Ethical and Social Issues Associated with Using Race and Genetics in the Study of Differential Drug Response

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DR. WINN-DEEN: I'd like to ask the committee to take their seats, please, so we can start the afternoon session.

This afternoon we're pleased to have another committee alumni with us. Wylie Burke is going to talk to us about ELSI issues. Particularly she's going to focus on the issue of race and genetics as it pertains to differential drug response.

She is currently a professor and chair of the Department of Medical History and Ethics at the University of Washington, and is a faculty member in the Public Health Genetics Program and in the Medical Genetics Training Program.

I think basically she needs little more introduction to most of us, so thank you for joining us, Wylie, and we look forward to hearing your presentation.

DR. BURKE: Thanks very much. I really appreciate the opportunity to be here, although I must say that this topic has had questions that are difficult ones. So my main goal is to try and convey to you what I think is the complexity in these issues when we start talking about race, genetics, and differential drug response.

We can start with the complexity of race. Race is a term that's used generally to identify or at least it's assumed to identify groups with shared ancestry. That's the way in which we use the term, and implicit in that use of the term is a strong belief, particularly I think in U.S. uses of the term "race," that race has a lot to do with genetics. So there tends to be a tight alliance between those two terms.

I want to talk about the complexity and why we need to think I think more in depth about that. It's currently understood to refer to five groups. African, European, Asian, Native American, and Oceanic. But as we think about the use of race and what we mean by race, I think it's extremely important to understand that the definition of racial groups has changed over time.

A conspicuous example in the U.S. has been a relatively recent allocation of people from the Indian subcontinent to Asia where they previously were not, and it has been used differently in different parts of the world.

In addition, when we look at countries like ours where there is a strong tendency to categorize people by race, in fact social factors are what determine what race you put down on your census form. So I think we have to be cautious about how the term "race" is used, and really a variety of different meanings that might be incorporated in the term "race."

Now, that said, there certainly is a relationship, though I would argue it's an indirect relationship, between race and pharmacogenomics. Self-reported race is correlated imperfectly, but correlated in a rough way with genetic measures of geographic ancestry. So researchers who have made efforts to identify highly variable markers that are particularly useful in identifying ancestry of the five major groups that I just referred to have developed marker panels that can be used for what is called ancestry testing. There is a rough correlation.

As a result, we do see some genetic differences, and they are generally differences in prevalence. So what we see is when we categorize people by race, or allow them to categorize themselves by race, we see that the prevalence of many gene variants, by no means all, but many vary with geographic ancestry, and therefore this indirect fashion with self-reported race, that of course includes variants that are associated with drug response.

So I want to give you an example of that. The CYP 2C9 which is one of the 450 genes, has been identified to have many variants, or several variants that are associated with reduced dose requirements for warfarin, the drug that's most commonly used for anticoagulation or blood thinning.

My colleague, David Veenstra, collated together a whole bunch of studies, and you can see the results here, that if you looked to people that were of European ancestry, the prevalence of variants associated with reduced dose requirements looked to be about 36 percent with a fairly wide range, but an average of 36 percent, whereas in African groups, it was 8 percent, Asian, 4 percent, and I have put the figure at 10 percent for Native American, but you'll note that it's just two studies. Both done in Canada. One where there was a zero prevalence of these variants, and one where there was a 20 percent prevalence, so we shouldn't generalize too much.

The other point I would make here is that the preponderance of studies is of people of European decent, and the majority of studies occurred in North America. What that means is that most of our data comes from just a small slice of the world's population. I think it's fair to say that we know relatively little about the distribution of these variants around the world.

But CYP 2C variants are associated with a clinically significant drug response. So people that have these particular variants not only require lower doses of blood coagulation, but have a higher likelihood of having bleeding complications. There at least have been some proposals that this may be a clinically important genetic trait.

What's interesting about it is that the one racial difference that has entered into sort of rules of thumb in clinical medicine is one that's not explained by CYP 2C9 variants. So there is a kind of clinical wisdom among people who do anticoagulation therapy that Asian patients tend to require lower doses.

If you go to the Physicians' Desk Reference, the drug labeling, you'll find this paragraph. The highlighting is mine, because I thought some of these sentences were particularly interesting. So they start by saying, "Asian patients may require lower initiation and maintenance doses of warfarin." They go on to cite their basis, and it's one non-controlled study of 151 Chinese outpatients, and they go on to show the lower dose requirements.

So I think we'll note, uncontrolled study, small numbers, and in fact it is not a broadly representative population of Asians. It's actually one ethnicity within a large number of ethnicities that are categorized as Asian.

These patients were stabilized on warfarin for various indications, so there might be a variety of clinical differences that also are important, and patient age was the most important determinant of warfarin requirement that's a known fact about warfarin.

So it's a rule of thumb that made it to the drug label. So there's enough conviction in the clinical world that this is clinically meaningful. I have certainly had docs who prescribed a lot of

warfarin tell me that they believe this is the truth, but the evidence base for it is not particularly strong.

In fact, there are many, many sources of individual variability in P450 expression, of which the CYP 2C9 drug is one. This is a slide adapted from a study that was just summarizing all the many factors that might influence someone's response to a drug, and as you'll see, most of them are non-genetic or distantly related to genetic factors.

So many environmental or lifestyle factors might influence how one's P450 is expressed, or genes in that family are expressed, and therefore how one might have differential drug response.

Now, it turns out that a subsequent study on a different gene actually provides evidence about a possible genetic contributor to this apparent Asian requirement for a lower dose of warfarin. That's a study published recently by my colleagues from the University of Washington that was looking at the association between warfarin dose and VKORC1 variant haplotypes.

They were able to identify, looking at haplotypes, two groups. Group A, which was a group of haplotypes that were associated low dose requirements, and then Group B, another set of variant haplotypes that were associated with higher dose requirements.

The evidence is on this slide. When they looked at all the patients in their sample, and they actually repeated this in two samples of patients at University of Washington and Washington University, you can see the correlation between what kind of haplotype someone had, and what their dose requirements were.

They also were able to take advantage of the fact that some of their patients also had the CYP 2C9 variants that were associated with lower dose requirements, and you can see the mutual effect of the two genetic factors in reducing dose requirements for VKORC1 for warfarin.

What is really interesting is that there does seem to be difference in prevalence between racial groups of these different VKORC1 variant haplotypes. Now, these data, the European, African, and Asian samples that were used to look at prevalence, were taken from the Coryell Data Repository.

What we have is that in Europeans, there is just under 40 percent who have that low dose haplotype, but close to 60 percent who have the high dose haplotype. With Africans, you can see that fewer of the haplotypes within the African population are explained by this Group A and Group B, but it's a different distribution. And then most interestingly, the Asian sample has a very high proportion of the VKORC1 haplotypes that are associated with low dose.

So this could be a genetic explanation for that clinical observation. Again, I want to note that the Asian samples were predominantly Chinese, so we continue mostly to know about this particular genetic issue in Chinese individuals.

This study also estimated the variants in drug response that could be explained by the CYP 2C9 and by the VKORC1 variants. Here is another important point. We certainly don't want to say we now know everything about why Asians might have lower dose requirements than other racial groups, because VKORC1 is only explaining 25 percent of the variants, and CYP 2C9 is explaining an additional 10 percent.

It is very likely that there are other factors, well, this tells us there are definitely other factors, and those other factors may be genetic, or they may be non-genetic. I think it's important to say at this point that either is a possibility. We await more evidence to understand this better.

I think there are a few issues here. One is that even on the genetic side, granting that both genetic and non-genetic factors contribute to drug response, even on the genetic side we're going to see complexity. So if you just looked at CYP 2C9, you got only a small slice of the story. If you just looked at VKORC1, you might get a slightly bigger slice, but it's still only a slice of the story, and there may well be other genes yet to come.

There are many genes that are involved in the metabolic processes by which the body responds to ingested warfarin. In fact, there was recently a study from Europe that identified variants in the APOe gene as having an effect on warfarin metabolism. Just one study. It comes from a group that has been doing lots of very good quality epidemiologic studies looking at APOe and its association with Alzheimer's disease.

It's the very same allele, that one that is associated with increased risk of Alzheimer's seems also to be associated with lower dose requirements for warfarin. We may well have others yet to come.

There are many exactly as you would expect, many well established non-genetic factors that are associated with warfarin response. I have listed the ones that seem particularly important in terms of clinical writing on this. The emphasis on nutritional status, GI disease has to do with the fact that one's Vitamin K level is very strongly influenced by the status of bacterial colonization.

So clearly the response to warfarin is complex. We are beginning to understand genetic contributors. They are very enlightening. They potentially will lead to important pharmacogenetic tests that will help us to prevent bleeding complications, and not surprisingly, we see some difference in distribution of the low dose variants across racial groups. But whether we are getting beyond race I think is not clear at this point. Hopefully I would argue, we are.

I want to get back to the point that races are genetically heterogeneous. Does it matter that all we know about VKORC1 so far is in Chinese individuals by and large? I think the answer is yes, we should care about that a lot. In fact, as I showed you with the CYP 2C9 data, most of our data comes from Europe and the U.S., and most of it is on people of European ancestry.

We're seeing an increasing amount of research going on in Asia, particularly in China and Japan, so we're going to see some more data from that sector. But there are a lot of areas where we are just at this point very limited in the data that we have.

One collection of data that I'm showing you on this slide shows why it is going to be important to do very broad sampling. This was a study that looked at the prevalence of APOe epsilon 4 allele in populations around the world. The fundamental point I want to make here is that if you look at three different populations in Africa, you find a range from 9 percent to 41 percent, five different populations in Europe, a range from 5 to 31 percent, and so on.

The only population where they didn't see that broad a distribution seems to be in the three populations that were of Oceanic origin. The point here is that we can't just take a sample of people that have four grandparents of a certain geographic ancestry and believe that we have sampled that geographic ancestry. Within racial groups, I think it makes sense to anticipate, and

these data support the notion that we should anticipate a lot of heterogeneity, another reason to be very careful about generalizations.

In addition to that kind of heterogeneity, and most of the studies that I just showed you were taken in situ, that is in the different geographic locations, we know that race and geographic ancestry in this country are related but not congruent. I'm just getting back to that point, and I just want to show you a few data points that were cited by Mike Bamshad in a very useful recent JAMA article on this point.

West African, most African Americans, at least most African Americans that came here as a result of the slave trade, or whose ancestors came for that reason, were originally from East Africa. If you look at geographic ancestry testing panels in African American individuals, you find that West African markers account for about 80 percent of the ancestry on average, but the range is from 20 percent to 100 percent.

If you look at people who are self-identified as European, a substantial proportion of them have less than 90 percent European ancestry. That mixture is even higher and more variable amongst people who identify themselves as Hispanic. Bamshad cites data that people of Asian and African ancestry in other developed parts of the country tend to have more heterogeneous geographic ancestry than we see in the U.S.

Of course the other point I would make is this is a snapshot in time, in an increasingly global village, where there are many movements of populations. I read an article recently that said that immigrants from Africa who have come from Africa voluntarily now outnumber the population that is derived from people who came to this country from Africa involuntarily. Many of those people come from different parts of Africa than West Africa.

So we have, for example, in Seattle a large immigrant population from Eretria, Somalia, and Ethiopia, and given that heterogeneity, that we may see across people of African decent, we may see additional genetic complexity in the population self-identified as of African decent.

So we get to a fundamental question. Is race clinically important in drug treatment? Well, race clearly captures many potential group differences, as I've said. Even if you account for heterogeneity, and you always have to have that heterogeneity in your mind, we do see broad differences when we group people by race. Not always, but sometimes in issues of diet, issues of housing, issues of occupation, and issues of environmental exposure.

There has been a lot of work done, for example, looking at the higher risk that African Americans experience to be in substandard housing, or to be exposed to medically significant environmental exposures, and as I've shown, we also do see a difference in prevalence of gene variants.

So it's not unreasonable to expect that we might see differences in drug response when you consider that all of these factors might influence how groups respond, or how individuals within groups respond to drugs. I think the question really is if we make such observations, what do we do with those?

The story of the VKORC1 and basically our growing understanding of warfarin's response says that it is worth investigating, and sometimes we'll find a specific genetic difference that may offer some explanation for a group difference. When we do, that genetic explanation will help us to identify individuals and move beyond the group.

So we can now envision a day where it matters what CYP 2C9 genotype you have, and what VKORC1 genotype you have, not what race you are, in determining your warfarin response. Other times it seems very likely that an observation of group difference will get us to an extremely important non-genetic difference that may be an important thing to address clinically.

In a recent editorial in Nature Biotechnology, the editorialist described race as "Simply a poor proxy for the environmental and genetic causes of disease or drug response." Now, crude markers can sometimes be very useful indicators to get us to questions that are important to research.

I think at this point it's very uncertain whether in the long run race is going to have sufficient predictive value to assist in drug treatment.

What are the implications of these kinds of observations for pharmacogenomic research? Well, clearly if we want to identify all the variants that are relevant to a particular drug response, we've got to study diverse populations in large numbers, because we run a real chance of missing important variants if we don't.

We need, as we do so, as we identify individual variants, to always have in mind that multiple genetic, social, and environmental factors are going to be important. So any one observation has to be sorted out for its place within that mix, and obviously gene/gene and gene/environment interactions are going to be likely in that setting.

I think also the issue of orphan genotypes from a point of view of ethics and policy is an extremely important one to think about. Rarer genotypes that predict drug response are likely just by their nature of being rare to be less studied, and could be neglected, particularly in terms of the information we heard earlier today about the use of genomic information and drug development, there would be a real possibility that people with rarer genotypes could miss out.

Given the preponderance of research occurring in the U.S., the preponderance of drug development occurring in the U.S., I think we have to worry about a particular category of orphan genotypes. These are genotypes that aren't necessarily rare, but are genotypes that occur predominantly in minority populations. So they are not rare worldwide, but they are rare within the U.S. population, or relatively rare.

The issue of loss of lactase leading to the condition called lactose intolerance represents a very interesting example of this. A group of researchers wrote an interesting article in 1999 in the Journal of the National Medical Association claiming racial bias in federal nutrition policy.

Their argument went as follows. That federal nutrition policy has, for a long time, recommended milk product intake as a very important source of calcium in the diet. But as this group points out, the inability to digest lactose, that is to tolerate milk products, and in fact the rate of GI symptoms when one tries is quite high in virtually all racial groups except Europeans.

I'm not sure there is data on Oceanic groups, so I should give that caveat. But amongst Africans, Asians, Hispanic Americans, and Native Americans, it is a very common problem. Milk is not a good source of calcium for people who have this problem.

Now, again, it's a prevalence difference, so estimates of lactose intolerance amongst African Americans run something like 70 percent versus something like 15 percent in Europeans. As we have been saying about other things, it is certainly not a simple racial trait.

So, for example, if you live amongst Europeans, lactose intolerance is much more common amongst people of Southern European decent than it is of Northern European decent. But what we have is we have basically something akin to an orphan genotype here, because we have policy having been made and billed upon the needs of a dominant group in the population who happen to have a genetic predisposition that is quite unusual worldwide.

I think it's a very important point that illustrates how careful we have to be about the orphan genotype issue.

I have said that one of the implications of thinking about race, genetics, and pharmacogenetics is that we need to do research in diverse populations. As we do so, we have a very important ethical concern to overcome. That is the existence of mistrust about genetics generally, and perhaps more specifically, about genetic research among minority populations.

I pulled out a couple of examples, but there are many examples. There is currently a lot of tribal mistrust in North America related to research misconduct in the past, or alleged research misconduct. So there have been examples where tribes have agreed to the collection of genetic samples for certain purposes. The most famous example is that of the Havasupai Tribe in the Grand Canyon who were very interested in the genetics of diabetes being investigated, because that was an important health issue in their group.

Then 10, 15 years later, a member of the tribe comes to a research presentation and discovers that the very same samples that were collected for that purpose had been used for ancestry, for migration studies, for studies of inbreeding, for studies of schizophrenia, for a variety of purposes that the tribe did not endorse and was in fact quite concerned that that research was done. That's one of many examples.

The other example is one of many examples. We do have data that suggests at least that there may be more mistrust and more worry about the misuse of genetic information amongst minority populations. Now, this is a study, the one I'm quoting, which is a survey of minority premedical students, had only minority students in the sample, so we don't have a comparative statistic. I would have liked in the survey data that we heard earlier to have seen a breakdown by race, because I think that would have been informative.

But certainly there is the worry there that discrimination has occurred on other bases, and this might be yet another basis for discrimination. So if we say that it's important in order for all groups to derive benefit from pharmacogenetic research in order not to miss the orphan genotypes that are really important, then this becomes a tremendously important imperative, to figure out how to develop partnerships, how to incorporate minority communities within the research enterprise to move forward together so that the research is done in ways that minority populations endorse and feel are good for their community so that they have assurance that the information will come back to them in ways that can be helpful.

I'm just going to end by talking about in summary what I think are the significant risks that derive from the use of race and genetics and the study of differential drug response, and then I'll make just a couple of remarks about how I think these issues apply more generally to ethical concerns in pharmacogenetics.

I have already made the point that we have inadequate research in minority populations, or if you want to put it in a global scale, we have too much research in the U.S. and Europe, and not enough in other parts of the world where the populations that are minority in this country are not minority.

We need very careful attention to the size and the sampling methods that are used for populations. We need to get away from the situation where we talk about Asian, but what we really mean is Chinese. We need, as we do that, to figure out effective ways to partner and address community concerns and have community concerns be incorporated within the research enterprise, and obviously fundamental obligations of research integrity must be maintained.

If people give permission for samples to be used in one way, they really can't be used in another way. That's fairly straightforward.

As we go forward of course we also have to think about multiracial groups. Now, there is no simple bright line between where Africa leaves off and Europe starts. One of the interesting things about ancestry testing is that it tends to focus on clear examples. But we have many parts of the world where it's not clear, where there is a lot of what ancestry testing researchers call admixture. But really what is the inevitable heterogeneity that comes from trying to draw bright lines and saying here is one group on one side and here is another group on the other side.

In many parts of the world, this is an important issue. In addition, we have an increasing number of people in this country and in many other countries who very consciously identify themselves as multiracial. Just as we need to be concerned not to leave orphan genotypes behind, we need to think in terms of an increasingly multiracial society.

Clearly a very important issue is to avoid the notion of genetic reductionism in drug response, the need to recognize that even when we find genetic predictors that help us to identify people that may have higher or lower likelihoods of either adverse effects or effective responses to a drug, that that's only one of many contributors, and we shouldn't inflate it beyond what it is.

We need to be particularly mindful as we go into pharmacogenetics and do the job we need to do of bringing in lots of people from lots of different populations that we categorize in racial terms because that's how we're used to doing it, to make sure that we're avoiding the error of misrepresenting race as a genetic entity.

We need to recognize that racial group differences may have many causes, but most importantly from the genetics perspective, genetic variation within racial groups is common.

Let me just step back and say if we think about pharmacogenetics from an ethics and policy perspective, what are the concerns? Well, I think one of them is that we've got lots of hypotheses of benefit, but relatively few examples where we actually have outcome data.

I think the CYP 2C9/VKORC1 example is very powerful. I would welcome research that would investigate the question of how much a panel that measured for those variants could assist clinicians in reducing bleeding complications of warfarin, and perhaps given that some of those variants are for high dose, getting people quicker to effective, therapeutic doses.

But I think the question has to be researched. We need outcome data. The hypotheses is great, it's very powerful. I'm sure at least some of these hypotheses will work out, but our experience

for medical research is that not all good hypotheses actually turn out the way we think they're going to. So we need to think about that.

I think we need to be very careful about defining and protecting against risks. One of the risks is of ancillary information. I mentioned that APOe4 has now been identified at least on one study as possibly a contributor. So you can imagine in that imaginary panel that you might put APOe into the panel, and it might possibly improve your ability to predict who is going to have bleeding complications.

On the other hand, you're also going to find that information about Alzheimer's disease risk that people may not want to have. That may be a more significant risk that outweighs the benefit that might be provided. So I think we have to think very carefully about that.

I think we have to think about the risks of the paradigm, the risks of oversimplifying the predictiveness of the genetic information and thinking that it's simple. The TPMT example that Jim Evans mentioned did undergo FDA review in context of a drug labeling issue. One of the concerns that came up in the committee that considered that was not the issue that TPMT homozygotes would benefit from being identified and given lower doses of chemotherapy that is dangerous for them, it is whether we would undertreat heterozygotes. So I think we have to look very carefully at those issues.

As with any health care intervention, try and be as global as we can about anticipating potential issues, and then evaluating them.

Then finally I would say that there is a fundamental ethics and policy concern that goes across the board in health care. It certainly goes across the board as we're talking about genetic innovations. That is as we find these wonderful new ways that we think will help to personalize and improve the quality of health care, can we be sure that everybody who could benefit from them will get them? I think that's a fundamental ethical concern.

I do want to give special thanks to my colleagues, Malia Fullerton, Ken Thummel, Susanne Haga, Karen Edwards, David Veenstra, and Julia Crouch, who is the coordinator of our Center for Genomics and Health Care Quality at the University of Washington, and our pharmacogenetics working group. Thanks.