved the one-year survival rate of heart failure patients by forty-three percent.

This trial, conducted on African-Americans alone in order to obtain Food and Drug Administration (FDA) approval for BiDil's patent-protected, race-based use, didn't prove that BiDil works better in blacks than in whites. But it did establish that the hydralazine/isosorbide dinitrate combination prolongs black heart failure patients' lives. To argue that the trial shouldn't have been conducted, or that the FDA shouldn't have approved BiDil based on this data, is to put opposition to race-based categories ahead of extension of life. This,

I submit, takes resistance to race-based therapeutics (and research) too far.

To be sure, as some have pointed out, BiDil could have been tested on a multi-racial, multi-ethnic patient pool.⁷ But as a practical matter, this wasn't an option for the small, start-up company that brought Bidil to market. Race-specific use meant extension of BiDil's patent protection from 2007 to 2020, enabling the firm to raise funds via equity markets to support a trial in African-Americans only. A multi-racial trial, by contrast, lacked a Wall Street constituency: impending loss of patent protection in 2007 made such a trial unappealing to investors and thus exceedingly difficult to finance. Thus the BiDil affair poses policy and ethics questions under third-best circumstances. Had the trial not been conducted in a single racial group,⁸ it almost certainly wouldn't have been done, given prevailing business incentives. Patients with heart failure would have missed out on the hydralazine/isosorbide dinitrate combination's life-prolonging benefits.

This would have been an unacceptable outcome, in my view. The opportunity to save lives justified the BiDil investigators' departure from the initial presumption against racial categories that I believe should govern. On the other hand, the controversy over BiDil's approval, despite the BiDil trial's stunningly positive results, points to the need to better manage the social risks of racial classification. When researchers use race on an interim basis, as a surrogate for poorly-understood environmental or genetic factors, reporting of results should be accompanied by clear explanation that race is a crude, temporary stand-in for causal influences that remain unknown. Journal editors should insist on this, and regulators at the FDA and elsewhere should underscore this message when they approve tests and treatments, labeling, or third-party payment on race-related grounds. Clarity of this sort, from those in position to shape public perceptions, would go far toward preventing reification of observed, race-correlated clinical differences as essential truths about human nature and worth.

Beyond this, it is essential that use of racial categories be temporary. Follow-up research aimed at uncovering the genetic, social, and other determinants that underlie race-correlated differences should be a high priority, to improve clinical outcomes and to discourage race-based stigma. Were rewards for scientific understanding and clinical advance the only drivers of medical research, this challenge would take care of itself. But perverse incentives in this area are a serious problem. Pharmaceutical firms, driven by the exigencies of FDA approval and intellectual property law, are the main

fundors of drug trials (and of many of the academics who perform them). That these firms seek business opportunity on behalf of their shareholders doesn't make them "bad"; to the contrary, they are required to do so to meet their fiduciary obligations under corporate law. But from a social welfare perspective, research efforts driven by business incentives are imperfect. Absent the prospect of economic reward, scientific questions risk going ignored.

Troublesome incentives of this sort could "lock in" use of race as a clinical indication, once a drug is approved (and patent-protected) for a particular racial group. From the perspective of the drug's maker (and prospective investors), follow-up studies aimed at finding genetic or environmental markers for the drug's effectiveness are likely to be a losing proposition. Once race becomes established as a therapeutic indication, discovery of factors that foretell treatment success for only *some* patients within the racial category is likely to be bad news for the manufacturer. Knowledge of these factors shrinks the set of potential customers from *all* members of the racial group to only those for whom these factors apply. Unless this shrinkage is outweighed by new customers (from other racial categories) for whom these markers predict treatment success, findings from follow-up study of genetic and environmental determinants will reduce sales of a product targeted toward a particular racial group.⁹

The risk of locking in race as a clinical indication is thus an example of a larger problem – the insufficiency of current regulatory and market incentives as drivers of clinically desirable research.¹⁰ Barring use of racial categories is a near-sighted remedy; the larger need is for correction of perverse incentives. Various strategies, alone and in combination, are worth considering. The most far-reaching approach is large-scale public financing for "orphan" research – research that is clinically important, even urgent, but that goes unfunded (and undone) under current arrangements.¹¹ This remedy would address a wide array of problems, including the paucity of comparative-efficacy studies, risk-benefit evaluations, and other research aimed at putting clinical practice on a more rational, evidence-based footing. To minimize interest group influence and to maximize the clinical and scientific value of the research performed, peer review panels should evaluate competing proposals for such studies and determine their priority for funding purposes, as happens now for grants awarded by the National Institutes of Health (NIH).

The NIH, in my view, would be the best venue for a program of this sort. Its prestige has proven to be a powerful safeguard against the sway of potent interest groups. Equally important is its durability, which

has enabled it to build a constituency of researchers who rely on it for funding and who are thus insulated, albeit not immunized,¹² from the enticements of the pharmaceutical and biotechnology industries. A public program along these lines, consuming, say, one or two percent of the more than \$2 trillion Americans spend on health care each year, would dramatically increase the resources available for "orphan" research, including efforts to uncover mechanisms responsible for race-related clinical differences.

A more modest approach would be to empower the FDA to condition approval of a new drug on its manufacturer's commitment to support follow-up research, including studies of comparative efficacy and of mechanisms that might underlie race-related clinical outcome differences.¹³ Ideally, this follow-on research should be planned and conducted by independent scientists, protected from industry influence by robust conflict-of-interest rules. Approval could later be revoked, suspended, or renewed, depending on the outcomes of this research. This would put the burden of performing such research on drug-makers, not taxpayers. It might slow the emergence of low-value, "me too" drugs while spurring research aimed at learning whether new drugs represent substantial therapeutic advances. For this approach to succeed, the FDA would need to be reconstituted in wholesale fashion, as an agency insulated from interest group influence and staffed (or at least advised) by leaders in research on clinical outcomes and pharmacotherapeutic mechanisms.

A voluntary, industry-wide commitment to follow-up research on genetic and environmental determinants of racial differences in drug efficacy would be helpful as an interim step. There are numerous precedents from other industries for international action of this sort when social and ethical concerns arise. Coffee, cocoa, and clothing manufacturers have come together to endorse fair labor standards, and firms that pollute have embraced voluntary limits on the befouling of water and air. To be sure, industry participation in such standard-setting has been less than universal, and participants at times fail to make good on their commitments. But as students of these voluntary efforts point out, they are most likely to succeed when they tackle high-profile issues (of concern to those who purchase an industry's products) and when a trade association can coordinate and cajole its members. Racial classifications in pharmaceutical research and treatment would seem to qualify on both counts: use of race as a biological indicator is bitterly controversial, to say the least, and the prescription drug industry may well have the most potent trade group in Washington.

Collective action by academic medical institutions and professional organizations would also be of much value. They should support the emergence of an ethical obligation to treat racial classification as an interim measure, pending the search for genetic and environmental determinants. This obligation implies a further duty to search vigorously for such determinants when race is employed as a clinical indication. Were clinical researchers to take these obligations seriously and to condition their collaboration with drug companies on corporate commitment to fulfilling these obligations – the risk of “locking-in” race-based therapies would be much-diminished. This underscores the urgency of dealing with a larger problem: financial linkage between clinical researchers and drug company incentives. Clinical investigators should be reasonably paid for the company-sponsored trials they perform, but their financial incentives should be unconnected to trial outcomes. Researchers should not hold stock options in the sponsoring firm, as the BiDil patent holder (who coauthored the study that led to BiDil’s approval) did; nor should they own shares outright. Other incentive arrangements should be barred, and the subsequent awarding of consulting fees, grants, and other benefits should be closely policed by academic administrators.

My bottom line message about race-based classification in clinical research is that we should start with a presumption against it, but permit its use when it might prolong lives or meaningfully improve health. Use of racial categories should be understood as an interim step; follow-up inquiry into the factors that underlie race-correlated clinical differences is important both to improve the efficacy of clinical care and to prevent race in itself from being misunderstood as a biological determinant. So long as we pursue such inquiry with vigor – and communicate effectively about the limited relevance of race as a surrogate for poorly-understood genetic and environmental influences – the pernicious effects of racial categories on public understanding can be managed. Perverse market and regulatory incentives create the danger that use of race will be “locked-in,” once drugs or other therapies are approved. Follow-up research into underlying determinants of difference in disease expression and therapeutic response risks shrinking markets for medicines approved on the basis of race. This risk is one

facet of the more general problem of under-funding for “orphan” research, studies that promise large clinical benefits but offer low economic payoffs, given prevailing incentives. Addressing this mismatch between therapeutic possibility and business opportunity is an urgent public health priority.

References

1. D. E. Roberts, “Legal Constraints on the Use of Race in Biomedical Research: Toward a Social Justice Framework,” *Journal of Law, Medicine & Ethics* 34, no. 3 (2006): 526-534.
2. J. N. Cohn, “The Use of Race and Ethnicity in Medicine: Lessons from the African-American Heart Failure Trial,” *Journal of Law, Medicine & Ethics* 34, no. 3 (2006): 552-554.
3. R. Bhopal, “Race and Ethnicity, “Responsible Use from Epidemiological and Public Health Perspectives,” *Journal of Law, Medicine & Ethics* 34, no. 3 (2006): 500-507.
4. This, of course, isn’t necessarily true in a quantitative sense: what has happened is not an indicator of the *probability* of the thing happening again, absent a sufficient number of similar past scenarios to make prior occurrence statistically meaningful.
5. *Id.*
6. J. Kahn, “How a Drug Becomes ‘Ethnic’: Law, Commerce, and the Production of Racial Categories in Medicine,” *Yale Journal of Health Policy, Law & Ethics* 4 (2004): 1-46.
7. Indeed, it once was, with disappointing results, achieved years before the current, state-of-the-art drug treatment for heart failure (an angiotensin converting enzyme (ACE) inhibitor) became standard. BiDil in conjunction with an ACE inhibitor has never been studied in a multi-ethnic population.
8. From a patent law perspective, BiDil’s developers could have chosen a racial or ethnic group other than African-Americans. In this issue, the BiDil patent holder, Jay Cohn (who licensed his intellectual property rights to NitroMed, the drug combination’s developer), summarizes the BiDil investigators’ scientific rationale for selecting African-Americans. Cohn, *supra* note 2.
9. M. G. Bloche, “Race-Based Therapeutics,” *New England Journal of Medicine* 351 (2004): 2035-2037.
10. See generally, J. Avorn, *Powerful Medicines: The Benefits, Risks, & Costs of Prescription Drugs* (New York, N.Y.: Knopf, 2004) (reviewing the pharmaceutical industry’s responses to market and regulatory incentives).
11. J. Reichman, unpublished manuscript on file with author.
12. Conflicts-of-interest arising from relationships with pharmaceutical and biotechnology companies have become a matter of controversy for NIH-employed scientists as well as for researchers who receive regular funding from NIH’s extramural grant programs. See J. Kassirer, *On the Take: How Medicine’s Complicity with Big Business Can Endanger Your Health* (New York, N.Y.: Oxford University Press, 2004). These conflicts present serious problems, but the problems would be even greater absent a large, dependable flow of funding allocated in non-commercial fashion by NIH’s peer review system.
13. This approach would fit well with more robust FDA efforts to induce drug makers to track prescription-related adverse events after the agency approves new medicines.