Perspectives from Industry
Eric Lai, Ph.D. and Walter Koch, Ph.D.

DR. WINN-DEEN: The next section is designed to give us some perspectives from industry. It's my pleasure to introduce two gentlemen that I have worked with in the past, and I know that they're both experts in their field and will provide us with some really good insight into the way the folks in industry look at this issue and what they're trying to do about it.

The first talk will be from Eric Lai. Dr. Lai joins us from GlaxoSmithKline. He's the vice president for research and has been involved heavily in the genetics and genomics efforts within GSK to integrate it both into the discovery process as well as looking at how to integrate it into the clinical trial process.

Dr. Lai?

DR. LAI: Thank you. Good morning, everyone.

First of all, I would like to thank the committee for inviting me. Second, a disclaimer. I certainly do not speak for the industry, nor do I speak for GSK in general. These are the slides that myself and a few of my scientific colleagues put together. Third, after Richard's excellent talk this morning, the two talks, I think I can go home now.

In the next 10 or 15 minutes, what I'm going to do is instead of sticking to my talk to cover some of these areas, what I'd like to do is try to focus on some of the topics that either were not covered in this morning's talk or answer some of the questions that have been brought up.

First of all, just a quick introduction of the genetic research in GSK. In 1997, GSK formally established genetic research as a separate functional line in R&D. What that means is that out of all the major pharmaceutical companies, we're the only one that has a separate division, a genetic division within R&D, and Allen Roses is the head of that. Now, that has a major impact on the research because we have about 600 people worldwide that are dedicated to genetic research.

The important thing that was mentioned a few times, and also this morning in Dr. Davis' talk, is that in order to do pharmacogenetics, you have to have the phenotype and the DNA samples. At GSK, we collect individuals in all of our clinical trials, Phase I, II, III, postmarketing surveillance. A number of other pharmaceutical companies have started to do this, but not all of them. But this is important. Without the DNA, you're not going to be able to do the pharmacogenetic studies. Right now, there are about 20-plus pharmacogenetic projects at GSK in different stages, from Phase I all the way to postmarketing surveillance.

Now, before we talk about pharmacogenetics, it is important to understand the current drug development process and how it affects pharmacogenetics, and why is pharmacogenetics important. Currently, in order to get a drug approved, you do Phase I study to make sure the drug is safe, Phase II to demonstrate that it's effective in certain populations, and in Phase III, with a much bigger collection of patients, to demonstrate that indeed you can replicate this in a large population, meaning in the neighborhood of a thousand or a few thousand.

That's how you approve a drug. Now, most drugs are effective only in a majority of patients, not everybody. This is not something that's new. It's been in the public domain and published way back in 2001. These are just different groups of drugs in different diseases with respect to their percentage of patients where they'd be effective. More importantly, all drugs have side

effects. There are no drugs that I can think of where if you take the wrong dose or in certain individuals that do not have side effects, and some drugs indeed produce a major adverse reaction in very small subsets of individuals. This is reality. So what has changed?

Here I'm trying to demonstrate what types of pharmacogenetics I'm talking about. Now, this is very important, because everybody talks about pharmacogenetics, but what exactly are we talking about? Here I show a number of hypothetical responses versus drugs with major adverse reactions. On the Y axis, this is the percentage of patients who will respond to certain molecules of certain drugs, and on the X axis is the percentage of patients with major adverse reactions.

Now, the first group would be up here. This would be everybody's dream drug in that it would be effective in everybody, no side effects whatsoever. Unfortunately, as far as I know, nothing like this really exists in reality. Then the second group is down here. These are the drugs that fail in that either they have no efficacy whatsoever or they have some efficacy but their major adverse reaction is so high that you would not carry on into the Phase IIb or Phase III. As a matter of fact, most of the molecules that we put forward, 90 to 95 percent, belongs in this group.

This is the group where PGx, pharmacogenetic studies, are not really necessary, because they are effective in the majority of patients and there is a very low percentage of patients with major adverse reactions. A lot of the over-the-counter drugs fit into this group. So most people do quite well on Tylenol. Some people using Tylenol does not work too well. They have to use ibuprofen, for example. For myself, Tylenol works very great, an excellent drug. But if I take two ibuprofen, I'll be on the floor now, and I've done it. So certain people react very nicely to other drugs, versus others.

Now pharmacogenetics is not necessary for that group of drugs because basically you can take it, it's cheap, a couple of cents, and if it doesn't work, it's okay, you recover, a few hours of stomach upset, not a major deal.

This is the group where efficacy pharmacogenetics is important. In this group, where you have a subset of patients that are very effective, and the side effects are in the percentage that it's okay for the general population, but it will be very important for that subgroup of patients. A lot of cancer drugs fit into this group. So, for example, Herceptin.

Lastly, this group are drugs that are effective in a majority of the population, but they also have pretty high percentage of adverse reactions. This is the adverse reaction pharmacogenetic studies. So basically when you talk about pharmacogenetic work, there are basically only two groups of studies, the efficacy or the adverse reactions. These two groups are the pharmacogenetic studies that we are talking about.

Now, what we are dealing with basically is looking into the risk versus the benefit ratio. What we are saying is that this group, the risk/benefit ratio, the benefit is so high and the risk is so low that it is okay, and we're trying to use pharmacogenetic studies to increase the benefit/risk ratio so that it will go up this way or go down this way, to get into this ideal situation. That's what we're talking about.

To address one of the questions that Richard brought up in the last talk about market subsetting and how pharmacogenetics is going to kill the idea of blockbusters, I think that is a myth in that when people talk about major drugs and blockbusters, they don't talk about 100 percent of the market share. No drug really, very few drugs, have 100 percent of the market share. You don't

need to have 100 percent of the market share in order to be a blockbuster, which is by definition a billion dollars.

For example, Herceptin is, by definition, a blockbuster, because it is I think in sales over a billion dollars, yet it's only effective in 25 to 30 percent of patients. So it is a myth that you need to have all of the market share in order to achieve that. A pharmacogenetic project just increases the benefit/risk ratio.

Now, just a quick slide on how do we exactly do pharmacogenetic studies. You have to start off with a whole bunch of markers. It would be genetic markers, it could be gene expression markers. You have to collect well characterized patient samples from the patients and the controls for all of your clinical trials so that you can have tissue and DNA, and usually, depending on which phase you're in, you're talking about a few hundred to a few thousand, and you determine the differences. You do the experiment -- it may be a genetic experiment, a genomic experiment -- to compare the genetic profile of the patients and control, and analyze the data, compare the differences, and then you come up with your answer.

In response to one of the questions earlier, I think that scientifically we are there. I do not believe that we need to get down to the thousand dollar genome and sequence everybody in order to achieve this. Scientifically, we're there. The problem is that there are a lot of other factors that affect the application of pharmacogenetics to medicine.

So these are some of the potential benefits that we can think of PG to health care. It will increase the impact and change this benefit/risk ratio, and then we can target a group of individuals most likely to benefit from the drug and not experience adverse reactions. So, for example, Herceptin. As a pharmaceutical company, we think that it will lead to a more evidence-based drug development approach, because for the ones that will not respond to a certain drug, it will give us a means to go into the pathway to ask why did they not respond and fill the gap between the current drug development practice to increase the safety and efficacy of medicine.

Now, I'm just going to go through three very quick examples. In looking at the agenda before we started, I picked examples that I thought would be covered by the time I gave my talk. Indeed, two of them are already covered extensively. The first example is HER2 testing. HER2 is an oncogene that is over-expressed in about 25 to 30 percent of breast cancer patients. Herceptin is the monoclonal antibody that binds specifically to this target. So you want to test first to make sure that your patients over-express HER2, and then you treat it. So it's a standard approach of using Herceptin.

Example number 2, TPMT, to test or not to test. This was already covered, so I'm not going to go through this, but I have the same question that was asked just a little while ago in the last Q&A session. I was not in this public meeting, but scientifically, as a scientist, if you look at this information, it is so compelling. You asked why are we not testing this? What hope do we have in coming up with 20 SNPs, haplotype profiles, in order to get it to test? Because scientifically, it's a great example.

So these are some of the things that we can think of, low cost or availability in the commercial world. I think that's already now commercially available. I don't know the cost of this. This could be one of the factors. Change in practice could be a factor, because no longer are you asking the doctors to tell the patients to take two of these and call me in the morning. You can't do this anymore because you have to do the test first in order to prescribe.

Lack of physician awareness. Well, if you just put it into the drug label, I don't know how many of you have actually read the drug label for TPMT. It is enormous. How many doctors are going to actually read that label and say, oops, in line 39 it changes. Now it tells you that we're recommending testing first. I mean, come on, that's silly. This is one of the questions that we addressed this morning. Is it really a lack of knowledge in the physician?

The last example is the P450 testing. That has been around for about 50 years now as far as the biochemistry is concerned. The molecular basis has been known since the 1980s. A few examples have been talked about this morning. So why have they not really been taken into pharmacogenetics and clinical practice? Well, it could be that it's a complicated gene family and the assays are difficult, and there's a limited awareness in the doctors. But I think that most importantly, it is how to get it. You have to have a place for people to order these tests, and more importantly, what do you use as a prescription decision? Meaning that in order for P450 to have a good clinical application, you have to have interpretations.

I just took this out of the Quest Diagnostics report on 2D6 and 2D19, and this is the one from LabCorp. Now they basically tell you if you test for 2D6 in this case, what are the drugs that are effective and how you should deal with it. So you have to have this kind of comprehensive information for the doctors. Without this, it's going to be very hard for it to be applied.

Another disclaimer. My wife actually works at LabCorp, just to make sure everybody understands the potential conflict of interest.

So lastly, what I want to talk about is that in order for PGx to be useful, you really have to look at the scientific part, and that is what the physicians perceive as the benefit; and then for the rest of the general public to be ready to adopt it. You go through basically from a scientific discovery to a validation to a demonstrated utility into routine clinical tests. Of the three examples that I've talked about, Herceptin would be up here in that it's perceived to be a very high benefit by the physician, everybody is ready to adopt it, it's being used, and you test first and treat later. P450 I would think would be somewhere around the middle. TPMT I think scientifically is very high, yet there's a barrier.

Now, as far as barriers are concerned, it does not take a whole lot of people in order to kill this. All you need is a very small percentage of individuals to come up with other factors that can inhibit the application of novel applications.

So in summary, over the next 10 years we think that there will be an increased application of genetic information into the prescription of some of the medications, not all of them. Integration of PGx into medicine will help to identify people that respond better than others and to eliminate or decrease adverse reactions. Definitely, that's one consideration for the policymakers to increase the health care.

These are the areas that we can think of for the committee to focus on. The first thing is we have to change the perception of prescription. No medication is totally safe, and that is a major problem in the general public in that if you tell people that everybody in the United States, that 100 people die in the United States because of auto accidents, nobody will raise their hand and say, well, we should ban all automobiles, that they're just too dangerous. Yet we have drugs that have been taken out of the market with as few as three or four individuals with adverse reactions. So this is an education. We have to educate people that nothing is totally safe.

PGx will increase and improve the benefit/risk ratio, but it's not going to totally eliminate it. We cannot promise that this is going to be individual medicine for every patient. We can only say that this is going to increase for a targeted population. The next person that you test will have a very different genetic background, and that person might have a side effect.

Fear of genetic testing is an important thing in that PGx does not change the patient, does not change the response or the disease. You're just trying to predict or giving a better chance for the prediction. So we need people to understand this and need protection insurance per the discussion yesterday.

Finally, we need the support of the research and health care environment in order to make this happen. So on the last slide, I listed a number of stakeholders in this in order to make this happen. In summary, this is a big dance. Everybody has to be a part of it and play their role in order to make it happen. Pharma can develop the molecules, can do the scientific discovery, but in order to make it into practice, a lot of the other bodies have to become involved.

Thank you.

(Applause.)

DR. WINN-DEEN: We'll take some questions after both speakers have given their perspectives here.

The other speaker in this session is Dr. Walter Koch, who is the head of research for Roche Molecular Diagnostics. Walter has a long history in the area of pharmacogenetics and was the project leader for the Roche AmpliChip, so I'm hoping that he can give his perspective.

I also want to point out while he's getting his slides up that the committee has received some additional information. Eric was kind enough to bring some of the GSK literature that they've put together to help with education of the community on human genetics, and Walter has brought a paper, a nice review on technology platforms for pharmacogenomic diagnostic assays, which you now have for reading on the plane on the way home. So we thank them for providing those additional materials.

I'll let Walter begin.

DR. KOCH: I appreciate very much the opportunity to bring my perspective as someone who is from the diagnostics industry to this committee. You'll see from my slides that I resisted the inclination to gratuitously promote the AmpliChip, and there's not a single picture in there, nor did I pay anyone to put them in other slide sets. But now that it's been introduced, I will use the test to provide you some examples of what some of the challenges were and how this will affect us going forward with various types of tests.

I wanted to broadly cover areas that really had more policy implications in where we are today, where we're going in the future, and what those challenges are. So the first of those would be developing pharmacogenetic tests of the sort that we've been discussing earlier this morning, for drugs that are already on the market. The new world is, of course, as we've also heard, the opportunity to develop drugs and diagnostics together, and there are various concepts around that that we can talk about. I personally believe there's a need for some very large-scale clinical studies of the sort that are challenging for an industry to take on by itself, and I'll address that.

Health care provider education has already been addressed, and then reimbursement I believe you covered yesterday pretty extensively, but I'll bring it up once more.

So thankfully, Dick made my job easy in presenting all these really well known examples, the warfarin, the azathioprine, the fact that we have many genetic determinants that influence drug response outcomes. I would like to say that genotype/phenotype correlations, although very strongly correlated when you have a complete lack of enzyme, are generally not perfect. They are, as Dick said, one component of an entire picture. So the idea that we'll be able to prescribe a very specific dose based on a genotype is maybe asking a bit too much.

I will say, however, if you look into package inserts for a large number of drugs that are on the market today, where there is a drug-drug interaction that leads to phenotypically exactly the same consequence as lacking the enzyme because of your genetics, there is already guidance for physicians as to what to do, to adjust the dose to the low end of a therapeutic range. So presumably, a physician could use this same sort of information which they cannot determine in any other way than with a genetic test, and then adjust the doses accordingly. I think physicians are very well used to adjusting doses and titrating them in their patients.

Nevertheless, clearly having some guidance would be helpful, and there are papers in the literature now that are starting to provide that based on clinical pharmacology and pharmacokinetics.

Now, the particular situation that we have with something like a P450 test is that these drugs are on the market and the companies, the sponsors for those drugs, typically are not sponsoring studies to show what the impact would be to have a pharmacogenetic test together with that. In that sense, then, the burden of clinical validity and utility falls on the diagnostics developer. For P450, we were fortunate enough that the FDA felt these were valid biomarkers, and clearly they're being used throughout drug development today, and they have been for 10 years. In fact, the reason new drugs are far less impacted by these polymorphic drug metabolizing enzymes is because those drugs are weeded out. If they have this liability, they often don't make it through the pipeline, or there are chemical means of modifying the structure so that it becomes less important.

Clearly, the FDA has expressed a very strong interest in some of these examples. I might just take this opportunity to tell you a little bit about what goes into developing a genetic test, and I'm using pharmacogenomics to cover both genetic and gene expression-based, although I will not talk about gene expression-based tests here at all. We just don't have the time for that. But clearly, this is another opportunity to use patterns of differential gene expression to predict drug response.

For 2D6, without showing all the slides, it's one of the most polymorphic loci that you could hope to work with. During the seven years that we were working on it, the number of alleles known and reported doubled. So it went from something like 30 to now over 60. So it was a bit of a moving target even as we were developing the test. It was challenging because it had all those kinds of variations that Dick showed before, duplications, deletions, just a plethora of different genetic variations, and how to get all of those with one test was not easy, but it was made possible with some very new and novel technology, microarray-based technology, that I think is opening doors for all kinds of multiplex assays that we'd never even contemplated before.

Other challenges. I can't resist to mention that there are intellectual property challenges. There was at least one allelic variant that I cannot report because there was no amount of money that

would allow me to get access, a license for that particular allelic variant. Analytical validation was challenging for allelic variants which were not very common. So although we worked with many investigators around the world to try to find genomic DNA samples that we would use to validate performance, in some cases we simply couldn't find a bona fide sample.

So what we did, and the FDA liked this, was to make those variants by site-directed mutagenesis and actually pool them back into real genomic DNA to prove that you could detect them. But those are the kinds of things that you have to do.

Having said that, even now, as we've gone into larger populations abroad, in China and Japan, we found new variants with the test that we had not had the opportunity to see before. So this starts to be a little bit like drug development in that in your Phase III trials you've got 5,000 or however many subjects, but when you go into 20,000 you start to see things you hadn't seen before. If it's really, really rare, perhaps it's not so important. But we found some that were not as rare as one might have thought and will lead to a second-generation test. As more and more variants are discovered, there will no doubt be updates.

One other thing, then, to address was points that have been made about clinical utility. We are actually sponsoring over a dozen clinical studies in various therapeutic areas, the largest of which is 4,000 psychiatric patients over about a two-year period, to try to bolster the clinical utility that many have seen in case studies and smaller studies that only have 100 or 200 subjects. But it's a pretty large endeavor to take on for a company like ours, and so the need for ultimately prospective clinical trials, where this information is used to make a differential drug or dose decision and show an outcome difference, those are ones where one could imagine that a public/private/academic partnership might be a good way to do those rather large studies.

Now, going forward, we're increasingly considering biomarkers during drug development and in some cases finding that these markers can stratify patients and predict who is likely to respond. For example, the Herceptin case. So the FDA, we're very pleased to say, has put a considerable amount of effort into providing guidance both in terms of workshops and public meetings, as well as guidance documents for the analytical properties of multiplex tests, for how data of this sort would be submitted by the pharmaceutical industry, and how drugs and diagnostics might be developed together. The most recent one is a draft coming out in April.

There are still a lot of details to be worked out around those, and when Felix shows a slide later on this afternoon, I think it's number 14, think back to what I'm going to say now in terms of the challenges of timing, those two endeavors, so that they are in synchrony with one another.

There are certainly some basic process questions about review processes going on within two different organizations. But most importantly, the guidance documents suggest that you would be able to make an analytically validated test basically in the preclinical phase. So when you go for the first time into man, you've got a test ready to go. With the exception of something well studied, like a P450 test, one frequently doesn't know what the marker is that predicts response, either efficacy or adverse reactions, until later stage Phase II studies.

Therefore, in order to demonstrate the clinical utility in the pivotal Phase III trial, you are unlikely to ever have a fully validated IVD test. I can tell you one reason why right off the bat. A one-year stability study takes one year, and I doubt very many pharmaceutical companies want to wait a year for that to be done, let alone all the other development work, which is a minimum of 18 months for a simple test. So the sort of questions we ask ourselves are if you have a well validated, from an analytical point of view, prototype test, and you use that during the Phase III

clinical trial to demonstrate the clinical utility and you retain samples, can you then cross-validate the IVD so that the two can actually merge and launch at the same time?

Absent that sort of an approach, it will be very difficult to have these two processes in parallel without delaying one or the other rather substantially, not to mention the risk on the diagnostic side that in Phase III a lot of these drugs don't make it, and you will have developed a test that never gets used. The notion that you might have to do two independent Phase III trials I think will make it very, very expensive to ever introduce pharmacogenomics into routine practice and would certainly hamper it.

I didn't mention so much, but I should, that humans are genetically rich, and our DNA reflects our ancestry, and it's a beautiful thing to see, but it's also challenging from a diagnostics perspective because people from different geographical origins have different variation in their DNA, and you need to be broad and encompassing in that genetic variation so that when a test is used in a country as diverse as ours, everyone is helped by this information. In fact, we put a great deal of that into that AmpliChip to make sure that it covered all peoples.

It's important, as well, we're starting to see, even in gene expression differences in somatically acquired mutations in cancer such as EGFR, where it looks like Asians may have differential responses. So it's not only in the genes that you inherit from your parents but potentially even how your cancers develop.

The CDC has provided these statements about the need for large clinical and epidemiological studies, and given what I've told you, that as you go into larger and larger populations you find variation that you wouldn't have early on, such studies would be, I think, enormously helpful and provide additional background information for both the pharmaceutical and diagnostics industry.

The NIH, we've heard about the Pharmacogenetics Research Network, and there is some translational clinical research there. I would hope that we would do more of that and that maybe a pivotal case such as the warfarin and CYP2C9 might be used as an example to show what the real validity and utility of these tests are. Warfarin is one of the most litigated drugs in America, and there's still, I understand, as many as 1 in 250 who die from the drug itself. So clearly, this is a situation where having such a test to help guide the therapy could be enormously useful. It's a drug that had 20 million prescriptions in 2003. So it's not something that's going away despite how old it is. It's still a much used drug.

We've talked about education needs, and maybe I shouldn't beat that horse to death. I'm reminded that package inserts have a lot of information for physicians in it if they are able to take the time to read it. Some of my physician friends have said, well, in fact, they don't get to read all that information. So what vehicle we use to make this information more user friendly and clinically actionable for physicians is a challenge that we all need to face.

The one thing I will say is that in areas where it makes a big difference, the physicians get it. I was at the ASCO meeting for clinical oncologists this year, and the overwhelming message at that meeting was molecular diagnostics are driving molecular targeted therapies. In areas of disease where life-threatening disease exists and therapy choices are crucial, this information is used and taken up very quickly. HIV drug resistance is an example for pharmacogenetics of a viral agent. But in oncology, this sort of information is increasingly driving therapeutic decisions and increasing the efficacy of treatment for patients with a dire disease.

So I think when there is a need and when there is a utility, the education comes more rapidly. Nevertheless, we still have challenges ahead of us.

So finally, I think I would just like to mention that we also believe that the current reimbursement system really isn't ideal for reimbursing these kinds of tests. When you're trying to find perhaps 10 percent outliers who have a genetic variation and therefore need to be treated differentially, whereas 9 in 10 are fine with the standard dose, the models for reimbursement really aren't there for that kind of preventive action, if you will. Initially, my guess is it will be used more when something untoward happens to understand why it did, but we are not yet at a point where we can readily incorporate this prospectively, although it would make great sense because the genetic test done once, in the case of something like CYP2D6 and 2C19, influences 15 percent of the drugs on the market. If it were in your medical record, you could benefit for life with other agents.

So then finally, I would also like to make a plea, as Dick did, for the partnership opportunities that exist in this area between academia, government, and the private sector, to try to bring pharmacogenomics to the clinic and provide patients with better health care sooner.

Thank you.

(Applause.)