Race-Based Therapeutics

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Are we moving into a new era of race-based therapeutics? The publication, in this issue of the Journal, of the African-American Heart Failure Trial (A-HeFT) (pages 2049–2057), a clinical trial of a medication intended for a single racial group, poses this awkward question. The study’s most striking finding — that the addition of isosorbide dinitrate and hydralazine to conventional therapy for heart failure reduced relative one-year mortality by 43 percent among blacks — will provoke wide discussion. The trial’s sponsor, NitroMed, which holds a patent on the fixed-dose combination of isosorbide dinitrate and hydralazine that was used, posits that heart failure has a different pathophysiology in blacks than in whites, necessitating different treatment strategies.

The reported 43 percent relative decrease in the rate of death due to heart failure among blacks is cause for celebration. There is wide agreement that blacks die from heart failure at rates disproportionate to those among whites. But to assess A-HeFT’s larger implications for the role of race in therapeutic design, it is important to be clear about what the study has not shown.

First, A-HeFT has not established that adding isosorbide dinitrate and hydralazine to conventional therapy for heart failure yields greater benefits for blacks than for other racial or ethnic groups. The study, which enrolled only self-identified blacks, did not test this hypothesis. The clinical and economic logic behind A-HeFT’s design has its roots in previous, multicentric studies that compared isosorbide dinitrate and hydralazine with other investigational drugs, administered in combination with different conventional therapies. These therapies were standard in their day but are inferior to the conventional therapy used today, which typically includes an angiotensin-converting–enzyme (ACE) inhibitor. Indeed, one of these previous studies helped to establish ACE inhibitors as standard treatment. This trial compared isosorbide dinitrate and hydralazine with the ACE inhibitor enalapril and demonstrated that enalapril resulted in a greater overall reduction in mortality.

An ill-defined subgroup of patients, though, did well when treated with isosorbide dinitrate and hydralazine and fared poorly with enalapril. Seizing on this opportunity, a biotechnology firm obtained intellectual-property rights to a fixed-dose combination of isosorbide dinitrate and hydralazine and sought approval from the Food and Drug Administration (FDA) in 1996 to market this formulation as a new drug. The FDA declined, citing statistical uncertainties in the trial data. That’s when race entered the picture. A group of investigators (including the holder of the patent on the combination treatment) reanalyzed the previous clinical-trial data according to race and concluded in 1999 that the combination treatment did as well as enalapril at prolonging the lives of black patients with heart failure. Other work suggested that ACE inhibitors were less effective in blacks than in whites.

At this point, it might have made clinical and scientific sense to add isosorbide dinitrate and hydralazine to conventional therapy (which by now typically included an ACE inhibitor) and to compare this combination to conventional therapy alone — for all patients with heart failure, regardless of race. Such a trial had not been performed, since the standard therapies used in earlier trials did not include ACE inhibitors. But race consciousness offered a faster way through the FDA’s regulatory maze. In 1999, NitroMed obtained intellectual-property rights to fixed-dose isosorbide dinitrate and hydral-
azine and said it would seek FDA approval to market the formulation as a therapy for heart failure in blacks. Two years later, the FDA indicated to NitroMed that successful completion of a clinical trial in black patients with heart failure would probably result in approval. This commitment gave rise to A-HeFT, and the publication of this trial’s results virtually ensures FDA approval. NitroMed’s race-specific strategy promises another large business benefit. Two years ago, NitroMed obtained a second patent, this one based on the use of the formulation in blacks. This patent, the first ever granted to a preexisting drug for a new, race-specific use, pushes back potential market entry by generic sellers of the fixed-dose combination from 2007 to 2020. Less than a month later, NitroMed went public, raising $66 million (even though isosorbide dinitrate and hydralazine are available separately in generic formulations, making it possible to closely approximate NitroMed’s combination at a cost of about 44 cents per dose).

Thus, the emergence of the combination treatment as a race-specific drug was driven in large measure by regulatory and market incentives. It remains unknown whether these two drugs in combination with an ACE inhibitor improve survival among patients with heart failure in general (or among patients in other racial groups) beyond the improvement achieved by ACE inhibition alone. But a treatment for all patients with heart failure, regardless of race, could not have extended NitroMed’s intellectual property protection by 13 years.

This is hardly to say that fixed-dose isosorbide dinitrate and hydralazine does not have differential effects, correlated with race. Evidence suggests that black patients with heart failure produce diminished levels of nitric oxide in their coronary and peripheral vasculature, putting them at greater risk than whites. The potential of the combination treatment to increase nitric oxide levels promises to reduce this risk differential. And more likely than not, other drugs will prove to have race-linked differential effects.

Proponents of exploiting these biologic differences to create new race-based therapies often say this approach treats race as a placeholder—a crude marker for genetic variations, not yet discovered, that lead to differences in responsiveness to drugs. They concede that skin color and other superficial features that culturally define race correlate poorly with genetic variations that shape the expression of disease. Finding these variations (and their physiological manifestations) and then linking these variations to differences in therapeutic efficacy should be our long-term research strategy; reliance on race is merely an interim step on the path to personalized pharmacotherapy.

This argument is a reassuring response to concern that emphasis on biologic differences among social groups risks stigmatizing some groups and, in recent history, has led to much worse consequences. But this response is problematic for several reasons. First, as A-HeFT illustrates, market and regulatory incentives shape research agendas. The ease with which race can be used as a crude marker for clinically relevant biologic difference makes it attractive as a basis for bringing pharmaceutical products to market. But once a pharmaceutical firm has obtained patent protection and regulatory approval, it has little incentive to sponsor research aimed at elucidating the relevant genetic variations and their physiological manifestations. Indeed, such research risks shrinking the demand for a
drug, by subtracting patients who lack the genetic markers that predict a good response. Such research is a classic “public good” in the economic sense: absent government support (or state-imposed obligation), it will tend to be undersupplied by market actors. And without the needed follow-up science, racial categories are at heightened risk of being reified as biologic.

Second, race is a very crude marker — ill-defined, indeed undefined. Again, A-HeFT is illustrative. Its investigators included patients who were self-identified as black. They thus delimited “blackness” in social and cultural fashion, poorly connected to underlying population genetics. People with one or a few (or even no) black ancestors who nevertheless experience themselves as black — or are stamped by others around them as black — are A-HeFT blacks. The probability of shared, clinically relevant genetics, connected to race, is diminished accordingly. The genetic heterogeneity of African peoples further reduces this probability. Our species is of African origin, and the African continent’s current population has had more time than its past emigrant groups to accumulate genetic variations. Other American racial categories are similarly heterogeneous and ill-defined. Latino descent encompasses multiple ethnic backgrounds from three continents; Asian origin represents a similar mix.

Third, group differences in pathophysiology and responses to treatment are not necessarily genetic. This fact is both obvious and often lost in the research literature on race-based therapeutics. A miasma of psychosocial, economic, cultural, environmental, and other determinants affects human physiology in ways that are poorly understood. There is evidence, for example, that social isolation, active versus passive coping styles, and confidence versus doubt about being able to handle life’s challenges influence both cardiodynamic and hemodynamic responses. To the extent that effects of this sort are not randomly distributed among racial groups, they play a role in racially disparate responses to treatment. We have hardly begun to elucidate these mechanisms. Focus on race as a genetic placeholder risks discouraging us from trying.

We need not shy away from the potential benefits of race-conscious therapeutics, but we should manage its downside risks. Greater awareness among physicians and the public that race is at best a placeholder for other predispositions, and not a biologic verity, would be a first step. Beyond such awareness, companies such as NitroMed — that stand to gain from taking account of race could commit a substantial portion of their profits to research on genetic, psychosocial, and other mechanisms that might underlie racial gaps in clinical response.

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