Q&A and Discussion of Pharmacogenomics in the Practice of Medicine

DR. WINN-DEEN: I want to thank you very much for that enlightening talk and throw the floor open for questions from the committee, and I recognize Deb as the first.

DR. LEONARD: This actually isn't directed -- it's inspired by your talk. But it's a question to the FDA. Why doesn't the FDA require TPMT testing before mercaptopurine can be used in a patient? Is that within the purview of FDA to have that kind of labeling requirement?

DR. WILLARD: Felix, do you want to try that one?

DR. WINN-DEEN: Felix, can you come to the mike? Feel free to sit at the table.

DR. FRUEH: Well, I was not at the FDA at the time this was actually discussed in the advisory committee. It was the first case that came to the FDA from the perspective of personalizing medicine in a drug label, and it's my understanding that at the time, although the evidence scientifically was pretty solid, the advisory committee didn't feel compelled enough that actually a test needs to be done and is required. So we settled to provide the scientific information in the label so that I would say an educated physician at least has the information and can move forward and do the testing.

Moreover, the issue at the time also was that there was no commercial test available. So that was another consideration that the committee felt was an issue that needs to be addressed for information that is going to be in the label if a test needs to be done. An example for it would be like Herceptin, where a test is required for the prescription of the drug, and at the time that was approved, a test had to be commercially available.

DR. LEONARD: But it's kind of a chicken and egg problem. Until the FDA requires it, then no one is going to develop it. I don't think, since FDA is directed to look at safety and efficacy, that it's right, if you want to use the term "right," for the FDA to make excuses why not to protect the percentage of patients who get this drug and die from it.

DR. WEINSHILBOUM: Maybe I can comment since I had the opportunity to be at both of the public hearings. I think it's fair to say that the committee attempted to approach this in a measured and judicious fashion. TPMT I think was the first example that had been brought forward, probably because of the dramatic effects of the toxicity in the population at which they were looking, which in this case was purely children with acute lymphoblastic leukemia of childhood. They were not examining the off-label applications in inflammatory bowel disease. So we need to be quite clear what was being discussed.

The concerns that were expressed -- and I want to be very careful because it probably must be clear to you that I can be enthusiastic about things. So I want to be measured -- were those of the hematology/oncology community, that they were balancing the possibility of worrying the physicians, and remember that we can now cure a previously fatal illness, and they were worried -- and I'm trying to express what they expressed. It's not a position that I agree with, but I'm trying to be balanced here.

The majority of the patients being treated, that the physicians might cut back on the thiopurine dose and that the net outcome would be increased mortality. I think that was a reasonable perspective. I did find it interesting, because there is this concern, that the public won't understand or resonate to these sorts of issues, and I think it's fair to say the most vigorous

advocate for testing were the parents of the children with leukemia, the patient advocates. One of the moms there had a child who had myelosuppression, and I think it's fair to say she was fairly vociferous in her position.

But where the committee came down finally was to recommend informing in the label. The information would be included in the label, but to not mandate it.

DR. LEONARD: But we've already clearly demonstrated that physicians don't understand genetics. That's published in the literature repeatedly. So you're putting out there information in the dark, hoping that someone will do something with it, and that doesn't seem to be a very effective approach.

DR. FRUEH: Well, I agree with you to the point that we also need to make sure that what we put out there can actually be applied in the clinic. So it's not just about providing the information but it's about providing a consequence of the information. So in other words, Dick mentioned the irinotecan example, for which we had an advisory committee meeting in November last year, where we are in the midst of updating the label because there is actually toxicity that is prevalent in a much higher frequency than for TPMT, where people that have a certain genotype with a prevalence of 10 percent in the population have a 50 percent risk of experiencing toxicity.

The question is, however, what are you going to do about the other 50 percent who do not and might benefit from the drug? So you need to be very careful of not excluding patients that are willing to take the risk of treatment because they have a severe disease if they want to do so. So I think it's about, at this point in time, providing information and to make an educated decision about treatment. I don't think we're at the point yet where we have sufficient information to, in every case, determine what the actual treatment should look like.

DR. WINN-DEEN: Can I ask Dr. Weinshilboum a follow-up question? Are there actually in the oncology community clinical practice guidelines that the hematologists have put together on how to use TPMT testing and how to adjust dose based on those results?

DR. WEINSHILBOUM: Of course, this committee was a pediatric hemonic committee. So what we were hearing there was their perspective. It's my understanding that those sorts of guidelines -- and people taking a leadership role here are Mary Relling at St. Jude through the pediatric hemonic community -- that those guidelines either are being developed or certainly are being discussed with regard to exactly how they should move forward.

I think in fairness, it was a lack of clearly defined guidelines and the kind of systematic clinical trials that might guide the practicing physician that was another of the concerns that was expressed. So going from the basic through the translational to actually developing practical information for the physician has proven to be a barrier, even for some of these more well-developed examples. I think that we need to be fair and realistic here and realize that we're just feeling our way into the translation of this information into the clinic.

DR. LEONARD: But didn't you say that Mayo has guidelines for how to dose in response to the TPMT genotype?

DR. WEINSHILBOUM: Mayo has the test available, and the homozygous low individuals either are not treated with the thiopurines or are treated with one-tenth to one-fifteenth the standard dose and are monitored. The bigger challenge and the one that remains controversial are the 10 percent of a European population that is heterozygous and has intermediate activity. It's fair to

say that there is no consensus at present that I'm aware of -- Felix may be aware of one -- with regard to the appropriate algorithm for dosing those patients. In general, the clinical studies have looked at outcomes. They've said actually these patients do a little better, although they have a little more toxicity for most diseases that are being treated.

So it is that intermediate stage between demonstrating that the polymorphism is important. For irinotecan, it's *28 UGT1A1 that has the tata box, and then developing clinically useful practical guidelines. That's not the sort of study that in the past the National Institutes of Health was all that enthusiastic about supporting. These are generally old drugs, so the drug companies are less than enthusiastic about supporting those studies also. We come back to what Dr. Davis was talking about. How do we actually develop practical, useful information in the real world? I think that's going to be an interesting challenge for all of us, and I would assume we'll be talking about that through the rest of the day.

DR. WINN-DEEN: Julio?

DR. LICINIO: Dick, I may be misquoting someone horribly, but Max Planck in quantum theory had this very famous saying where he said that the current generation was not going to understand it and they just had to die, and then the new group would come.

DR. WEINSHILBOUM: My graduate students say that about me every day.

(Laughter.)

DR. LICINIO: So do you realistically think -- and I'm not sure about this -- that people who are out there in the trenches practicing are going to then start requesting TPMT or whatever test it is to adjust their therapeutic decisions? Do you think the current generation is trainable and able to make that kind of conceptual paradigm shift, or we just have to train young people and hope that one day they'll take over?

DR. WEINSHILBOUM: As someone who clearly is of the geriatric generation, I like to think that we are still educable. My facetious comment about gastroenterologists notwithstanding, the fact of the matter is we have no choice but to train the current generation of health care professionals. As a matter of fact, I've been quite impressed, Dr. Davis' comment notwithstanding and one that I heard stated a good deal more vociferously at Cold Spring Harbor, that physicians are educable.

I have to tell Felix that I made a presentation for our internal medicine group about irinotecan and was talking about the tata box and UGT1A1, and I got done, and someone of my generation, one of my colleagues came up to me and said that was wonderful. What the hell is a tata box anyway?

(Laughter.)

DR. WEINSHILBOUM: So we have a vocabulary problem that we have to overcome. But as a matter of fact, this is not a vocabulary problem that is insurmountable, because when I was in medical school, nobody knew what a tata box was either. So my answer is that I actually have great confidence that if we can convince physicians that this is important for their patients, it will happen. There is a commercial test for TPMT which is available, but still I think it's fair to say, Felix, that it's not being all that widely applied.

DR. WINN-DEEN: Ed?

DR. McCABE: Two points, both in follow-up to Deb and Julio but directed to the FDA. One is this issue about who is reviewing. If physicians don't get genetics, then you have people reviewing who may not get genetics. You have some pharmacogeneticists there, and my degree is in pharmacology, so I'm not saying anything negative about pharmacogeneticists. But are there any geneticists on those review panels when you're dealing with pharmacogenetics?

DR. FRUEH: Yes, more and more. I'm heading up a group in the Office of Clinical Pharmacology and Biopharmaceutics that is dedicated to genomics, and I will be talking about this a little bit in the afternoon. But we are realizing that there is a lack of expertise, and we are reacting to it. A lot of expertise already has existed at the time that TPMT was discussed, and Larry Lesko and others certainly were leading the way. But it definitely needs more attention. I agree with you.

DR. McCABE: I would just argue that even though this is a drug used in pediatric hematology/oncology, when you have the parents asking for it, when you have the hematologist/oncologist not understanding the genetics, I would just hope that the panels could be constructed in a way that there will be a knowledgeable review rather than a naive review.

DR. WINN-DEEN: James?

DR. EVANS: I need to borrow Ed's microphone. Mine isn't working. I should probably take a hint.

I was just wondering in the context of Emily's introductory remarks about what the catalytic factors are that will really propel this kind of information into the mainstream. In that context, have there not been lawsuits brought by patients? You cite patients who have suffered great harm or families that have had deaths. I'm surprised, and I would think that a single such case would have a catalytic effect.

DR. WEINSHILBOUM: I'll let Felix answer, but actually, to this point, I am unaware of any such case.

DR. FRUEH: Yes, me neither. But actually, we do hear more and more. I heard it yesterday at a presentation at the FDA. I've heard it in very strong words at the conference I attended on Monday about targeted therapies.

DR. EVANS: I think when attorneys catch on, it could change the base.

DR. McCABE: I've somewhat and only semi-facetiously said the way we could propel pharmacogenetics into daily practice of medicine is not to speak at medical conventions but to speak at the bar associations.

DR. WINN-DEEN: Muin?

DR. KHOURY: I have a question that starts with TPMT in relation to leukemia treatment but sort of uses that as a genetic example for sort of the value added of pharmacogenomics in practice. A couple of years ago I read an article by David Venstra from University of Washington that was talking about the cost effectiveness of pharmacogenomics in general, and he used I think TPMT as an example, and he had some nice graphics which I keep in mind.

But here's the gist of the argument the way I understand it. Of course, we know the biology of TPMT in relation to treatment, but there are two sort of opposing factors. If the allele frequency is very rare, and I'm not sure what we're dealing with, half a percent or maybe 1 percent of the population --

DR. WEINSHILBOUM: One out of 300 Caucasians is homozygous, 10 percent of the population is heterozygous.

DR. KHOURY: So I guess he was modeling the homozygous frequency. He showed that there is -- he did some sensitivity analysis on cost effectiveness, and he showed that the cost effectiveness, the way it would turn out, it's very sensitive to allele frequency. So even a drop from 1 percent to 0.3 percent, depending on the genetic test cost, et cetera, it would make it from a population perspective not very cost effective. So that's on the one hand.

On the other hand, the question is the balance that I think he raised and other people always raise is, is there any other non-genetic way to try to get at the same thing? In other words, if you are monitoring the levels of the drug and you might be able to find out that a person already spiked and it's very high, maybe it's too late -- I don't know enough about the pharmacology of 6-MP and TPMT, but the question is, which is a genetic one, is there any value added for using a pharmacogenomic test from a population perspective if you can monitor the levels of the drug and the toxicities rather than use an expensive test to basically screen the whole population, especially if the prevalence of the genotype is fairly rare?

DR. WEINSHILBOUM: I had no intention of this becoming a TPMT symposium, so please forgive me. It is a fairly dramatic example, and it serves to raise a series of issues, and I think it's only within that context that it's of value here.

With regard to the sensitivity analysis, all I'll say is that I received a request from the National Health Service of the U.K. They're setting up genomic testing for TPMT and wanted standards from us. So some group that is looking at this from that perspective is already moving in that direction.

Number two, I mentioned to Tim during the break that the patient who I got the call about two weeks ago, a 24-year-old young man, in this case with inflammatory bowel disease, has basically destroyed his bone marrow, and they're looking at a bone marrow transplant as the only way to retrieve this patient. So one has to look at not just the cost of the test but the downstream. I will just say that at one hospital that I'm aware of, a 4-year-old child was hospitalized for four months in isolation with recurrent platelets, red cells, et cetera, and finally survived. The cost of the hospitalization was about a half a million dollars.

So I think it's those sorts of concerns that have driven the National Health Service in the U.K. to be thinking along these lines, and obviously I have no stock in any company that sells TPMT testing, so that's not the purpose.

The other question, though, is an interesting one, and that is why not just measure some other phenotype. That is, the white blood count. That is what we heard, Felix, as some surrogate for the genotype. In this case, myelosuppression. It happens very rapidly with TPMT.

But when I put this in the context of my activities as a poor benighted internal medicine doctor, when I prescribe a drug which I mentioned was in the old original Goodman and Gilman, digitalis, William Withering -- now we're really going back -- one of the problems with digitalis

is that in a patient with low potassium, I can induce cardiac arrhythmias. So I have a choice when I prescribe digitalis in the hypertension clinic. I can either measure the potassium or I can administer the drug and see if the patient develops PAT with 2 to 1 block, which is a good surrogate endpoint for digitalis toxicity.

I will have to tell you that I generally measure the potassium first, and if I see the PAT with 2 to 1 block I know I probably made an error, and the test cost will go down. So that kind of an argument which I hear repetitively is Tim drives down the cost of genetic testing and we have all 3 billion nucleotides on everyone will become a moot issue anyway. So, as a matter of fact, in the tradition of medicine, where we learn how we can prevent the adverse effects of drugs even so widely used as Digoxin, I really find it difficult to understand some of these arguments that are made. But I'm from Minnesota.

DR. WINN-DEEN: Okay, one more question, and then we have to move on.

Hunt?

DR. WILLARD: Well, this might serve as a segue into the next two talks. But all the examples you've spoken about, which serve as excellent examples, is really pharmacogenetics, not pharmacogenomics, and you made that point. So if we have these challenges and difficulties with demonstrating clinical efficacy, difficulty with translation and adoption by the clinical community, for a single gene where we know exactly what to look for and exactly what in principle to tell physicians to do, give us some insight into the difficulties when we're actually looking at hundreds of variants around the genome that we may not actually understand the mechanisms of but we'll have solid evidence of their interrelationship and combination and the effect that those would have on drug response. If your colleague at the Mayo doesn't understand what a tata box is, what's going to happen when we're dealing with SNPs that are spread hither and yon around the genome?

DR. WEINSHILBOUM: I can tell I'm going to get in big trouble with the CEO of Mayo, who probably doesn't know what a tata box is either. But the bottom line is this: These demonstration projects are very useful to roll out on the road to stimulate the kinds of discussion of issues that we're having here. I put warfarin up there for a very good reason. It's not just CYP2C9. It's beginning to be much more complicated than that. Probably there's an apolipoprotein that shows the genetic polymorphism that's involved in transport of Vitamin K into the hepatocyte. So we probably will have three or four different genes we'll have to examine in order to begin to narrow down the beginning doses for warfarin.

If we could do that, though, if we could do that, we would save a lot of money for the system, and a lot of morbidity and mortality. So the fact of the matter is we need TPMT and 2D6 to make the point. They in essence are the Huntington's disease or the cystic fibrosis equivalents in diagnostic medicine on the pharmacogenomic side. They get a little boring after a while, but nevertheless they highlight the issues.

Where we're going, though, I think is where you have implied. It will be haplotypes scattered across the genome, and eventually 20 or 30 genes for many drugs. That's why I made my spaghetti factory explosion analogy and showed the pathway for irinotecan. I teach medical students every day, and graduate students, God bless them. I really have great confidence that if this information will eventually be made cost effective because of the kinds of technology advances that Tim and his colleagues do, that it will find its way into medicine, and we have to find a way to validate it to prove to our colleagues that it truly will help them care for their

patients, and I have every confidence that actually it will become a standard part of medical practice.

What we want to do is to accelerate that process, and we're having to learn from TPMT and 2D6 and irinotecan as we go.

DR. DAVIS: Just a very brief follow-up. I think that to the extent that this are illustrative examples, they're very good ones. I think the AmpliChip example is a really great one because it's a wonderful chip and it's gone through licensure, but I think that there will be a lot of resistance to its use because a lot of the clinicians are going to say show me the evidence that my use of this chip is actually going to improve outcomes. That's what we really need. The biologic underpinnings are very well known. It's tons of fun to read about. But I think the clinicians will hold us to the standard of show me that it either cuts costs or makes my patients happier or improves outcomes, or some mixture of those, and there's nothing ongoing to do that right now.

DR. WINN-DEEN: Okay. I want to thank everyone for the lively discussion. I think we need to move on or we're never going to get through the whole realm of perspectives that we're trying to cover today.