The Race to Prescribe

Drug for African Americans may debut amid debate

Ben Harder


Most modern medical research into race or ethnicity focuses on the disturbingly long list of health disparities among different groups. For example, compared with whites, blacks are 30 percent more likely to die of heart disease at any given age and 40 percent more likely to die of a stroke. Overall, blacks have an average life expectancy that's 5 years shorter than that of whites.

Identifying such inequalities is one step toward helping each population get appropriate medical care. Sometimes, that requires making the same tests and treatments available across the board, but it may also mean tailoring medicine to particular groups. For instance, a controversial new drug for heart failure may soon be approved specifically for African American patients. The drug, developed under the trade name BiDil and now being reviewed by the Food and Drug Administration, is likely to become the first therapy that the agency approves specifically for treatment of an ethnic or racial group.

Many physicians hail BiDil, which is produced by NitroMed in Lexington, Mass. Not only is it a lifesaving medication for a defined population of patients but it also serves as a promising new model for drug development. These proponents argue that research embracing racial differences in biology could lead to safer new treatments.

Race-based medicine could be a steppingstone to the higher goal of "targeted treatment," says Lawrence Lesko of FDA's Center for Drug Evaluation Research in Rockville, Md. Lesko and other advocates of this approach envision treatment tailored to people according to the results of genetic tests. They say that race-based medicine is just a first step toward discerning people's genetic makeup for the sake of better individual treatments.

Some researchers and medical-policy analysts, however, are troubled by the implications of practicing medicine according to patients' racial identities. They emphasize the incomplete correlation between genes of medical importance and labels of race or ethnicity (SN: 4/9/05, p. 232: http://www.sciencenews.org/articles/20050409/bob9.asp).

Cautious voices also warn that the wrong precedent by FDA in its handling of BiDil could contribute to, rather than reduce, health disparities between blacks and whites. Government endorsement of race-based therapies could spare companies the trouble of searching for biological beacons that could guide treatment in all populations, says Phyllis Griffin Epps of the University of Houston's Health Law and Policy Center. "As we move toward individualized medicine, race-based medicine might generate more problems than it solves," she says.

"There's only one human race," says cardiologist Anne L. Taylor of the University of Minnesota in Minneapolis. "But within that race, there are subpopulations that have small variations. Those variations can have an impact, and we have to explore them."

Heart of the matter

BiDil is a combination of two drugs that have had a roller coaster history in heart failure therapy. At one time, they were seen as the most promising combination therapy available, but drugs such as ACE inhibitors eclipsed them in
the early 1990s.

But while the newer medicines were more effective than the older compounds in cutting heart failure deaths in whites, the disease remained a stubbornly persistent killer in blacks. Today, among 45- to 64-year-olds, blacks are nearly twice as likely as whites to have heart failure and are 2.5 times as likely to die from it.

There’s evidence that isosorbide nitrate, one of BiDil’s ingredients, strengthens the heart by chemically donating nitric oxide to tissues. Nitric oxide widens blood vessels, reduces inflammation, and performs other functions essential to cardiovascular health. Researchers hypothesize that hydralazine, BiDil's other component, relaxes blood vessels while also, as an antioxidant, keeping nitric oxide active.

Several studies have suggested that active nitric oxide tends to be less abundant in blacks than in whites. That could partially explain why heart failure is a more serious disease among the former group, says Taylor.

Nearly a decade ago, FDA considered but rejected an application by a small biotech company to market BiDil. The application followed a trial that included patients of various ethnic backgrounds. The drug had showed only an inconsistent beneficial effect.

In 1999, University of Minnesota researchers reexamined the earlier data. They found that black people with heart failure had tended to benefit from the combination, while most whites hadn't.

With the support of NitroMed and the Association of Black Cardiologists in Atlanta, Taylor in 2001 launched a trial to test the effectiveness of BiDil specifically in blacks. The researchers asked patients with advanced heart failure to identify their ancestries. Only patients claiming African descent were invited to join the trial.

The study ultimately included 1,050 patients at 161 sites around the country. All the volunteers were already receiving heart failure drugs. Half of them then got BiDil in addition to their preexisting therapy, while half had a placebo added to their treatment.

The experimental therapy was a major success. Patients receiving BiDil were 43 percent less likely to die during a year of treatment than were those not getting that medication. The difference was so profound that a group of independent scientists monitoring the study recommended last summer that it be brought to an early end so that volunteers on the placebo could be switched to the potentially lifesaving treatment.

Taylor and her colleagues ended the study on July 19, 2004, and published their results in the Nov. 11, 2004 New England Journal of Medicine.

Now, FDA is reviewing their study as part of the evidence that the agency may use to approve the patented combination pill for use in blacks. Given the strength of the study's results, approval is widely expected, if not universally welcomed.

Many of a kind

While BiDil would be the first drug approved specifically for use in a racially defined subset of people, a patient's racial and ethnic group is already an important consideration for doctors prescribing certain treatments.

At least 29 medications have varying effects in different racial or ethnic populations, says biologist David B. Goldstein of the University College London. In the November 2004 Nature Genetics, he and his colleague Sarah K. Tate gave a detailed account of these treatments, which range from antipsychotics to cancer-chemotherapy drugs.

"Many differences in drug response associated with race or ethnicity are due to environmental [factors such as diet] rather than population genetic differences," they say. "In the case of BiDil, it is not currently known whether it works differently in African Americans and European Americans because of genetics, environment, or both."

Genetic traits do appear to underlie some differences in disease susceptibility and response to therapies. For example, researchers have noted for years that because of differences in enzyme activity, people of Asian descent metabolize cholesterol-lowering statin drugs more slowly than other people do. As a result, some studies suggest, Asians are more susceptible to side effects at a given dose of statins. FDA recently advised physicians not to administer the highest allowed dose of one such drug, rosuvastatin (Crestor), to people of Asian ancestry.

The biological mechanism remains opaque in other instances where medications have differential effects in various ethnic groups.
"Our understanding of race and drug response is at best very superficial," says Lesko. Basing medical decisions on a patient's self-reported race, rather than on clinically meaningful genetic traits, he says, is "like telling time with a sundial instead of looking at a Rolex watch." All the same, he and others say, the proverbial sundial is useful when no high-accuracy wristwatch is yet available.

"Until such time as you can go and directly sample [the relevant genetics of] an individual, the question is going to be, What proxies can you use?" says pediatrician and professor of law Ellen Wright Clayton of Vanderbilt University's Center for Genetics and Health Policy in Nashville. "The big one is going to be race."

Defining groups by the external cues used to indicate race is far from ideal, Lesko says. "But in the absence of other alternatives, we need some way to group patients," he adds.

That makes the shortcut of judging patients' races—or asking them to categorize themselves—an appealing alternative for doctors. BiDil is "the first racial drug," says Troy Duster, a sociologist at New York University. "That means there's going to be a second, and a third."

**Push for precision**

Scientists have a "critical obligation" to identify the medically essential genetic variations that correlate with racial identity, Clayton says. It's those variations, not the identity, that should ultimately guide treatment, she says.

In some cases, scientists have already progressed from a racial distinction to a genetic one. Researchers at Vanderbilt and elsewhere noticed several years ago an overall difference between the reactions of groups of white and black patients to the anti-HIV drug efavirenz. That agent was considerably more likely to cause side effects in blacks than in whites. Instead of simply recommending a lower dose of the drug for the black patients, the researchers decided to investigate further.

David W. Haas of Vanderbilt and his colleagues identified a single genetic site with natural variation in both races. One genetic variant, which is seven times more common in blacks than in whites, slows metabolism of efavirenz. That accounts for the different risks of side effects in the two groups, the scientists reported (SN: 2/21/04, p. 117: Available to subscribers at http://www.sciencenews.org/articles/20040221/fob6.asp). An individual's variant at the genetic site is more useful for guiding treatment than is his or her self-reported race, Haas says. However, there's no commercial test currently available for distinguishing those variants.

Taylor and her colleagues are working to move BiDil treatment from a race-based to a gene-specific approach. They're examining genetic differences in a subset of the BiDil trial's volunteers to look for a deeper biological explanation of how the drug works and for whom it's best.

Unearthing specific segments of DNA that explain individuals' differences in drug response would be ideal for patients, Clayton says, but economics might be working in just the opposite direction.

Testing patients' genetic differences is more costly and time-consuming than is interviewing them about their ancestry. Furthermore, Lesko says, there's no point in approving a drug for genetics-based clinical use unless a test for the relevant genetic trait is widely available to doctors.

FDA has released guidelines on how pharmaceutical companies can develop such diagnostics, and last December, it approved the first commercial screening test for a gene that affects drug metabolism. That test can guide physicians in the dosages that they prescribe for certain antidepressants, antipsychotics, and chemotherapy drugs. However, relatively few drug companies see potential for profit from such products, Lesko says.

What's more, pharmaceutical firms may find it better for business to delve no deeper than racial differences. Lesko says that information identifying which patients won't benefit from a drug might narrow, rather than expand, the number of people for whom the drug can be recommended.

On the other hand, he adds, both drug companies and patients would benefit from genetic tests that flag people—of any race—most likely to suffer drug-related side effects. In the case of the HIV drug efavirenz, for example, doses could be adjusted for the whites, as well as for the blacks, who have the genetic trait that's been associated with problems.

Fewer side effects mean less regulatory hassle for the companies, so the pursuit of drug safety could drive research that pulls back the veil of race, Lesko says.

Given today's concern over drug safety, that improvement in treatment precision could make a difference in
patients' lives and on companies' bottom lines, ultimately advancing the prospect of individualized medicine. One
day, people may be treated not by the color of their skin but by the content of their genome.

**Part I of this series: "Code of Many Colors," appeared in last week's issue. Available at**

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**References:**


**Further Readings:**


- For information on the African American Heart Failure Trial (A-HeFT), go to http://www.aheft.org.

- For further information about the Association of Black Cardiologists, go to http://www.abcardio.org.
For information about BiDil®, go to http://www.nitromed.com/BiDil.asp.

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