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**HEADLINE:** **Race Is Seen as Real Guide** To Track Roots of Disease

**BYLINE:** By NICHOLAS WADE

### **BODY:**

Challenging the widely held view that race is a "biologically meaningless" concept, a leading population geneticist says that race is helpful for understanding ethnic differences in disease and response to drugs.

The geneticist, Dr. Neil Risch of Stanford University, says that genetic differences have arisen among people living on different continents and that race, referring to geographically based ancestry, is a valid way of categorizing these differences. Dr. Risch's position was prompted by an editorial last year in *The New England Journal of Medicine* asserting that "'race' is biologically meaningless," and one in *Nature Genetics* warning of the "confusion and potential harmful effects of using 'race' as a variable in medical research."

Dr. Risch's assertion, in a paper in the online journal *Genome Biology*, comes as researchers and physicians are trying to interpret the DNA data streaming from the Human Genome Project and to make sense of the fact that the pattern of data differs among ethnic groups.

All humans have the bulk of their genetic heritage in common and possess the same set of genes. But because of mutations, or changes in DNA, each gene comes in several slightly different versions, and some of them are more common in one ethnic group than another. These genetic differences often have medical significance, since some occur among genes that affect susceptibility to disease and the response to drugs.

It has long been known that some diseases are not evenly distributed. For example, a mutation that causes hemochromatosis, a disorder of iron metabolism, is rare or absent among Indians and Chinese but occurs in 7.5 percent of Swedes. A common mutation that causes sickle cell anemia is prevalent among Africans and is thought to have originated among Bantu-speakers before the Bantu

expansion 2,000 years ago.

Lactose intolerance, the loss of the ability to digest lactose after weaning, is the default condition of humankind but among Northern Europeans the ability is often retained into adulthood. The reason is a mutation that may have been favored among early cattle farmers.

The apparent correlation between race, genetic data and disease has prompted at least two schools of thought among biomedical researchers. One holds that race is so poorly defined that it is not a reliable biological concept and should be banished, if possible, from scientific vocabulary. This is the view espoused by The New England Journal of Medicine.

Many population geneticists, on the other hand, say it is essential to take race and ethnicity into account to understand each group's specific pattern of disease and to ensure that everyone shares equally in the expected benefits of genomic medicine.

Meanwhile a proposal for avoiding racial labels, at least for drug trials, has recently been made by Dr. David Goldstein, a population geneticist at University College, London. He has suggested that patients be assigned to different genetic groups by analyzing their DNA. The process gives much the same result as asking people to identify their ethnicity, but yields a more accurate division in terms of how people respond to drugs, Dr. Goldstein says. He adds that the expense of the genetic testing will be affordable in drug trials.

In asserting that race is a valid concept for medical research, Dr. Risch has plunged into an arena where many fear to tread. He also takes issue with Dr. Goldstein's race-sidestepping proposal, saying it will lead to confusing results.

Race, as Dr. Risch describes it, has arisen because of the numerous small genetic differences that have developed in populations around the world. Many studies, Dr. Risch writes, have shown that these differences cluster into five major groups, which are simply the world's major continental areas.

When modern humans spread out of Africa and across the globe, these early populations bred for many generations in substantial isolation from one another, allowing genetic differences to build up between groups. These five geographically isolated groups, in Dr. Risch's description, are sub-Saharan Africans; Caucasians, including people from Europe, the Indian subcontinent and the Middle East; Asians, including people from China, Japan, the Philippines and Siberia; Pacific Islanders; and Native Americans.

There are also many peoples who are genetic admixtures of the major groups. Somalis and Ethiopians, on the boundary between Caucasians and Africans, are an admixture of the two, Dr. Risch said, as are African-Americans.

Dr. Risch calculates on the basis of existing surveys that testing a person's DNA at

100 random sites along the genome, or at 30 specially chosen ones, would be sufficient to distinguish the major racial groups. It would require tests at some 50 specially chosen sites to distinguish people from different ethnic groups within a race, he said.

The ancestral human population would have contained within it many genetic differences and alternative gene forms inherited from the predecessor species. This shared pool of differences still accounts for 85 percent to 90 percent of those seen in the global human population, according to many measures. The differences between ethnic groups account for the other 10 percent to 15 percent. This well-known analysis, however, is based on commonly occurring versions of genes, and rare versions of genes, when measured, may show a greater tendency to be specific to different populations, Dr. Risch said.

Dr. Risch believes that race, when self-defined by continent of ancestry, is a true reflection of these genetic differences, including those important for understanding disease. "There is great validity in racial/ ethnic self-categorizations, both from the research and public policy points of view," he says.

Editors of both the journals criticized by Dr. Risch expressed respect for his views. Dr. Robert Schwartz, the deputy editor of The New England Journal of Medicine and the author of its editorial, said Dr. Risch's article was "a serious piece of work and merits a lot of thought."

Dr. Bette Phimister, editor of Nature Genetics, said that "Risch's point that there is a high and useful degree of correlation between ethnicity/race and genetic structure, is well taken, and one with which we agree."

Both editors also expressed support for the proposal advanced by Dr. Goldstein, that of bypassing race by going directly to the genetic markers in each patient that might correlate with drug response or disease.

Dr. Goldstein, too, said he agreed with Dr. Risch that "the geographic patterning of genetic variation is real and has medical implications and one does need to take account of it."

"Neil is arguing against some people in the medical community who say racial labels have nothing to do with drug response, and he is right," he said.

But Dr. Goldstein says he believes the genetic variation can be studied directly, without invoking race. In an article last year in Nature Genetics, he and colleagues analyzed genetic markers in people from eight ethnic groups. When the people were regrouped according to their genetic markers, that proved a better guide to drug response than did their ethnic group, Dr. Goldstein reported.

But Dr. Risch said it was unsatisfactory to sidestep race, because it might lead researchers to ignore the many other factors besides genetics that are associated

with race. Dr. Goldstein's genetic marker system, which divides people into almost exactly the same categories as does geographically based race, would compel a researcher to think the only differences between two groups were genetic. If the two groups were Caucasian-Americans and African-Americans, say, the researcher might be blinded to other explanations, like a difference in access to medical care.

Dr. Goldstein said that to understand the geographical pattern of human genetic variation, "you want the best representation you can find, and it is a technical question as to whether explicit genetic representation or racial labels are better."

"That's an argument we will have in the scientific literature, and Neil will lose," Dr. Goldstein continued.

Race and ethnicity have become important considerations for biologists hunting for the variant genes that predispose people to common diseases. Failure to take ethnicity into account can confound a study, particularly if the disease in question is more common in one ethnic group than another.

Scientists often hunt for genes in laboratory animals by mutating them with radiation or chemicals. No one would think of inducing informative sets of mutations in people, but nature has already performed the experiment by shaping the human population into groups with differing susceptibilities to disease. This genetic differentiation among races is one that some gene hunters would like to exploit.

Dr. Stephen O'Brien, a geneticist at the National Cancer Institute, said that the conclusion that race was not a valid concept "comes from honest and brilliant people who are not population geneticists."

"That doesn't mean they are insincere," Dr. O'Brien said. "It's just that they haven't really looked at it. What is happening here is that Neil and his colleagues have decided the pendulum of political correctness has taken the field in a direction that will hurt epidemiological assessment of disease in the very minorities the defenders of political correctness wish to protect."

Others play down the medical usefulness of racial differences. "We can't wish away these boundaries," said Dr. Aravinda Chakravarti, a population geneticist at Johns Hopkins. "But I'm not convinced that knowing these boundaries is necessarily useful for genetic research."

Dr. Risch concludes his review by noting that every race and ethnic group within a race has its own set of diseases and clinical priorities, which a new arsenal of genetic tools is poised to address. "We need to value our diversity rather than fear it," he writes. "Ignoring our differences, even if with the best of intentions, will ultimately lead to the disservice of those who are in the minority."

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**GRAPHIC:** Photo: Dr. Neil Risch says ignoring race in gene studies will "lead to the disservice of those who are in the minority." (Peter DaSilva for The New York Times)(pg. F2)

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