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The Genome in Black and White (and Gray)

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Imagine that you have heart failure. What can medicine do for you? It depends: are you white or black? If you're white, your doctor may prescribe one of the drugs that seem to ease the symptoms, maybe a beta-blocker or an ACE inhibitor. And if you're black, your doctor may still prescribe those drugs, but they might not really help.

That's about to change. In the not-too-distant future, if you're black and have heart failure, drug-company researchers predict you'll be able to go to the doctor and walk out with a prescription tailor-made for you. Well, not tailor-made, exactly, but something that seems to work in people a lot like you. Well, not a lot like you, exactly, except that they're black, too. In this not-too-distant future, if you're black, your doctor will be able to prescribe BiDil, the first drug in America that's being niche-marketed to people of a particular race -- our first ethnic medicine.

BiDil, expected to be approved early next year by the Food and Drug Administration, is on the leading edge of the emerging field of race-based pharmacogenomics. It signals a shift in perception, a new approach to medicine that has at its core an idea at once familiar and incendiary: the assumption that there are biological differences among the races.

BiDil is also a feat of creative repackaging. Five years ago, the F.D.A. rejected it for use in the general population because it was found to be ineffective in the treatment of heart failure, a common complication of cardiovascular disease that affects some five million Americans and leads to 300,000 deaths a year. But in 2001, the manufacturer, NitroMed, asked permission to test BiDil exclusively in blacks, whose heart failure tends to be more severe and harder to treat. The company reasoned that the drug's effect on nitric-oxide deficiency, more common in black heart-failure patients than in nonblacks, might make it especially suited to them. With the collaboration of the Association of Black Cardiologists, NitroMed embarked on a large clinical trial involving more than 400 black women and 600 black men, all of whom had heart failure.

Last summer, investigators called an early end to the study because they thought BiDil was so effective that it would be unethical to continue to deny it to people in the control group. Thus, a drug that had been deemed ineffective in the population at large seemed to work so well in one racial subgroup that the scientists thought everyone in that subgroup should get it.

Pharmacogenomics has for years been touted as the ultimate benefit of the genomics revolution. But to many, this revolution has a troubling side. For race-based niche marketing to work, drug developers first will have to explore the ways that blacks, whites, Asians and Native Americans are biologically different. And the more they explore and describe such differences, critics say, the more they play into the hands of racists. Even the broad-minded might inadvertently use such information to stigmatize, isolate or categorize the races. Could it be that this terrain is too dangerous to let anyone, no matter how well meaning, try to navigate it?

In two weeks, a major scientific journal, *Nature Genetics*, will publish a special issue on the genetics of

race. This comes on the heels of several conferences on the subject, most recently one held last Monday by Johns Hopkins University, as well as editorials in the science press, including one in the Journal of the American Medical Association just last week. All of these forums pose some thorny questions: Can genes tell us anything meaningful about race, beyond the obvious connection to things like skin color? Do the races differ biologically in terms of drug response or disease susceptibility? Can genes say anything about how "race" -- which is itself all but impossible to define -- is related to complex traits like behavior and intelligence?

Looking for biological determinants of race is nothing new. It has a potent history, with poisonous associations dating back to the early days of eugenics. But contemporary science has given these efforts a new respectability. In the wake of the completion of the Human Genome Project, geneticists are trying to arrange pieces of the genome like a Rubik's Cube, searching for patterns of variation that align into some useful matrix. Their goal is to generate information that will help prevent and treat common diseases. But in the process, they're generating information that might also lead to declarations about the biological meaning of race.

The new interest in racial genetics comes at a time when the softer sciences, like anthropology and sociology, have declared that race is a cultural construct, without any biological significance. The social designations go back at least to the 19th century, when humans were generally divided into five races that were loosely tied to skin color; this has lingered as the basic grammar of race even into the 21st century. But in a 1998 position paper, the American Anthropological Association called race a social invention, with a variety of pernicious consequences ranging from day-to-day bigotry to the Holocaust. Racial beliefs are myths, the anthropologists wrote, and the myths fuse "behavior and physical features together in the public mind, impeding our comprehension of both biological variations and cultural behavior, implying that both are genetically determined."

Geneticists, too, have gone on record as saying that race has no biological significance. "The concept of race has no genetic or scientific basis," said J. Craig Venter in June 2000, standing beside President Bill Clinton to announce the completion of the first draft of the human genome sequence. Venter was at the time the president of Celera, the private company that competed with the National Human Genome Research Institute, a publicly financed international team, to sequence the genome. (It was declared a tie.)

Venter's scientific rival, Francis S. Collins, the head of the genome institute, stood at the podium that day on Clinton's other side -- two male, middle-aged white scientists saying we're all brothers and sisters under the skin. Collins made much of the fact that humans share 99.9 percent of their genome with one another -- and that the remaining 0.1 percent probably codes for variations, like skin color, that are for the most part biologically insignificant. In fact, there is more variation within races than between them. A few months later he made the point more informally, playing his electric guitar and regaling his co-workers with a musical ditty he had written to the tune of Woody Guthrie's "This Land Is Your Land":

"We only do this once, it's our inheritance,
Joined by this common thread -- black, yellow, white or red,
It is our family bond, and now its day has dawned.
This draft was made for you and me."

Today, the two men have parted company on this narrow strip of common ground. Venter says he still believes the genome is colorblind. "I don't see that there's any fundamental need to classify people by race," he says. "What's the goal of that, other than discrimination?"

But Collins sees the matter differently now. Maybe in that 0.1 percent of the genome there are some variations with relevance to medicine, he says. And maybe identifying them could help reduce health disparities among the races. He is using his bully pulpit at the genome institute to urge scientists to study whether these variations can, or should, be categorized according to racial groupings.

"It's always better to face up to a controversial scientific issue, to tackle the issue head on and not run

away from it," Collins says. "And if we don't do it, someone else will -- and probably not as well."

One reason to focus on the genetics of race is to try to make a dent in health disparities: the frustrating gap in the health status of different racial groups that stubbornly refuses to close or even to be adequately explained. In terms of national measures of physical well-being -- life expectancy, infant mortality, some chronic diseases -- blacks tend to do worse than whites. Many factors account for this health gap, including the fact that minorities suffer disproportionately the effects of low income, lack of health insurance, poor diet, exposure to environmental toxins, discrimination and stress. But some geneticists think that at least some part of health disparities can be explained by genes. Social scientists think genetic explanations might obscure the all-too-real social and economic causes.

Take hypertension, which affects black Americans at a higher rate than white Americans. Geneticists try to explain this difference in terms of genes: genes for salt retention, genes for low levels of renin in the kidneys. But a classic study found that one thing that correlated most strongly with level of blood pressure was, surprisingly, skin color. Among black subjects of low socioeconomic status, the darker the skin, the higher the blood pressure. Social scientists' explanation is that people with darker skin are subject to greater discrimination, and therefore to greater stress.

"If you follow me around Nordstrom's, and put me in jail at nine times the rate of whites, and refuse to give me a bank loan, I might get hypertensive," says Troy Duster, a professor of sociology at New York University and at the University of California at Berkeley. "What's generating my increased blood pressure are the social forces at play, not my DNA."

But pharmacogenomics researchers presume that health disparities can be addressed, at least in part, by exploiting tiny group differences in DNA. If the BiDil experience pans out, other companies are likely to try their own versions of race-based drug development. Some candidates already exist. People known as slow acetylators, for instance, take a longer time than fast acetylators to clear certain drugs from the liver. This means they're more likely to build up toxic levels of some common drugs. The proportion of slow acetylators in different racial groups ranges from a low of 14 percent among East Asians to a high of 54 percent among whites. Some whites, therefore, might benefit from a different version of medications that are cleared through the liver.

The ultimate goal of pharmacogenomics would be for everyone's genome to be analyzed individually, so that doctors could gauge how much of a medication, and which type, is most likely to work for a specific patient. Even the BiDil investigators are moving in that direction. Michael D. Loberg, the president of NitroMed, says that the company asked each participant in the BiDil trial for permission to take a DNA sample and that he hopes to get a total of at least 400 such samples. These will be sequenced, he says, "to see if there's some genetic marker that predicts which of the trial patients responded to BiDil favorably and which didn't."

But at this point, geneticists cannot sequence individual genomes in a cost-effective way. Until they can, they may view race as a handy shortcut, a way to make some useful generalizations about how an individual patient will fare with a particular drug. But while using race this way might increase the odds of finding the right medication, it is an imprecise method, a kind of roulette in which the physician is making educated guesses based on probabilities.

The temptation of race-based medication is clear: it's convenient for the investigator, and it suits the way drug companies' products are sold. "The mantra of pharmacogenomics is that drugs will be fine-tuned for the individual," Duster says. "But individuals are not a market. Groups are a market." And one typical way to identify markets, in a country where skin color seems to count for so much, is race.

In terms of our genes, we humans are all the same -- except for the ways in which we're different. The human genome comprises 3 billion nucleotides, strung together in a specific order along the chromosomes. About 99.9 percent are identical from one person to another, no matter what that person's

race, ethnicity, continent of origin or bank account.

Among our 3 billion nucleotides, an estimated 10 million are locations of common variations. Where most people will have a nucleotide represented by the letter A, for instance, a big group of people might have a T instead. Elucidating where those spots are, and whether replacing a T with an A has any clinical significance, are what occupies today's geneticists.

The most common type of variants are called single nucleotide polymorphisms, or SNP's (pronounced "snips"). Usually they occur in regions where the nucleotides seem to be doing nothing. This means the SNP's don't have any function, either, or at least none that has been discovered yet; they're just there.

Still, SNP's tend to occur in different patterns in different populations. Say there's a SNP on Chromosome 12 in which a person might have either an A or a T. At this hypothetical SNP, 20 percent of Africans might have an A, and 80 percent a T. At the same spot, the frequency might be flipped in Europeans: 80 percent might have an A, while only 20 percent have a T.

So while SNP patterns don't reveal anything about the function of the genes, they can say something about an individual's continent of ancestry -- and, by extension, something about migration pathways through human history. SNP's tend to be inherited in clusters, called haplotype blocks. Like SNP's, varieties of haplotype blocks occur at different frequencies in different regions of the world -- and that's how population geneticists have managed to reconstruct the story of human migration.

The biggest variety of haplotype blocks occurs in Africa, because modern humans arose there more than 150,000 years ago, and variations have had the longest chance to accrue simply because of random mutations. About 55,000 years ago, a small group of modern humans, who carried in their genomes a subset of the original haplotype varieties, traveled to Australia; later, in sequence and timing that are still a source of controversy among paleoanthropologists, other small groups migrated to parts of Europe, Asia and the Middle East.

As time went on, there were some evolutionary changes in response to the new environments. In Northern Europe, for instance, people carrying mutations for lighter skin color thrived, probably because the scarcity of sunlight made dark-skinned people especially susceptible to Vitamin D deficiency and rickets. But most of the variations occurred in the nonfunctional regions of the genome, with no effect on an individual's appearance or health. All that the variations did was allow geneticists, some 2,000 generations later, to assign a continent of origin to the descendants of these original travelers based on the descendants' DNA.

To the dismay of Troy Duster, several private companies are now taking these findings about SNP's to a new level: scanning the genome for variations that can say something about an individual's race. Last year, a company called DNAPrint Genomics made headlines by telling law-enforcement officials in Louisiana that they'd been looking for a serial killer of the wrong race. Eyewitnesses had offered different accounts of the race of the suspect -- some thought he was black, others white -- and authorities had focused their search on white males between the ages of 25 and 35 based in part on an F.B.I. psychological profile. But based on crime-scene specimens, DNAPrint said the murderer was probably black -- in fact, the company said it could detect 85 percent sub-Saharan African ancestry and 15 percent Native American -- and even gave an assessment of his skin tone. When a black male was apprehended, his DNA was found to match that at one of the crime scenes. He was convicted of second-degree murder in August.

For some, this would be a story of science advancing police work. But for people like Duster, the forensic use of genetic markers raises troubling questions. Can a DNA screen of a person's blood or hair really tell you anything more than where his ancestors probably came from? Would it lead to witch hunts based on some uncertain appraisal of skin color? Would it be used, wrongly, to give a patina of scientific authority to group prejudices?

Worried, Duster approached his friend and colleague, Francis Collins, to suggest that Collins might want to use his position at the genome institute to mount an investigation into the genetics of race -- before the drug manufacturers and genomics companies set the tone for the public debate.

Collins says he was already thinking the same thing. The two men approach the venture from different perspectives, less because Collins is white and Duster is black than because one is a geneticist and the other a sociologist. As Duster sees it, race is a relationship, largely dependent on social context. Take a Tutsi and a Hutu and set them down in Los Angeles, he says, and they're both the same race, both black. But put them back in Rwanda, and they're two different races, different enough to slaughter each other.

There may be biological dimensions to race, Duster says, but that doesn't take away from his belief that race should be understood as a social construction. "The myth is that somehow the biology is real and the social forces are unreal," he says. "In fact, the social forces can feed the biological forces."

Collins, for his part, recognizes that social forces explain many of the observed differences among the races -- but says he thinks something else might be involved as well. "We need to try to understand what there is about genetic variation that is associated with disease risk," he says, "and how that correlates, in some very imperfect way, with self-identified race, and how we can use that correlation to reduce the risk of people getting sick."

Taking up Duster's challenge, Collins knew, meant walking into a quagmire. A decade earlier, another top government scientist lost his job by discussing the genetics of urban violence (though his case was egregious: he compared young black men with male monkeys). But Collins said he believed the idea, risky as it was, was worth pursuing because it offered the best chance of converting new genomic information into something of medical significance.

The genome institute, part of the National Institutes of Health in Bethesda, Md., currently spends some \$31 million for studies into human genetic variation. The institute is also a major contributor to the Hap Map project, a \$110million international collaboration that by late 2005 will have put together a coherent almanac of human variation using haplotype blocks. The Hap Map is meant to help scientists in their search for common disease-causing genes, but in the process it will also generate new information about the specific ways in which populations from the places being studied -- China, Japan, Nigeria and, in the United States, Utah -- differ from one another genetically.

Collins is clean-cut and homespun, emphatically tall, with a fringe of sandy hair that makes him look younger than his 54 years. He exudes an aw-shucks earnestness when he talks about his favorite topics, which include his rebirth as a Christian during his medical training. Each time he makes a scientific discovery, he says, he gets a glimmer of insight into the workings of the mind of God.

But for all his personal sincerity, Collins is finding that some of his allies are wary of this newest undertaking. They know that even a man with the best intentions can muck it up when it comes to race.

While writing this article, I took a trip to the Holocaust Memorial Museum in Washington. I wanted to see the museum's current exhibit about eugenics, the scientific movement of the early 20th century that looked for evidence of biological racial differences to promote creation of a "fitter" species. In a very short time, eugenic ideas were subverted to support Nazi policies of ethnic cleansing and racial extermination. Since last spring, when Collins called to suggest that I might be interested in his institute's plan to investigate the genetics of race, I had talked to more than two dozen scientists about the issue. Uncomfortable questions about where such inquiries could lead underscored a number of those conversations -- the sort of questions that, as a white person in America today, I don't usually have to confront. I went to the Holocaust museum looking for resonances.

How disturbing it was to see that the activities of the early eugenicists resembled, from a certain perspective, the activities of specimen collectors of the early days of zoology -- as well as those of

genomics researchers today, going around collecting specimens of human variation. The eugenicists engaged in some straightforward scientific studies that can seem almost harmless, even ordinary. And that's what makes it so troubling to look back.

With rulers, calipers, charts of eye shapes and elaborate reconstructions of family trees, eugenicists of the 1920's and 30's took great care to describe physical characteristics of different racial groups. They photographed subjects, measured their noses and mouths, made plaster casts of their faces and documented variations in facial features and head proportions. Is it possible that the difference between then and now is that the tools have changed -- that instead of using calipers and scales, scientists now use DNA-sequencing machines?

Connecting contemporary genomic studies to the Holocaust is too glib, of course, and it obscures one crucial point: that the anthropometrics of the early eugenics movement turned ugly once fanatics perverted the information. But the exhibit is a sobering reminder of how easy it would be to travel down that path. "I think our best protection against that -- because this work is going to be done by somebody -- is to have it done by the best and brightest and hopefully most well attuned to the risk of abuse," Collins says. "That's why I think this has to be a mainstream activity of genomics, and not something we avoid and then watch burst out somewhere from some sort of goofy fringe."

Collins doesn't quote the Bible often -- he tends to neither hide nor flaunt his religious faith -- but he quotes it now. He chooses a line

from the New Testament's Book of John, in which Jesus says to his disciples, "And you shall know the truth, and the truth shall set you free."

Reducing health disparities and catching criminals are serious reasons for pursuing the genetics of race, but there's also a small but growing trend toward something its practitioners call "recreational genomics." To satisfy curiosity about their heritage, more and more people are experiencing race-based genomics as a mail-in test, for which they pay up to \$400, that will tell them how much of their genome is black, white, American Indian or Asian. These companies go beyond old-fashioned genealogical services, the kind that involve scouring archives and huddling over microfiche machines, and trace genetic linkages back many generations to a particular geographic location. Critics say that what these companies are doing sanctifies the genetic distinctions among racial groups, as if the question of whether race has a biological basis has been settled.

The services, with names like GeoGene, AncestryByDNA and Roots for Real, begin by asking clients to mail in a cheek swab to get some stray skin cells from which DNA can be extracted. Though the process may feel like a parlor game, the results can be deeply affecting. One of those who traced his genetic lineage through a company called African Ancestry is Andrew Young, former United States ambassador to the United Nations and now chairman of an organization called Good Works International.

Young was looking for information about his maternal lineage only; he assumed, he told me, that his paternal lineage would be "contaminated" with white DNA, a bitter memento of slave rape that he didn't feel ready to confront. (According to Rick Kittles, a cofounder of African Ancestry and a geneticist at Ohio State University, about one-third of blacks who do a paternal lineage analysis, himself included, find that there is European DNA somewhere in their past.)

When a black client discovers that there's white in his genome, the results can be shattering. Last year, the ABC News program "Nightline" profiled a 50-year-old California man who had assumed his whole life that he was black. But a recreational genomics analysis by DNAPrint Genomics indicated that his genome was 57 percent of what the company called Indo-European, 39 percent Native American, 4 percent East Asian -- and zero percent African. So what is this man: the race he has always thought himself to be, or the race his genome says he is?

Young's reaction to his African Ancestry report is an indication of how much weight we ascribe to genes, how much we believe our DNA reflects not only our racial identity but our individual identity, too. When Young heard that the company had traced his DNA back to what is now Sierra Leone, he was disappointed because he considered Sierra Leone to have a "snobbish" middle class. But the report got much more specific: the people whose SNP pattern most resembled Young's, it said, were from the Mende tribe. Whether a few SNP matches can allow such precision is a matter of debate, but it fit happily into Young's self-image. Young, who got his start in the civil rights movement, was raised on tales about the Amistad slave-ship rebellion of 1839, for which the Mende were responsible. "I always had a spiritual connection to these stories," he says. "Now I have a genetic connection."

So is there such a thing as race? It depends on whether you're defining it in terms of culture or biology. Culturally, there is no denying it. In the United States, with its race-stained legacy dating back to slavery, the government has tried for centuries to define a person's race. The Census Bureau has been asking about race on its forms since 1790, most recently giving individuals the opportunity to check off more than one race if they so desire.

But the more vexing question is whether there's such a thing as race in terms of biology. Genetic variations do seem to cluster differently for people with different continents of origin, but is this race? And what does it mean if it is -- or if it isn't? Do we need to agree on whether race is a biological entity, since we can so readily agree that it's a social one?

"Race is a reality in this country, no matter what the genome tells us," says Vanessa Northington Gamble, director of the National Center for Bioethics in Research and Health Care at Tuskegee University. "If I can't get a cab in New York, it's because my skin is black. And I can't hold up my DNA and say: 'Wait a minute! I'm just the same as you!'"

Some critics worry that the more we find out about genetic differences among people of different racial groups, the more such information will be misinterpreted or abused. Already there are fears that the biological measures of racial differences might lead to pronouncements about inherent differences in such complex traits as intelligence, athletic ability, aggressiveness or susceptibility to addiction. Once such measures are given the imprimatur of science, especially genomic science, loathsome racist stereotypes can take on the sheen of received wisdom.

Looking for racial genetic markers does indeed risk creating categories that can get us in trouble. It bears remembering, however, that the "slippery slope" argument is itself a danger. Rather than abort a whole field of research because it might bolster cranks and demagogues, maybe one solution to our national angst over race is to let scientists hunt down the facts -- facts that will no doubt affirm, one way or another, that the human genome is indeed our common thread.

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