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Perspective Roundtable

Race in Medicine — Genetic Variation, Social Categories, and Paths to Health Equity

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Introductions

DR. MICHELE EVANS: Welcome to the Race and Medicine Roundtable hosted by the *New England Journal of Medicine*. My name is Michele Evans. I am the deputy scientific director at the National Institute on Aging. I will serve as the moderator today. In addition, I'm a member of the NEJM editorial board.

I'm joined today by several esteemed panelists: Dr. Joseph Graves, Dr. Ruth Shim, Dr. Sarah Tishkoff, and Dr. Win Williams.

DR. JOSEPH GRAVES: My name is Joseph Graves, Jr. I am a professor of biological sciences at North Carolina A&T State University. My research concerns the genomics of adaptation as well as biological and social conceptions of race in humans.

DR. RUTH SHIM: Hi, everyone. My name is Ruth Shim. I am the Luke and Grace Kim Professor in Cultural Psychiatry at the University of California at Davis. I'm also the associate dean of diverse and inclusive education at the University of California at Davis and the School of Medicine. My background relates to structural racism as it relates to mental health, and the outcomes of racism and the impact on mental health.

DR. SARAH TISHKOFF: Hello, my name is Sarah Tishkoff. I'm a professor in the Departments of Genetics and Biology at the University of Pennsylvania. I'm also the director of the Center for Global Genomics and Health Equity at the University of Pennsylvania. My research focuses on studies of the human population genetic diversity with a focus on Africa. I study human evolutionary history in Africa and the genetic basis of both normal variable traits as well as disease risk, with an emphasis on people of African ancestry.

DR. WIN WILLIAMS: Hello. My name is Dr. Win Williams. I'm the associate chief of the Division of Nephrology at Massachusetts General Hospital and an associate professor of medicine at Harvard Medical School. I'm also the founding director of the Center for Diversity and Inclusion at MGH, and also

a deputy editor at the New England Journal of Medicine. My research interests are health disparities in transplantation and molecular biomarkers in kidney transplantation and end-stage renal disease.

DR. EVANS: Medicine and health care are parts of U.S. society, as we're all aware, and therefore are affected by and contribute to structural racism that thwarts equal treatment as well as equal educational and professional opportunities in medicine. It also thwarts us as a nation achieving health equity. This, as you all know, is a multi-level problem that will require a strategic examination by all stakeholders in medicine and health care and in the biomedical research enterprise.

Today's discussion will focus on the use of race in medicine and its perceived role in disease and treatment. Discussions like this may be a critical first step in acknowledging how structural racism functions in health care and, perhaps, can inform our efforts to dismantle health care inequities.

I think we all feel that the goal is to find the best path forward to health equity, but we have to realize that this path may be envisioned differently by different constituencies. And there are many questions that need to be asked and answered. And they include: Exactly what *is* race? And how *should* it be used in medicine and biomedical research? Is race a disease indicator, or a risk factor that should be considered in diagnosis and treatment? And as most people say well, race is really a social construct and not a biologic one, so if that's true, then what is the basis for including race adjustments in clinical algorithms, particularly when they may in fact increase disparities in health or health care? Is it possible that we should abandon these adjustments? How can clinicians more specifically evaluate the influence of social determinants of health for which race is often incorrectly used as a proxy?

Everyone is aware of the complex intersectional relationships that exist between education, income, occupation, housing, racial identity and ethnic identity, and genetic ancestry. However, there is really no genetic evidence that supports the existence of discrete racial groups. But in some cases, I think it's clear to most of us that racial categories sometimes do correlate to some extent with genetic ancestry. Unfortunately, I think we all agree that we haven't learned everything that genetic variation has to teach us about disease and disease risk, and in large part that's because we haven't been as successful as I think many of us would have liked in terms of being very inclusive in the populations that we have engaged in genetic studies on.

So therefore, when we use these self-identified ethnic and racial categories, it's possible that they're not the best surrogates for genomic variation and are at best imprecise. So what is it that we as physicians, we as biomedical researchers should do while at least we try to improve our genomic cohorts to perhaps give us a better handle on genetic variation? Should medicine and biomedical researchers just stop using race as a proxy for genetic variation?

I think everyone's goal is to improve health and facilitate health equity. We need to find a common ground upon which to build. And that's probably the most important reason for us to have this discussion today.

The History of Human Classification

DR. EVANS: So let's open the discussion with some very basic questions. To what extent is race a social construct? Entirely? And if it's entirely a social construct, then do we continue to use that construct?

What are the downsides of that? And so perhaps I can turn to you, Dr. Graves, to begin the discussion with an answer to that question?

DR. GRAVES: From my perspective, there are two race concepts that are often conflated by both people in the lay public but also by professionals. The first is the biological conception of race, which has a very long history in the study of biology, going back at least to the 5th century BCE, when naturalists began to study the variation in the organisms around them. It moved through a series of criteria that were initially based upon special creationist ideas, starting with simply the physical differences between organisms -- and when I say organisms, I mean all organisms, not just people.

And then, later on, when Linnaeus writes his *Systema Naturae* in 1735, the concept of the variation was already established within people studying nature. It is notable that Linnaeus does not talk about human varieties until the 10th edition of the book, which is published in 1758. And this, I argue, is associated with the onset of the social definitions of race that are deeply connected to colonialism and chattel slavery.

Later on, in the 19th century, Louis Agassiz presents us with the zones of creation, in which he felt there had been special acts of creation for different regions around the globe, including different species of human beings. And this was called polygenism. However, after the publication of *On the Origin of Species* in 1859, the classification of human beings moves towards an evolutionary foundation. And in the early 20th century, the definition of races begin to be associated with the frequency of specific genetic variants in those groups. And so, by the time Theodosius Dobzhansky writes *Genetics and the Origin of Species*, he defines races simply as being different frequencies of genetic variants, whether they be aversions or specific alleles. And by Dobzhansky's definition, there would have been many, many more races in the human species than are defined by our social conventions.

Now, moving forward after really the culmination of the, what we call the neo-Darwinian synthesis, which unites Mendelian genetics and evolutionary theory, we come up with more sophisticated ways of examining the variation within populations. And when we do that, we really come to the conclusion that there is no nonarbitrary way to apportion human populations into so-called biological races. And so I argue that in fact we have no biological races within the human species. And in fact, the races that we recognize in society and unfortunately in biomedical research and clinical practice are socially defined groups.

Now, the difference between the social definition of race and the long tradition of biological classification of variation is that the social definition is associated always with systems of social hierarchy and can be arbitrary. They're historically and culturally contextual. And so what counts as race in Brazil does not count as race in the United States or in the U.K. or in China. And so here's where the problem lies, because while the science, I think, of human biological variation has told us some very clear stories, that has not been translated into the lay public, and unfortunately not into the medical community as well.

DR. EVANS: That's an excellent overview, Dr. Graves, thank you. Dr. Tishkoff, would you like to add to that?

DR. TISHKOFF: I think that we have to be very careful about classifying populations using phrases that imply a biological basis to race. So one of the ones I hate the most is "Caucasian." I think that should just

be banned -- it should be banned from the literature, it should be banned from the clinic. Because when people use that, it implies a biological classification of race. So the way we describe classifications of people, refer to groups of people, can have an important impact. And I think that part of the problem has been that historically, as Dr. Graves pointed out, there's been a mixture of biological and cultural definitions of race, with people's personal cultural beliefs being put, imposed on top of that, often looking at so-called races in a hierarchical perspective. And so we clearly do need to move away from that.

At the same time, we cannot ignore that genetic diversity exists. However, the diversity that we see amongst the entire human species, all human populations, is relatively small between populations compared to within populations. So generally, we see somewhere around 10% of the variation being between populations and around 90% being within populations. And if we look at the level of the entire genome, we're greater than 99.99% similar. And this reflects a relatively recent African origin of all modern humans. The modern human species evolved in Africa within the past 300,000 years or so, and it was only in the past 50,000 to 80,000 years or so that relatively small numbers of people, could have been in the hundreds to thousands, migrated out of Africa, giving rise to populations across the globe. So because of that demographic history, it shapes the pattern of variation that we see in modern populations. We see more variation in Africa compared to anywhere else in the globe -- not just within populations, but between populations. And this should eliminate any idea of an African race, because we see more variation between different groups in Africa, from eastern and western and central and southern Africa, than we may see across the globe.

And so, yeah, so I think the point is that we share quite a bit more than we differ. But we can't ignore that there are differences. And those result from our demographic history, population history, and adaptation to different environments. So natural selection can sometimes cause random mutations, that may be associated with risk for disease, to rise to high frequency. So we can't ignore that either, and we have to -- you know, one of the things we should discuss is what's the best way to take that into account, not ignore it, but not classify people as biological races.

The Social Construct of Race

DR. EVANS: So, Dr. Shim, how do we get people to understand, how do we use race in the context of social determinants of health in the United States? Because what's happened is, in medicine particularly, it's sort of a "proxy" for these social determinants. What are your thoughts about that?

DR. SHIM: Yeah, it's interesting, because it is a proxy, and I would argue it's not a very good proxy -- it's a very imprecise proxy, in a space where, within medicine, we try to be as precise as possible. And so I very much appreciate Dr. Graves giving us this history of the establishing of racial categories. What's so important about that is that is history that is typically not taught. So I did not learn anything like that in medical school. I had to do additional self-study in order to understand that history that Dr. Graves walked us all through. And the average physician, the average practitioner does not get that information at all, in any type of educational setting. And so we are left with this social construct, which has huge implications on the health and outcomes of people because we know that social determinants have huge implications on health. We know that the majority of the differences that we see in outcomes, the inequities that we see around health, have to do with social determinants. And so this social construct,

this *huge* social construct and political construct of race is probably the greatest of all of these social determinants, in that it is driving a lot of -- it is the hierarchy that is driving a lot of the negative outcomes and the inequities that we see.

So then the question becomes how do we convince providers, one, that we're saying that race is *not* biological, but yet, it's still extremely significant because of the way that it has been constructed and because of the significance of oppression and hierarchy and how that impacts health and how that leads to bad health?

And so I don't really have an answer, unfortunately, but I definitely think that we have to start really zoning in on what is relevant, which is the fact that our social construction of race has led to deep inequities because of oppression, because of hierarchy, but not because necessarily of biological or genetic differences between populations.

Race as Risk Factor

DR. EVANS: So, Dr. Williams, I think Dr. Shim sort of has teed up the ball for us to discuss understanding structural racism in health care. And it operates clearly on many, many levels. How do you think we've gotten to the place where we are in terms of health inequities? Is it solely physician-based? Or is it physicians are just members of society, and just bring that to their interactions with patients?

DR. WILLIAMS: Structural racism, in my mind, refers to the mechanisms in which our society fosters racial discrimination through systems of a variety of resources that should be equal and have equal access to all, including housing, including education, employment, earnings, benefits, access to banking and credit, media access, health care is one, and even, I think more importantly, the criminal justice system that reinforces discriminatory beliefs, values, and distribution of resources. And I think this historically has developed in a number of different ways, in terms of structures of these kinds of disparities that are, I think, hard-wired now in many sectors of our society. But one historic reality has been redlining, for example, where there were structures that were put in place in the '30s and '40s to systematically deny African Americans and other ethnic minorities access to mortgages, property ownership, and generational development of equity and wealth on that basis. This has led to substantial wealth disparity in minority communities that are extant to this day.

According to a 2015 report from the Boston Federal Reserve entitled "The Color of Wealth," White households in the Boston metropolitan area were noted to have a median net worth of about a quarter of a million dollars, \$247,000, while Black households had a median net worth of just \$8 -- really deep wealth inequity between these two communities.¹

This differential in wealth has led to deep, substantive inequities in communities, such that if you look at results of redlining in the 1930s and '40s, between 1945 and 1959, African Americans received less than 2% of all federally insured home loans. And so I think that makes a difference in terms of access to resources and even health equity as it translates to the current day.

DR. EVANS: Well, do you think that that is an example of, sort of, race being viewed as a proxy for social status? You know, in a 2009 paper by Vence Bonham, where they asked doctors whether or not they thought race was important in clinical diagnosis or management, both Black and White doctors thought

that race was an important factor.² But when asked, well, how is it that race matters in medicine, they sort of were amorphous in their responses. Some thought that race equals cultural practices, that because of different diet, physical activity, care-seeking behavior. Others thought that racial status, income, or neighborhood, as you're pointing out, may be reflected in race, as well as educational achievement. Or others thought that race was in fact a proxy for genetic makeup. So I think the material that you're presenting certainly suggests that that link, that race is a surrogate for marginalization and lack of access to capital, education, and occupation, then reflects on physicians, who then feel that well, this is one of the things that's making people ill, and therefore race does exist.

DR. WILLIAMS: The effect of residential segregation, for example, in my field, on kidney health outcomes has been fairly well documented. So if you look at, there's an analysis in the United States RDS registry looking at patients initiating hemodialysis between 2000 and 2008, and that study found that among Black Americans exclusively, residence in highly racially segregated areas was associated with an increase to mortality.³ And I think the effect of structural racism can be observed across a number of different parameters. If you look at the U.S. food system, greater availability of healthy foods has been noted predominantly in White and higher-income neighborhoods. This can pose significant challenges for individuals with diet-sensitive health conditions such as diabetes, hypertension, and chronic kidney disease. And so, I think this dovetails, too, in terms of environmental exposures, such as lead in our water systems and air pollutants, where geographically, minority communities, disadvantaged communities are disproportionately exposed to these environmental disasters.

DR. GRAVES: You know, while scholars, such as ourselves, know full well the gravity and the immense amount of the racial wealth disparity in the United States, the vast majority of Americans who are not associated with sociology departments do not understand this huge difference. And in fact a recent paper published in a social psychology journal actually gave White Americans an opportunity to rate what they thought the wealth disparity difference was.⁴ And so they did a series of experiments and found that the vast majority of White Americans rated the wealth disparity as essentially nine tenths -- or Black Americans were, you know, 10% less wealthy than White Americans. And then they revealed the actual numbers, which, nationally, it's about *one* tenth. They revealed the actual numbers, and instead of the White participants in the study reexamining what they thought about the present, they then reexamined what they thought about the past and concluded, well, then, I guess the past wasn't so bad -- that slavery and Jim Crow must not have been that terrible. And so instead of coming to a logical conclusion that there's this long, historic wealth disparity in the United States and that, in fact, might have real social consequences, they came to the exact opposite conclusion.

DR. SHIM: You would think that when presented with this data, the average person could take it and make a reasonable assumption based on that data. As Dr. Graves pointed out, they often don't. And what ends up happening, unfortunately, what we see a lot is that with this information, with even the data on redlining and the data on residential segregation and the data on all of the discrimination, the next logical step that many health care professionals make in their mind is not "Oh, there must be these huge structural racist forces that are causing these differences." They make this leap to "There must be some sort of intrinsic, biological difference between these populations that explains why you see these differences." And that is the piece that we have not done a good job of educating people on what is actually driving these differences. And there is a significant number of people that are very entrenched in the belief that these are in fact biological or genetic or some type of intrinsic differences that are causing these huge differences.

Workforce Diversity and Understanding of Racial Inequities

DR. SHIM: So when we think about, one, part of that has to do with the existing workforce. Part of that has to do with the fact that medicine, unfortunately, has a terrible history of teaching racist ideology around health. And so, we have -- I was taught, and I went to great medical school, but I was taught racist assumptions about why people had different outcomes. These are the things that are passed down from generation to generation historically. And so the workforce being what it is today, it takes an, it takes until somebody is sitting in that spot who is of that race -- it took me sitting in my medical school classroom thinking, "Well, they're saying that I'm inferior. They're saying that I'm biologically somehow less than. Is that true? Is that really the case, or do I need to do a little bit more explanation — exploration of this?"

So the work of creating a diverse workforce is so critical. Because we need to have people question the way we've been teaching, the scientific conclusions that we draw based on when we do research and when we do studies — we need to have all of this be questioned.

I'm very excited because what I'm noticing is that we're seeing the glimpses of a new workforce, a much more diverse workforce, at least in medical education, that is really questioning and asking their professors -- "Wait a minute, you say that there's this difference in outcomes by race. What's driving that difference?" And not accepting just "Oh, it's just a difference; we don't really know why."

DR. GRAVES: Many of your viewers will be familiar with the paper that was published in the *Proceedings of the National Academy of Sciences* in 2016 that came out of the University of Virginia's medical school, and it asked first-year, second-year, third-year, and resident physicians questions about biological variation associated with various clinical attributes of people.⁵ And the number of false conceptions about Black and White differences were amazing.

And I'll just read a few that, again, for example -- you all probably heard about Black nerve endings less sensitive than Whites'. Well 12.7% of first-year med students thought that; 19.4% of second-year med students thought that. Now, they dealt with this effectively by the third year, and the number went to 0%, but the residents still were 14.3% of them believed that Black nerve endings were less sensitive than Whites'. And there were a number of these errors, including ones which the authors themselves got wrong — because I reviewed the paper, and I said, "Wait a minute! These things aren't true either!" And so they thought they were true. So in that sense, we have a lot of work to do.

And I'll reveal to your viewers that I'm actually a paid consultant for Elsevier, and I'm one of the people who's working on the 11th edition of *Robbins Basic Pathology* to remove all of these incorrect claims about human beings associated with race. And we've been doing a lot of work because we've had to remove a lot of material. So we're hoping that this 11th edition, which is widely used around the country and around the world, will be a resource that will help with regard to these ongoing misconceptions about human biological variation.

DR. EVANS: So, Dr. Tishkoff, as a biologist and a geneticist, where do we go from here? What do we need to have a refix or a reset on at the level of medical education and graduate school education, and how best can biomedical researchers communicate to the public that there really is no race?

DR. TISHKOFF: I do believe that all medical students should have a basic understanding of population genetics. I think they should understand what the nature is of genetic diversity within and between populations, and when they better understand that, they will better understand that there are not these discrete differences that correspond with biological concepts of race. So first they need to have a better understanding of that.

At the same time, I think that we can't ignore, as I said, that genetic differences do exist at the individual level and at a broader population level and that there can be differences in disease risk that may have a genetic basis, or there may be genetic risk factors.

However, there's no doubt that social inequity, systemic racism is having perhaps *the* major impact on health inequities, but that's not — and health disparities, but that's not to say that there aren't genetic risk factors as well, and that one of the most challenging things is to distinguish the interaction of genetic and environmental, social factors that are influencing disease risk.

So I would also argue that we can't ignore diversity -- I think that actually would do harm as well, if we ignored that. And in regards to the need to include a more diverse workforce, we also need to include more diversity in biomedical research and in terms of subjects. So in the area of genomics, for example, we wrote a Perspective a couple of years ago and showed that if you look at all of the genome-wide association studies that were done as of 2019, around 80% of the individuals included in those studies were of European ancestry. Only around 2% were of African ancestry; about 1% were of Hispanic ancestry, Native American ancestry, less than 1% everybody else, and I should also say 10% East Asian.⁶ And so that's going to also lead to disparities, because we're going to be missing important information.

Gene-Environment Interactions

DR. TISHKOFF: Dr. Williams, something I wanted to ask you about was you mentioned differences in terms of risk for kidney disease. Now, we also know that *APOL1*, that variants at *APOL1* have been found that play a role in risk for disease in people of West African ancestry, and it's been shown in a beautiful paper that was done that the variants that are associated with risk for disease may have become common in some parts of West Africa because they're protective against trypanosomes which can cause sleeping sickness.⁷ So in that respect, genetic ancestry could be important to know as well. And I'm wondering about your thoughts about that.

DR. WILLIAMS: I think it's extremely informative. I think it's a great example of why you can't, in a sense, throw the baby out with the bath water. And what I mean by that is it is one thing to say that race is a social construct, but there are genetic ancestral markers that can inform really potently about disease expression in particular ethnic minority groups. In your example, variation around G1 and G2 at the *APOL1* locus does confer an increased risk for chronic kidney disease and even rapid progression to end-stage renal disease in about 12 to 13% of African Americans who are homozygous for those variants. That's an important area in kidney disease to really delve into and explore, without the idea that somehow this is a racialized construct. It happens to be evident that those variants rose quickly in natural selection because they were protective against African sleeping sickness, and it warrants, I think, rigorous study.

DR. GRAVES: Dr. Evans, again, if I can speak to that — I think the real question that Dr. Tishkoff has identified is the complexity of gene-by-environment interactions with regard to how genetic variants, particularly in new environments, may predispose individuals to disease. Now, I happen to be on the executive board of the International Society for Evolution, Medicine, and Public Health, and we approach disease from an evolutionary lens. And one of the major factors we see contributing to disease in modern human populations is environmental mismatch. Environmental mismatch can occur in a number of ways. Some of the obvious ways are the amount of food that we currently have, and particularly high-caloric-content food that we didn't have when we evolved in Africa. But then there are also other aspects of environmental mismatch that aren't really well understood, and this is what Dr. Shim was talking about earlier with regard to the impact of structural racism and the neural endocrine effects that it has on human beings. And so while it would seem that the Just-So Story of renal end-stage disease is natural selection, anti-trypanosome, you know, put it in the absence of trypanosomes, it contributes to end-stage renal disease. But we actually don't *know* that that's the *reason* that it contributes to end-stage renal disease. For example, in a racially equitable society, the variant may have absolutely no impact on end-stage renal disease. And so what I --

DR. EVANS: It may be the interaction with poverty, because in our own work, when we look at chronic kidney disease, in our study we didn't find a difference between Blacks and Whites until we did the univariate analysis looking at poverty.⁸ And poverty was a driver of severe kidney disease, chronic kidney disease in African Americans but not in Whites. So poverty had an important virulence factor. Was it related to *APOL1*? Not probably. But we did find interactions with obesity, with food insecurity, with housing insecurity, as well as illicit drug use — all of which are social factors that are driving disease. So, I think what Dr. Tishkoff has said is so important, and I think that's one of the reasons that we have a difficulty in communicating this, not only to the lay public but also even within the health care provider community, is because it's a complex message. And how do we tailor it so that people understand these complex intersectional relationships, because we need to be assessing *interactions* — race in the context of the environment, of the social determinants of health is driving disease. And also is driving disease in low-SES Whites, but that's another very understudied group of people.

DR. GRAVES: And one of the things that I want to get across to the listeners is what is the research protocol that's going to allow us to be able to dissect the complex interactions of genetics and environment? In fact, that's the very focus of my research. It's one of the big questions that the NSF funds — you know, the genotype–phenotype map. And frankly — I'm not trying to insult anyone — the level of understanding of this complex question in biomedical research is very low. And there's a real need to, you know, move the research protocols to a level to where they can actually dissect and falsify hypotheses about genetic and environmental influences, which, given the way things are currently being done, they simply cannot do. And so that's one of the reasons why I teach evolutionary medicine in our graduate program at North Carolina A&T, and I've taught it at some medical schools around the country, but I really think that one solution to this would be a wider adoption of evolutionary medicine within medical and premedical curricula.

Improving Research

DR. EVANS: So are there better proxies for social determinants, race, genetic ancestry? How do we make our research protocols better?

DR. WILLIAMS: One way is to include those very targeted populations that we're concerned about. So, you know this well, Dr. Evans: minority folk are underrepresented in virtually all randomized clinical trials across the spectrum. That's one thing we want to try and address, as you know, policy-wise, but the dearth of minority participants in clinical trials is a real problem in terms of discerning disease mechanism and therapy.

DR. SHIM: And I would just like to add to that that, you know, it feels to me that everything always comes back, unfortunately, to structural racism. Because one of the reasons we have this dearth of minoritized populations in research and that we don't have adequate samples or the right amount of participants has everything to do with the historical nature of how racist experiments have been towards minoritized populations since the beginning of time. And so, you know, I'm glad that I'm hearing the medical community move towards trying to establish and focus on trust, and establish trust, but it also requires a complete shift in the focus and the priorities of researchers. I think that research has been traditionally a much more exploitative process and much more about funding and getting funding and what funding is interesting and how many research dollars are you going to get for what you study, and these questions have not been supported adequately in the past and are not currently supported by funds. So we don't get to see the investment in asking these questions and answering them, because we don't see a commensurate investment in funding these questions and really trying to get to the bottom of this.

DR. TISHKOFF: There's also not enough investment in terms of industry, I would say, looking at diversity. So, for example, if people are developing therapeutic treatments, if they're just looking at people of European ancestry, that's not going to cut it. That's not going to benefit people of all diverse ancestries. So I think we need to be considering that as well.

And in terms of — Dr. Evans, you asked what might be a better proxy than race, I would argue that it depends on the question. So if we are interested in social determinants of health, race actually may be proper, the proper way to classify. However, if we're interested in genetic risk factors, typically ancestry is better. And certainly, knowing as much as you can about an individual's ancestry is important, because somebody may self-identify one way, but you might find out that they had grandparents from different regions, and most people have diverse ancestries, and one of the things we see in almost all human populations is admixture. So the problem is that when people classify based on what we refer to in the population genetics world as global genetic ancestry — and what that can mean is, for example, in the African American community, people who have done genetic studies have shown that people who self-identify as African American would typically have on average 20% European ancestry, on average around 80% West African ancestry. That's an average — people can have from 0% European ancestry to perhaps 90% or more. And so when someone tries to determine a treatment based on these broad classifications, that can be problematic, because even if there were genetic risk factors, and even if they did differ between groups of different ancestries, at any particular region of the genome, someone might have — you know, who self-identifies as African American — could have 100% European ancestry, 100% African ancestry, or mixed ancestry. So ultimately, what we want is more precision medicine. We want to understand individual genetic risk factors. But until we get to that point that everybody gets sequenced — and not only gets sequenced but we actually understand what all that diversity is doing and how it's impacting disease, you may need some kind of a proxy. And maybe it just depends on what the question is.

DR. GRAVES: And I would go even further, because one of the things that I've had an opportunity to do while working on the revision of *Robbins* is I'm working very closely with a lot of practicing physicians. And they question the use of proxies, period. So one would think that the only reason to have a proxy, at least from clinical practice, is in the emergency room, where you need a quick useful heuristic to try to figure out what's going on with this patient. But my physician colleagues are telling me that that's a really bad way to go and that you will often make mistakes — in fact, critical mistakes which could cost the patient's life or some serious harm. And so if proxies are not useful in the emergency room, then they're definitely not useful in biomedical research, where we have plenty more opportunity to find out real answers to the environmental and genomic variations which are associated with the phenotype in question. And especially given, again, what Dr. Tishkoff pointed out in terms of sequencing — sequencing is really cheap now compared to what it was even 10 years ago. And so the ability to do this if you're doing human biomedical research, sequencing costs are not the issue with regard to studying the question. And so I question why people are adhering to this notion that you have to have these proxies instead of doing the real work to try to, you know, give us an accurate view of the phenotype -- genotype-to-phenotype map. I don't see the utility of that anymore.

Paths Forward

DR. EVANS: So what do each of you see as the most promising route to dismantling structural racism in medicine? Funding better research that asks some of these questions — that's one thing that's come up. Really working on the area of diversity in clinical trials — that's another, where — but, again, that's using people's self-identified race and ethnicity. Making sure we are training students to understand population genetics, both at the undergraduate as well as at the medical school training level. And then, really trying to conceptualize how we go forward to evaluate patients, as we've most recently been talking about. What are we evaluating when we say "race"? Should we be taking a better social history so that we can understand the environmental factors that may be influencing disease, because it's not race — it's race as an indicator of what the risk factors that are part of the life experience of that patient may be? But what are other things that we need to put on the table for consideration?

DR. WILLIAMS: So I see, Michele, you want us to go another hour, I guess. [Laughter]

I think what you're talking about really hits a lot of different levels, in terms of really sort of how we conceptualize disparities in health and health care, and so there are system-level barriers, there are provider-level barriers, as you indicated, and even patient-level barriers, and so I think if you look at these various tiers, if you look at the system, how our health care systems are organized, in and of themselves, in terms of sort of insurance products, for example, that are available to vulnerable communities or communities that have lesser access to high-caliber insurance products, that would be an organizational impediment to ensuring equality in access to health care resources.

And on the provider level, I think you're right — I think how we teach providers to communicate, our students of medicine, and even faculty of medicine presently — their attitudes, their knowledge base, whether in fact they are culturally competent in the way they deliver messages to vulnerable populations, I think is really important as well.

And then there are patient issues that we've all sort of hinted at, I think, during this roundtable, that patients who are, for example, African American patients rightfully have a large measure of distrust in structured system of health care because of — the benchmark, of course, is Tuskegee, where African American men were subject to the natural history of syphilis played out in those who were enrolled in that program without their knowledge. And so I think there's a deep distrust of health care systems based on historical legacies of mistreatment.

So those are various tiers — system, provider, and patient — and I think they all converge when you look at the demographic challenges of poverty and segregation, some of the social, cultural norms we've been discussing, that lead to really a complicated outcome that is disparate in terms of quality.

DR. SHIM: You know, it's a really old study, but McGinnis and colleagues published something in *Health Affairs* in 2002 that looked at determinants of health and their contribution to premature death.⁹ And they said that about 15% had to do with social circumstances — 15% of the contributors to premature death. Ten percent was health care; 5% was environmental exposure; 40% was behavioral patterns; and 30% was genetic predisposition. And so, I often teach my medical students, if you think about those breakdowns, about behavioral patterns, environmental exposure, health care, social circumstances — all of these things are social determinants of health. And so that's really 70% of the reason why people die early has to do with social determinants of health, and about 30% has to do with genetics or ancestry or a predisposition that you have in your family history. And so it's certainly not saying that we need to discount genetics, and we certainly do not need to do that. But if we're talking about how do we address inequities, how do we move towards accomplishing health equity, I think we have to do a better job of teaching people to identify and address the social determinants. And then race becomes the, kind of, the most salient of those social determinants. And so, I think if we're going to get to a place where we are better at achieving health equity, we have to teach everyone how structural racism shows up in medicine, how it affects outcomes in health, and what providers — what physicians and nurses and any health care providers — can do to actually combat the negative forces of structural racism. So I'm in favor of education, and I think that we have to really do a much better job of making sure this information is spread — widespread and readily available to people.

DR. WILLIAMS: You know, there are examples of racialized medicine that are a part of structural racism as it plays out in medical practice. For example, one of the examples that we see in chronic kidney disease is the example of the race correction for estimating glomerular filtration rates — that's a marker of performance of kidney disease. And I think all of us on the panel know that over the past year, there's been a great hue and cry about how the equations that report a higher estimated GFR, that kidney performance number, for Black individuals, suggesting that they have better intrinsic function at a certain level of serum creatinine is a disadvantage that causes them to be categorized with higher levels of renal function, when in fact that is not true on a measured basis. And that inequity in and of itself is one that has led to a great deal of concern about redefining the utility of these equations and whether in fact this kind of misclassification does deep disparity in terms of the access of ethnic minorities, Black patients in particular, to renal replacement services along an entire continuum — having best practices for renal replacement therapy, timely referral to nephrology, timely placement of dialysis access, timely referral for transplant evaluation, as a few examples. And I think addressing these vestiges of racialized constructs is important — is an important mission for us as well.

DR. EVANS: Dr. Tishkoff, so from the perspective of a basic scientist, what do they need to contribute to this conversation? The biomedical research enterprise I think is critical as we move forward.

DR. TISHKOFF: So I think there needs to be more of an emphasis both in regards of the funders and the researchers, that they must include more diversity in their research. And sometimes, we as geneticists actually get penalized when we try to include diverse populations. When you're going through review, a reviewer might say, "Well, your sample size isn't big enough." We can't get as big numbers as those who are looking at people of European ancestry. So for a genome-wide association study, you'd want tens of thousands of people — that might be challenging. Or they might say, "Well, your population is too genetically heterogeneous — that's going to be a problem." They need to change the attitude. It's got to be seen as a positive, and it doesn't matter how big the sample size is. It doesn't matter. It still adds important information.

And then, in addition, I think having more diversity in the workplace and in the workforce is going to be important, because, as we've heard so eloquently explained by Dr. Williams, there's a huge distrust among many groups that are underrepresented both as subjects in biomedical research, and that's not going to change until the people doing that research start looking more like they do and reflecting that diversity that exists in the U.S. So I think that's also going to be important.

DR. GRAVES: We aren't going to be able to make reforms in medical training and clinical practice and biomedical research without addressing the elephant in the living room, which is structural racism in American society. Now, that doesn't mean that you don't do all the things that my esteemed colleagues have outlined. Because I've been working on that — I've sent more African Americans to medical school and graduate school than my entire departments have over the course of my career. But that's not enough.

Systems produce what they're designed to produce. So when you look at structural racism in the United States, it is designed to produce a deficit in African American health, and it's doing it really well, and it's done it really well for 300-plus years. And so therefore, we have to address this elephant in the living room. If we really want a society in which everyone can live up to their genetic potential, then we must address these structural impediments to do that.

And one of the simplest ways, based upon, again, what Dr. Shim said earlier, is universal health care. But that is one of the things that many constituents in the medical community and biomedical research are the most against. But far more than biomedical research — and again, I'm a scientist; I do scientific research; I think it's important. But if my goal is to eliminate health disparity, biomedical research isn't going to do it. Universal health care would do it. A massive jobs program would do it. Childcare for women would do it. And you might note that in the massive infrastructure bill that is sitting in the Senate right now, the parts of infrastructure that dealt with helping human beings be healthier were the parts that they cut out.

And so I would argue that if we want a society where people have an equal opportunity to life, liberty, and the pursuit of happiness, that we must address structural racism. We absolutely must dismantle it.

DR. EVANS: So, I think this has been a very illuminating discussion. I think everyone has really brought to the forefront the complexity of the issue, the altitude to which we must climb to make progress. But rather than finding this polarizing, I find it invigorating in that it's just understanding where we have to

go that helps us take that first step. And the fact that we have so many people in different aspects of health care as well as biomedical research who are recognizing this, to me is a note of optimism, that there are many of those who are going to take that challenge to move forward as we try to provide opportunities for health equity for everyone in the United States.

So I thank each of you for your wonderful contributions, and look forward to interacting with you offline, as we have many areas of research and interests in common. So thank you very much.

DR. WILLIAMS: It was good to be with all of you. Thank you.

DR. GRAVES: Thank you all for your perspectives.

DR. SHIM: Thank you.

DR. TISHKOFF: Thank you for a fascinating and important discussion.

Disclosure forms provided by the participants are available at NEJM.org.

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