

Pharmacogenomics Session
Q & A and Committee Discussion III
Facilitator: Emily S. Winn-Deen, Ph.D.

DR. WINN-DEEN: Thank you very much, Wylie.

On our schedule now we have a little bit of time for discussion of ELSI issues. We'll let Wylie sit in the hot seat without the benefit of fellow panel members. So be kind.

But I think we identified a fairly long list of ELSI issues, and I don't want to necessarily confine our discussion of ELSI issues to the narrow topic that Wylie brought up if we have other things that we'd like to bring up. I'm sure she may have some comments on a variety of issues as well that could inform our discussion.

Are there questions? Kevin?

DR. FITZGERALD: Again, Wylie, thanks very much for your presentation and the issues that you raised.

I'd just like to expand upon one. You talk about our need to be careful with our sort of genetic reductionism or our geneticization of the issue. I'm also wondering, in your experience with these various groups, there is also, I might argue, the risk of a geneticization or a medicalization of risk and benefit overall.

So when you mentioned risks and benefits, you did tend to kind of be medical, but that's, I'm presuming, just because of the examples that you gave. I was wondering if you could speak more about just that whole idea of defining risk, period, as a group.

DR. BURKE: I think the point is well taken. Actually, and I agree completely with it, I think with pharmacogenetics, we are dealing in a more narrow area usually because we're talking about someone that has a health problem for whom we're considering a drug treatment.

On the other hand, if we got to a point where there was some genetic trait that allegedly identified people who felt themselves to be perfectly healthy who somehow now needed a drug, we definitely would have to look very carefully at the issue of medicalization. That goes more broadly across genetic risk information.

MS. BERRY: Julio?

DR. LICINIO: It was a really wonderful presentation. I had a question related to the issue of like mixed populations. Here, in the states, for example, people think very much like are you African American or Asian. You mentioned a little bit about people who consider themselves of mixed ancestry.

But in places like Hawaii or Brazil, where I'm from, those concepts are very different. People really are a true admixture of several countries. There are countries like parts of Malaysia or even India, et cetera. There is this kind of clear concept. It is even kind of almost non-existent.

How can this type of approach, like medicine that's given for hypertension in blacks here in the states, how is it going to be used, for example, in Brazil or in Cuba? Should people take it or not

take it? What do you think of this same issue in a culture in which the concept of race is very different from what it is here?

DR. BURKE: I think it's a very good point. What we can say, and I think most of my remarks are very specific to how we think about things in the U.S.

I think the fundamental answer is the same. Your point speaks to the extraordinary importance of making sure that research occurs in other populations, and that we don't exclude populations like Brazilian populations or Hawaiian populations where there may be less clarity about these racial categories that we're used to thinking about.

In fact, really the movement should be in the other direction, drop away from these racial categories that will have increasingly less use and less utility, and just do good population sampling to look for the variants that are relevant, or other factors, non-genetic, that are relevant.

DR. WINN-DEEN: Muin?

DR. KHOURY: Thank you, Wylie.

As always, I learn a few things from you every time. I was expecting to hear about BiDil, but I guess that didn't happen in your particular presentation.

As we think about sort of public health issues around pharmacogenomics, you being at the previous committees, I mean, you sat where these guys used to sit, trying to give advice to HHS agencies here.

I'd like you to for the next two minutes put that hat on and sort of help Emily and the group sort of think through the kind of recommendations to HHS. Some of them were already in your slides.

I want you to take BiDil first, because it is such a hot topic, and I'd like to see how it fits in the contract that you presented this afternoon.

DR. BURKE: Well, BiDil is a very interesting example. BiDil, from my point of view, has nothing to do with either pharmacogenetics or differential race response. So let me just start by saying that, and that's why it didn't show up as an example in my slides.

Let me explain why I have that view. The components of BiDil, isosorbide and hydralazine, have been known to be effective in congestive heart failure, which is the indication that BiDil is being promoted on, have been known to be effective in congestive heart failure since at least the mid-1980s. The first systematic study of those two drugs in congestive heart failure was published in the mid-1980s called the VHAFT1 trial. It was a VA trial.

It was predominantly a white population. There were some minority participants. It resulted in a 36 percent reduction in mortality for people who got that drug combination, compared to people who did not. So I don't think there's any question that the components of BiDil work in people other than African Americans.

The story of how it came to be proposed as something that might be marketed as a drug for African Americans, I think it's an interesting story. Jonathan Kahn has written a lot about it, and I

think it has more to do with the regulatory procedures and the laws around getting patents for combination drugs than it has to do with anything specific to race.

But the one other trial I'll comment upon is the AHAFT trial. What happened was the researchers who were involved in the VHAFT1 and then a subsequent VHAFT2 trial, both of which showed effect of this drug combination in predominantly white populations, actually asked for a patent. There is a special kind of patent that I think is called the methods patent, but I will stand corrected by the FDA folks.

This is a patent that allowed them to create a combination drug even though the two drugs would still be available generically. That was denied. It was only after that denial that a subsequent reanalysis of VHAFT1 led to the suggestion that there might be a greater response to isosorbide hydralazine amongst African American participants in VHAFT1 as opposed to European American participants.

Now, the study was not designed or powered to answer that question, it was merely a hypothesis, and I think it remains a hypothesis.

What was done then was the AHAFT trial. The AHAFT trial enrolled only African Americans, so it did not address the question of whether there is a differential response. What it did do, which I think is very helpful, was it showed that the combination of isosorbide and hydralazine remains an effective therapy. This is for folks with congestive heart failure that are on standard therapy. The question is whether an additive of hydralazine and isosorbide adds additional benefit. The AHAFT trial said it did, a 43 percent reduction in mortality. So it was a very striking benefit. I think that's helpful.

The trial was only African Americans, but I don't see that those trial results say that it only works in African Americans. We have prior data that says that European Americans benefit. I think we have a long history of testing drugs in one group, and then extrapolating those results to other groups. Most conspicuously perhaps testing men, and then saying women will benefit.

I actually think the AHAFT trial is a wonderful demonstration that this particular drug combination has value and may benefit some congestive heart failure patients. I don't see it as evidence that only African Americans will benefit.

Let me make one more comment while I'm on the BiDil story. That is that BiDil is a very expensive drug. The two components of BiDil remain available as generics. The price differential is something like \$400 a month versus \$60 a month. So I don't, speaking from the perspective of underserved patients, I don't see BiDil as being a breakthrough.

I do think the evidence that isosorbide and hydralazine are helpful is useful, and that physicians can use that information when they think about the patient on standard therapy who may need something additional. So that's my comment on BiDil. I'd be happy to answer more questions on that.

Getting back to the other point that Muin raised, what can HHS do? Well, I think the HHS perspective starts with the research perspective. I would say the tremendously important thing here is thinking very carefully about inclusionary approaches, about making sure that broad selection of populations is done. I think there is an argument perhaps for trying to encourage studies outside of the U.S., and clearly all of the ethical concerns that go along with approaching

communities that haven't been involved in research and that may have some mistrust. I would say that's a leading issue.

From more of the clinical integration side, I think there is also a research piece. That is how do we fund outcome studies? How do we do post market studies after a drug has become available to look carefully at whether the drug is delivering on the promise that we said it was doing.

Then I think finally there's an HHS imperative to think about access. In the newspaper article that was referred to this morning regarding Herceptin, they had a price tag, something like \$42,000 a year. It made me wonder whether patients in this country who are underinsured or uninsured get Herceptin when they need it. So I think those are policy issues that are important.

DR. WINN-DEEN: Joseph?

DR. TELFAIR: Thank you for your presentation. You have actually answered part of my question with your last set of comments.

But the other part of it that I think also would be really helpful is the understanding that in order to even get where you just suggested requires education, education both from the student level, all the way up.

So I was wondering, did you have any recommendations of how that might occur? You know, what I'm asking is that it's an infrastructure question really, and if you have any recommendations in that area, or any thoughts, I would appreciate it.

DR. BURKE: I'm not sure I have any thoughts that are going to be more specific than the very important point that you just made. I think as we view this wave of genomics that's coming our way, we have to think very carefully about how can genetics be integrated into our expectations of school curriculum right from the beginning on up. So I think there is definitely a sort of public education curriculum issue that comes up.

I would highlight two other issues. We have to think carefully about how we're going to educate health providers. There has got to be a point of service. I get it when I need it, I don't get it when I don't need it because I'm not going to pay attention because I've got too many other things to do. So I think there really has to be a lot of thought as to what models are really going to work to help health care providers.

Then finally I think we have a need for education about what research is and why it matters, and what assurances we can give to the public that we will do research in appropriately respectful and appropriate ways, because there is a lot of research that needs to be done, and probably the most important resource in that research effort is the human participants that are willing to be part of it.

DR. TELFAIR: I appreciate that because that's your information. One of the other things I guess I was also getting at when I was thinking of infrastructure is that those who make decisions on how information gets disseminated, it goes and makes decisions on even how you structure the research process. In other words, make decisions about what populations to study, why to study them, and give information on that.

Because, as you know, many of us who do research tailor a lot of how we approach or even write the grants based on the guidance we get, and the guidance itself comes from, well, you know the process.

SACGHS Meeting Transcript
October 19-20, 2005

So I was wondering if you had any thoughts about education, not necessarily about just the public or even providers, but those who are in the process of having to make decisions about what do we focus on. Even in training of the health care profession, and this is something that was in the Institute of Medicine report on public health, and I know this is kind of outside of what you are talking about, but it to me structurally fits.

How do you begin to even get those kind of steps of decisions, who are responsible for the public health care infrastructure or workforce to begin to think about this? What kinds of things would they need to know? That is what I think is what is important to us as well.

DR. BURKE: Yes, I would just say I think you're making very important points, and I think there are important issues that I'm not quite sure the best way to deal with.

Following the point you're making, it seems that one of the issues is how do you convene leadership in different, for example, NIH institutes to think very carefully about how to help the public in the best possible, most efficient manner? I can only say it seems to me those are tremendously important things.

DR. TELFAIR: Thank you, ma'am.

DR. WINN-DEEN: Other questions for Dr. Burke while we've got her at our beck and call?

(No response.)

DR. WINN-DEEN: Thank you very much.

DR. BURKE: Thanks for the opportunity to speak with you.