Q&A and Discussion of Perspectives from Industry

DR. WINN-DEEN: In keeping with trying to keep us on time, what we're going to do is take about the next 15 minutes for questions and answers for the two speakers who we just heard from from industry, and then we'll move directly to the public comments and on to our lunch break.

So I'd like to ask if there's anyone from the committee or the ex officios who would like to kick it off.

Kevin?

DR. FITZGERALD: Just to get a better sense of where both companies are coming from, and I'm not asking you to speak for all of industry or anything like that, but one of the comments I think both of you referred to was when you're looking at developing various either diagnostic tools or drugs or whatever, there's this argument that keeps coming up about the size of the subgroup, and eventually, of course, with genetics, you could pretty much break it down to we're all individuals except for identical twins, and even then you might find enough differences.

So what cutoffs do you use in your industry for saying, okay, we've got X amount of market out there potentially to develop this product? I only ask because, again, in these sorts of partnerships that you're looking to develop, the question will be to know what are your cutoffs, what are your bottom lines, and then how does academia, how does government, how do the rest of them come in to help with those kinds of partnerships?

An example that comes to mind, currently we heard about the testimony going on today about the BiDil drug and the use of that for a particular group. Well, let's say somebody discovers that the Native American populations, after they crossed the bridge from Asia, developed some sort of cytochrome P450 variant and no one is going to be running around developing drugs or products for Native American populations because it's not just that big, I would presume. So it would fall into a kind of orphan drug category. So that's why I'm interested in getting from you where you would see your cutoffs or limitations.

DR. LAI: Well, I'm a scientist, so I'm not a financial person. So I'll answer the question scientifically. I'm not aware of any hard cutoff percentage number. But on the other hand, you can look at history and look at the record. Herceptin is about 25, 30 percent. Urisa is about 10 percent, something like that. So there are examples out there that give you some of the percentage.

DR. FITZGERALD: But you said yourself, I believe, Herceptin was about a $1 billion market?

DR. LAI: Yes.

DR. FITZGERALD: Right. And is Urisa similar?

DR. LAI: I don't know the number of that.

DR. FITZGERALD: Okay. I was just wondering if you knew those kinds of details. I think that's something that would be helpful in the discussion as we go forward to talk about these kinds of partnerships and where various emphases may lie and who has to push in what direction for that kind of thing.

DR. KOCH: Perhaps many of the early examples are based on the science, not necessarily the market size. Gleevac, used to treat particular leukemias that have one specific translocation, not a huge number. Nevertheless, the drug is doing well and there are diagnostics available for that. Just this last spring we found out when drug resistance arises, there are now follow-up therapies for that. So when there's a real medical need and a benefit for both therapy as well as diagnostics, I think it's going to be used because the science is driving it.

DR. WINN-DEEN: Debra, and then Tim.

DR. LEONARD: So I was interested to hear your comments that the diagnostic-therapeutic combo guideline that has come out of the FDA is not really very feasible. I haven't heard the corporate perspective on that. I've only heard the FDA's perspective, and I assume that that's feedback that the FDA has gotten. Do you have any hopes of ever seeing a diagnostic-therapeutic combination coming to the FDA? That's more directed at Joe.

DR. HACKETT: Do you want me to go first? We're assuming that they will come in. We don't know what their frequency will be. You have to remember, for that combination, it's a situation where there is such a risk with the drug itself that there must be a diagnostic test, as with Herceptin. But it's too early to tell at this point in time how frequently that's going to happen.

DR. LEONARD: But the Herceptin -- that combination didn't come in together, I don't think, the Herceptin --

DR. WINN-DEEN: They came in together. They had panels on the same day.

DR. LEONARD: Oh, really?

DR. WINN-DEEN: Yes.

DR. HACKETT: They were both developed at the same time.

DR. KOCH: Well, I've heard the history wasn't quite so smooth. But in any case, going forward, you would like to do it in a concerted way together. I wouldn't say that it's infeasible. I would just say that if you don't know what the markers are that are informative for your drug response until Phase II, and often that's what I see in the real world of pharmaceutical companies that I deal with, including our own, then there's no way to have an IVD final product ready for the pivotal Phase III. So that's one conundrum about how you align those two processes so that they come together at the end.

DR. LEONARD: So are ASRs and lab-developed tests discounted in the ability to bring drugs to market without the diagnostics that's needed?

DR. HACKETT: ASRs are a possibility, but our position is that microarrays are not ASRs.

DR. LEONARD: I wasn't referring to microarrays. I was referring to lab-developed tests and ASRs that -- so many of the pharmacogenetic kinds of tests, you publish the variant and we can do it in the laboratory. So it doesn't require an FDA-approved, cleared test in order to be able to do that kind of testing. Does the FDA take that into account?

DR. HACKETT: Yes, we're looking at that as we go along. But the main object is communication, the earlier the better, so we can get together with industry and start working out these problems and try to develop them, including how are we going to deal with ASRs.

DR. WINN-DEEN: Tim?

MR. LESHAN: To shift subjects a bit, I want to go back to your discussion about the reimbursement issues. If you could just give us a little bit more background about the reimbursement around the AmpliChip and where that stands?

DR. KOCH: I'm no reimbursement expert, but I laid out for our reimbursement folks what the steps in the test were, and typically the CPT codes are used for DNA extraction and amplification and so on. So the thing that I think is misaligned is using technical steps to put value on a test. My view is it's what the clinically relevant information is that you're providing that should drive the reimbursement for the test. So if I perform the same procedures and can predict nausea and vomiting from a drug versus whether you're likely to respond to a chemotherapeutic agent and cancer, I think those two tests' predictive information have very different value associated with them even though they might use exactly the same steps. That's sort of where I'm coming from.

DR. WINN-DEEN: Okay, we've got Barbara, and then Muin.

MS. HARRISON: Just to follow up on Kevin's comment from before, I was just wondering, when these pharmacogenetic and genomic studies are undertaken, and we can use the example of TPMT in the literature, you mentioned that the allele of concern with TPMT is present in 1 in 20 people of Northern European descent, and that's when you mentioned that it's not necessarily present in Asian populations that you studied. I was wondering, is there an expectation, not necessarily a cutoff but some kind of expectation that there be a diverse population studied before there's a guideline that's put out about what should be watched out for or not?

DR. WEINSHILBOUM: Maybe I can just tell you that, for example, in the Pharmacogenetics Research Network, I mentioned that in all the resequencing studies, samples from African Americans, Caucasian Americans, Hmong Chinese Americans and Mexican Americans are a standard part of what we do. No surprise to a sophisticated audience like this, we find rather striking differences in allele frequencies and types in the different populations.

Now remember, these are large studies. But nevertheless, it's a relatively small number of subjects, and I think the point that Walter just made about going to China and seeing in an Asian population some different variants that are of functional importance is a lesson that we all understand, and clearly that was the implied message. In fact, it's what I heard Francis Collins say on Public Radio this morning with regard to the 42 percent decrease in mortality -- I mean, it's quite striking -- in the BiDil population, the African American population treated with that drug, whereas no benefit could be demonstrated in the Caucasian Americans. What Francis was basically saying was what we really need to do, and I think it's going on right now, is to understand the underlying molecular mechanisms that are responsible.

But the answer is, yes, there's a great sensitivity to examining as diverse populations as possible.

DR. WINN-DEEN: Muin?

DR. KHOURY: I wonder if we can put up slide number 5 from Eric Lai's presentation, because I'd like to kind of talk around that. Obviously, the promise of pharmacogenetics and pharmacogenomics, sort of there is that balance that we all talk about. On that slide you had on the two axes the percent of patients with major adverse effects versus the percent of respondents.

The next one. Just finish it up, because it has sort of that balance where you have on the one hand everyone's dream drug where almost everyone responds and there are no side effects in the population, and on the other hand you have 90 to 95 percent of the drugs that have failed because of large side effects and low response.

Now, if you put a third axis, which is sort of the potential, I think that's coming back to your point earlier, the target audience. So if you're developing a drug to treat children with acute lymphoblastic leukemia, you have the drug and then you have TPMT, that's a very limited segment. I don't know what the incidence of ALL is, but it's not the same as the incidence of heart attacks in middle-aged men. So you have that third axis of the potential populations to be targeted, and I wonder if we can have a little bit more discussion about those gray zones.

For example, go back to TPMT. Again, I don't want to beat a dead horse, but the percent response is very high, and you have the percent of patients with major adverse effects is less than 1 percent, the homozygous, 1 in 300. So where is that? That's not your dream drug, obviously. It's almost saying that pharmacogenomics is not necessary, if I read this chart correctly. Can you elaborate on that?

The second question is the pipeline of new failed drugs, the 90 to 95 percent, is there no room for pharmacogenomics there? Because there is a lot of stuff that's being discarded without being studied. Is there a way to save some of these drugs?

DR. LAI: So with respect to your first question on TPMT, I think that you have to understand this graph is basically used for illustration. So how big those circles are, sometimes they can overlap. So you could potentially, for the adverse reaction PGx, go a little bit to the left, 0.5, 0.25 percent. It really depends on a particular drug and how bad the adverse reaction is. It could be just, like I said, a stomach discomfort for half a day.

DR. KHOURY: I guess my question is what is the decision analytic framework here, if there is one? I mean, is this just in the hands of the practice of medicine to figure out those pros and cons, or there is something more overarching in terms of devising evidence-based decision analysis model here?

DR. LAI: Well, that's what I'd like to bring up. I think that's for the committee and the FDA to discuss. I mean, basically my understanding on the TPMT is they're saying that percentage is not big enough. That's my understanding, that it does not quite get to the circle to the right. That might be the wrong interpretation, but there are overlaps and there are a lot more factors than just signs.

Now, economic definitely needs to play a major role in this, not just the economics of the disease and how much of a market there is, but also I think that we need to keep coming back to this benefit in that it's not just the side reaction or the adverse reaction that you see on day 1, which you mentioned. It's actually a long process. When somebody has to be in the hospital for three months because of one dose, that's very costly. So you actually have to develop pharmacoeconomic models for adverse reactions. I think that in Europe they are ahead of us because the government is the one actually paying for the drugs. So that's why they developed

these models and they figured out that, well, for certain drugs it is indeed worthwhile to prevent the reaction, even though they are much less frequent, because in the long run that makes sense.

It's just like preventive medicine in dental care. Now insurance companies pay for preventive care in dental because they've figured out that it's cheaper than until you develop a major problem. So that's the answer to the first question.

The second question is, on the failed drugs, I did cover that a little bit on the benefit of PGx. A lot of those fail because either they are the wrong target, because they have high toxicity, they get into the wrong P450 and so forth. By doing pharmacogenetic studies, you actually can figure out some of them why they failed. That's why in one of my subsequent slides I said provide more evidence-based drug development process.

DR. WINN-DEEN: We're going to take one more question from Deb, and then we have to move on to the public comments.

DR. LEONARD: I realize I have a gap in my knowledge. Dr. Weinshilboum, can you explain to me what the Pharmacogenetic or genomic Research Network does? Do you do pharmacogenetic testing for clinical trials? Is it like a core facility kind of function?

DR. WEINSHILBOUM: I'm sorry that I kind of threw that up, here's a map, and didn't explain. This is a network supported by multiple NIH institutes. The National Institute of General Medical Science takes the lead. It has approximately a dozen research centers and one knowledge base/database at Stanford. The research centers do both basic pharmco -- that's why I had the balance between basic and translational -- both basic and translational studies, generally translational studies which are related to the nature of their laboratory-based activities and includes, in the same way that Dr. Davis was pointing out, molecular epidemiologists, statistical geneticists, laboratory-based investigators.

So in our center we're resequencing genes, as I pointed out, doing functional genomics, but immediately translating that into studies of breast cancer and psychiatric illness that is drug therapy. In other centers the focus is on cancer, on cardiovascular disease, on asthma, ranging from laboratory-based studies, discovery of new polymorphisms and haplotypes, functional characterizations, and testing in translational studies whether this information will help us to better either enhance efficacy or decrease toxicity.

You'll have an opportunity this afternoon, when Dr. Rochelle Long is here -- she is responsible at the administrative level for coordinating the Network -- to perhaps ask additional questions. I don't know whether I've answered your question or clarified anything, but it's a series of research centers across the United States, and academic medical centers, supported by UO1 cooperative agreement grants from the National Institutes of Health. It's been going for five years. We've just been through a competitive renewal phase, and next week here in Bethesda the centers involved in the next five-year period will be meeting.

DR. LEONARD: I was just wondering if it was a thing like NCI has set up, sort of core facilities to provide certain kinds of analysis very broadly across many research programs. I was wondering if that's the kind of function that this had that could interface with clinical trials in doing sort of blanket pharmacogenetic testing as clinical trials are ongoing.

DR. WEINSHILBOUM: It's very interesting that you should mention that because as part of the Roadmap there is this regional translational research center proposal which has now gone by the

board, and you are looking at someone who on behalf of our network was given the opportunity to write for the network, to do with clinical trials. Why do you think I mentioned clinicaltrials.gov? Exactly what you're proposing. As you know, the NIH stepped back from the regional -- we proposed that a region be the United States of America. We were told that in some cities in the northeast that Longwood Avenue would be a region, but I won't go into that.

But as a matter of fact, the concept that you're proposing is exactly the type of concept which within the Network is one of the things we're thinking about in terms of raising the profile of the discipline throughout all of biomedical science.

DR. LEONARD: What would it take to do that?

DR. WEINSHILBOUM: It would be nice if the kinds of proposals that we put in, if there were at least some consideration and competitive arena for an opportunity to do that.

DR. WINN-DEEN: I'm going to have to cut off the discussion here because I think we do have an obligation to reserve the time that has been allotted for the public commentary.

I'd like to thank the morning panel very much for the information, for the education, and more importantly for your many comments on the things that we could address. I hope that we can come back to you all as we struggle to sort these comments out into some kind of bins that we can manage and try to prioritize our work as a committee for additional advice and comment.

DR. WILLARD: Thank you, Emily, for taking care of the morning for us.