Questions and Answers with Wylie Burke and Nicholas Dracopoli

DR. McCABE: Could we have both of our speakers join us at the table here, please? We'll have some discussion.

Any questions from Committee members?

DR. LANDER: First, let me thank both of the speakers for tremendously lucid presentations covering a very wide range.

In terms of precedent here, we sometimes talk about how genetic information is no different than other medical information and all that, and maybe with respect to privacy all that was true. But listening to you guys, there's just no way that's true with respect to interpretation of genetic information. The privacy issues, sure. But the interpretation seems to me unlike anything that I've ever seen.

We have massive numbers of bits of data, very small numbers of studies for each particular type of application. We have zillions of combinations of all the different loci you're talking about and what to make of them, and it's not like testing a drug where you run one big clinical trial to basically answer one yes/no question, or a small number of yes/no questions.

You're asking a zillion possible questions, and you're interpreting very complex patterns, and there are many ways to interpret them. You're in a situation where, at least people who work directly in the field -- or I'll speak for myself, working directly in the field. I don't know what to believe. I read the papers and it takes me a very long time to first decide is Apo E and Alzheimer's right, and then what actually is the relative risk. These things come and go because people are attempting to find things on the cutting edge, which is very important.
We've got to be able to say things that could be wrong and might be flukes and all that. Yet, we could have a world where all this gets translated instantly into direct-to-consumer products.

Is there any precedent that we can appeal to where, in medicine, anything this complex, where you've got to worry about that the scientists can't necessarily understand it yet? Well, they understand it; they just don't know what to believe. The practitioners, I think I've got to argue that most medical doctors are going to have a hard time being able to keep up with tests on 10 to the 4th different possibilities, even the very best of them. The consumer, I think, not wishing to be in any way paternalistic and wanting everybody to have access to everything, it simply isn't realistic to expect most people to be able to evaluate the claims.

So all of that makes me ask: Can't we appeal somewhere to find that this isn't as novel as I think and this is routine and it's been solved somehow, or not?

DR. McCABE: Do either of you have a comment on that?

DR. BURKE: Well, I'll make a brief comment. I'm not sure I can address everything.

I think the kind of complexity that comes with RNA expression profiling data, for example, does seem fairly unique. It's certainly fair to say that over the past 50 or 75 years in medicine, there's been a constant

and steady onslaught of new technologies and medicine has had to figure them out, and maybe that's comparable.

But I think the important message in your comment is really how important it is for us to be thoughtful about when we're still in the research phase and when we're ready to move into clinical prime time, and even not very complex examples provide really powerful lessons. What's been happening over the past year, for example, in our knowledge of estrogen therapy, there's a moral there, because for 15 or 20 years, hormone replacement therapy was being proposed to reduce heart disease, maybe even reduce Alzheimer's disease risk on the basis of some observational data, and it turns out that on both fronts estrogen may increase risk rather than decrease risk when it finally comes to the data.

So I think those lessons should be taken to heart as we think about the need for robust clinical research where there's a good clinical hypothesis but caution about when it's ready to move into clinical care.

DR. LANDER: I'm all in favor of caution, but are you saying more that we have to have a clear and sharp distinction between lots of interesting research results and some bright line as to what is accepted clinical wisdom that has had some level of proof? I'm not saying how that happens in any regulatory fashion or whatever, but that somehow, in practice, the medical community has to come around and say this has crossed the threshold where we believe this result means something, and if we don't do that, we will simply have complete chaos in terms of information.

DR. BURKE: My guess is there's never going to be a bright line. In fact, genetic testing would suggest to us that we're going to have situations where a genetic test makes a lot of sense for a small subset of families with particular unique characteristics, but isn't ready to span. So I think there's going to be an evolution. We know this and can do this, and don't know that and can't do that.

DR. LANDER: I don't mean a bright line as to whether we do or don't do. What I mean is does there have to be some way where the community comes together and attempts to agree on a consensus of what we think we know about something? Which may be that we don't know, but it still might be tremendously helpful for the general public to have a way to go to someplace, whether it's just a website or a regulation, and find out that we actually don't know diddly about X despite all these exciting headlines, or the general consensus is that this does have some predictive value despite the fact that there's nothing you can do about it.

DR. McCABE: And the problem is, too, that it may have predictive value when you're looking at a patient with symptoms. It may have a very predictive value if you're using it for population-based screening. So I think we also have to educate ourselves and the public and develop educational tools to allow people to understand those differences.

DR. DRACOPOLI: Just to get at your question, I think it's very clear that clinical trials are designed and focused on getting a yes/no answer about efficacy within certain parameters relating to safety. They are not designed, empowered, to do genomic analysis. So the sample sizes you often have are usually too small to get the level of sensitivity and specificity we would like with these assays. So I think what you will see happening is these being applied retrospectively in postmarketing, in Phase IV, that you will see things emerging onto the market without tests, some of them with maybe hints of tests.

Gleevec is a relatively unique example in the sense that there are not that many oncology mutations that are present in 90 percent of all that type of tumor. So what you will see, in essence, is basically I think a much greater amount of work in Phase IV, in postmarketing analysis, collection of samples, to get the sorts of numbers you need in order to drive tests with a level of sensitivity and specificity that people will

believe. But ultimately I think every test is going to have to meet very, very strict criteria, although who sets that criteria, I don't know, sensitivity and specificity.

DR. LANDER: I'm pleased to hear you say it, because we all struggle with these things. I'm curious about what the thinking in pharma is today about if one does these sorts of things in Phase IV, papers will come out in some interesting journal or something. But what's the thinking in pharma as to whether or not you kind of let those things randomly drive the clinical usages of the drug or whether you really try to go for a label around those sorts of tests? I realize these are complicated issues.

DR. DRACOPOLI: Let me give you an aspirational and pragmatic answer. The aspirational answer is we're trying to make better drugs.

DR. LANDER: Indeed.

DR. DRACOPOLI: Certainly in oncology, and you could argue in many other therapeutic areas, whether it's infectious disease and you're looking at pathogen identification or oncology. Understanding the disease, subdividing the patients to drive efficacy is going to be really key, and that's the way forward. The industry cannot continue to bring drugs forward into the marketplace that only work 10 or 15 percent of the time.

The pragmatic answer is that if the industry doesn't do it, it will be done to it. There is already in the market opportunities for third parties to be running pharmacogenomic tests independent of the drug maker. The drug companies spend a huge amount of money basically doing life-cycle management to try to drive their products as effectively as they can. But if they're not doing pharmacogenomics, they're essentially handing over information into the public domain that will basically drive the use of their compounds broadly across the market.

So I think that the pragmatic answer is that the companies have to do it. I mean, there is no choice, and it is also good clinical medical practice to do this. I'm not sure about the right way to phrase it, but there is always the perception that I get asked, why do you as a scientist and a drug company want to segment your market? Is that not in your interest to do so? But I think when you look at it scientifically, it's very much in the company's interest to do so, with the goal of bringing better, more effective drugs to the market.

DR. LANDER: I'm not surprised to hear you say it, but it's great to hear you say it. That's good.

DR. McCABE: I have two other people, Reed and Emily, and then I think we're going to take our lunch break, and we can pursue some of the discussions at the roundtable.
DR. TUCKSON: I really appreciate the line of questioning that Eric has just engaged in, and I think it certainly makes me anxious to hear from, at some point soon, our FDA and other colleagues about where is the current state of rules, regulation, rationality in what looks like chaos. It looks to me that given the incentives of the marketplace, Eric, I fear that without some rational controls here, we are going to see a whole bunch of people marketing diagnostic tests and therapeutic interventions directly to the public without the kinds of controls and guidance that are necessary.

On the other hand, let me hasten to say I would be obviously sensitive to not stifling innovation in the scientific community, bringing better drugs to all of us. Since that work has been done, let me ask you this, and this is probably to you, Nick, more. I am worried about what the costs are going to be. It is hard to ignore the juxtaposition of our conversation with the conversations in Congress at this very moment

around trying to figure out how the heck we're going to get some basic drugs to seniors, lots of people dying who can't afford diddly squat.

If you have a smaller market and, as you've said, better drugs targeted to the right people, it would seem worrisome that the base around which you're going to spread your development costs are smaller. We have to be worried, and maybe we can be less worried because all these 4 million SNPs in the public domain means that your research effort is being aided by Collins, et al., and therefore, since the public and the government have funded your research, you'll decrease the costs on the back end. Can we hope for that?

DR. DRACOPOLI: Yes. Let me try and answer that. Clearly, the Genome Project has changed the way drug companies do their research and apply that work to drug development. I would argue that was one of the intended fruits of the Genome Project, to do that. The pragmatic approach is -- the biggest problem for the industry right now is the paucity of compounds we're bringing forward into the marketplace. The attrition rates in preclinical, early clinical development are getting worse, and I believe -- and this is the scientist in me, maybe not the economist -- that the use of pharmacogenomics can really help that.

We have modeled across an oncology portfolio, and the conclusion we generally came to was that reducing the attrition rate, where roughly 10 percent of the compounds we take into Phase I will eventually make it to market, which really drives costs -- that's what drives the $800 million cost you see from the Tufts study per compound. It's not $800 million per compound. It's that compound plus all the nine others that failed that we're developing.

If you can reduce the attrition rate even marginally so we don't have to have 60 compounds in early development to have 30 compounds in early clinical development, to have five or six compounds in full development, to make one launch a year, if you can thin down that whole pipeline, you would totally and utterly change the whole economic picture for development.

So I think in an area like oncology, where you have such low efficacy of your compounds, there really is room for improvement in the sense that you reduce attrition, we get to the point of bringing forward drugs that have maybe 30, 40, or better, hopefully, efficacy rates. It's a lot easier to run the trials. We can run smaller trials. We can do those compounds more quickly. So I think in oncology, I think there is a good answer to your question.

DR. TUCKSON: So we get lower-cost drugs.

DR. DRACOPOLI: I would hope so. I would hope you would get more of them. I don't know. I'm not sure that I'm the right person to be asking about cost. But what I would hope from a research perspective is that we could bring more forward from the $2 billion that BMS invests every year in drug development, that we could maybe get more launches out of that, and that should ultimately impact cost.

DR. McCABE: Chris, very brief follow-up.
DR. HOOK: That is a major concern, though, because if you look at Gleevec, which went from research to marketing in a relatively rapid fashion, it still costs the basic patient $2,300 a month. That's the base price that they can get for the standard dose, and that makes it inaccessible to a number of patients, unfortunately.

DR. DRACOPOLI: Absolutely, yes.

DR. WINN-DEEN: I wanted to ask a follow-on question for both the speakers in the morning, and that is that it's clear that in the new drug development process, the whole genomics concepts are starting to get incorporated. But what do we do about all the drugs that are already out there on the market which didn't have this sort of parallel track marker development along with the drug development? I think the example that Wylie gave for Factor II, Factor V, and warfarin is a really good example. Here we know the underlying genetics, we know that 2C9 genotype affects how you should dose warfarin, and even so we're really not making use of that information in standard clinical practice.

So what do you guys see as the barriers to really getting things that are even reasonably well clinically validated out into standard-of-care clinical practice?

DR. BURKE: I'll just address this and reflect back to the point that Eric raised earlier. Clearly, to use 2C9 data in clinical practice, we need some outcome data. So we need some clinical trials, and that gets back to the point of what do we need to do. I think we need to develop some methods to bring the right people together to think wisely about where clinical trials are now merited and worth doing, which I would argue they are with 2C9. We really need to know what's the gain from 2C9. Do we in fact, as predicted, see less bleeding complications when we profile people with 2C9? And what happens to the people who are found to have the low-risk genotype? Can we save some money by backing off on the surveillance of those patients, or should we not? Those are the kinds of outcome data we need.

DR. WINN-DEEN: So whose role is it to do those studies?

DR. BURKE: I think that's the interesting question. The interesting question is who is going to fund those studies. You can't fund a clinical trial on everything. And it speaks to, I think, the larger question, which is what are the criteria? It's not really what are the clinical practice guidelines for a particular genetic test, but rather what are the criteria by which we should determine when a test is ready to use? For that particular test, it seems to me, and that's the opinion I'd throw out to a group discussion, that we need some clinical outcome data, and I think it's that discussion of what kind of data do we need, followed by how can we most cost effectively get that data, obviously, as well as who will fund it.

DR. McCABE: Nick, do you have a comment?

DR. DRACOPOLI: Yes. I would say you could look at two things. There are a couple of examples you could look at. In the public sector, I think what's being done with TPMT through Dick Weinshilboum and the group at St. Jude's is an example, and I think there are others involved as well. We're taking an existing generic but important therapeutic for ALL, which basically has a severe impact on roughly 1 in 300 kids who are homozygous for a mutation of TPMT. That genetic testing is now standardly used at medical centers using that therapy, and that was a public effort which was driven by real medical need for an important drug that had high efficacy.

The other examples you can look at are several examples where you can look at small genomic biotech companies who are now running clinical studies of marketed therapeutics. Those therapeutics that are in that list right now are largely currently patented, relatively high-priced therapeutics. But clearly, their goal is that they see a market opportunity for developing tests that are independent of the manufacturer. The issue is, as we mentioned earlier, how good those tests are. But I think there clearly is for many compounds where there is an opportunity for diagnostic companies to actually run those clinical studies that were never run before.
For new compounds, I think you're going to see more and more Phase III, Phase IV. We're pushing towards this. But for the existing compounds, I think it's a combination probably of smaller genomic-driven biotech companies running independent studies and publicly-sponsored research-driven work.

DR. McCABE: Thank you. I'm going to cut off the discussion so we can have some lunch.