U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SECRETARY'S ADVISORY COMMITTEE
ON GENETICS, HEALTH, AND SOCIETY

Seventh Meeting

Thursday,
June 16, 2005

Grand Ballroom Salon D
Marriott Bethesda North Hotel and
Montgomery County Conference Center
5701 Marinelli Road
North Bethesda, Maryland

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C O N T E N T S

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P R O C E E D I N G S (8:32 a.m.)

DR. WILLARD: Good morning, everyone. We need to start on time just in case Reed is at home watching us on the Web. Good morning, Reed, and good morning everyone. Welcome back.

The first order of important business, of course, since we like to look after everyone's stomach, is to remind the members and the ex officios that if you would like to order lunch, you should do so at the table out there next to the registration desk no later than 9 o'clock, and then, as yesterday, your lunches will be delivered here.

Let me also acknowledge and welcome Jody Brown, who is here from the Health Sciences Policy Division of Health Canada. We're delighted to have you with us. Hope you learn something, and I hope we, in turn, will have a chance to learn from your activities north of the border as well. So welcome.

Let me point out to the committee, you have in front of you the clean copy of the final recommendations that we voted and approved unanimously yesterday on coverage and reimbursement of genetic tests and services. This is simply for your information so you have a clean copy to take home and look over.

We have another full day ahead of us. Today

we'll be hearing a number of perspectives on the current state of the field of pharmacogenomics and the important policy issues that we identified as a committee when we went through our prioritization process a couple of years ago. The entire day will be devoted to policy issues.

We have a number of outside speakers that have been put together by Emily Winn-Deen and her Task Force on Pharmacogenomics and, of course, our indomitable staff. Bio sketches for today's speakers are found in your table folders, and at this point I'm going to turn it over to Emily Winn-Deen, who will lead the discussion today and will begin by giving us an overview of the task force's work in this area and the goals that they've identified for us today.

Emily?

DR. WINN-DEEN: Thanks, Hunt.

We're going to start today with an overview of the work that led to having this session on pharmacogenomics. Pharmacogenomics was identified as one of the four issues warranting in-depth study during our priority session last year, and since then it's been increasingly apparent that this field has the potential to have a large impact on health and health care and needs to be considered carefully.

Pharmacogenomic testing may offer more

individualized approach to medicine through the identification of genetic variants or biomarkers that help to target the appropriate pharmaceutical interventions to individuals based on their molecular nature, their disease, and their individual genetic variation. The field of pharmacogenomics will allow further integration and transfer of the human genome data from the Human Genome Project into the practice of medicine.

There's been a lot of data on the number of deaths that occur. The latest figure is about 100,000 deaths per year that occur due to adverse drug reaction, and there is the hope that pharmacogenomics will also play a role in reducing the number of deaths.

During our priority-setting discussions within the task force, we focused on physicians' need for relevant and practical advice on the application of pharmacogenomic data in the clinical setting. I'd like to acknowledge the task force and all the members who contributed, both the folks within the SACGHS committee as well as our ex officios: Kevin Fitzgerald, Chris Hook, Julio Licinio, Deb Leonard, Ed McCabe, and Hunt Willard, and ex officios Susan Feetham, Steve Gutman, Alan Guttmacher, and Joe Hackett.

When the task force first began to develop a framework to guide the work of the committee, we identified four areas to begin a review of the field. We wanted to

try to put everybody on the committee on sort of a level playing field and get everyone oriented, and that's I think the goal of today's session. The four areas that we decided we would focus on is state of the field of pharmacogenomics today, where are we with translational efforts in pharmacogenomics, what are the ethical, legal and social issues that this branch of genetics might raise, and what is the role of government agencies, keeping in mind our charter as an advisor to HHS.

The key translational issues that were identified included regulatory issues, funding of pharmacogenomic research and translational research, the potential to create new orphan drugs or diseases through patient differentiation via genetics. We wanted to include the perspective from different sectors of both the community as well as the industries that are affected by this, and to try and find some cooperative approaches in the spirit of public/private partnerships that might help move this field forward.

In addition, pharmacogenomics may pose some unique ELSI issues, and we wanted to make sure that we did not overlook some of these, and we're most concerned about not having any exacerbation of health care disparities or access issues.

Finally, we wanted to make sure that we did a

good overview of what's going on already within HHS, and hopefully today's discussion will give us an idea of where we are today, as well as where we'd like to be in terms of any gaps that we identify.

Prior to this session, we sent out a request to the various HHS agencies and asked them two questions. The first was what does your agency see as the most important policy issues, concerns or voids in the field of pharmacogenomics; and then from your particular agency's standpoint, what are the specific questions that our committee could address for each policy issue?

The issues identified by the agencies included the following: applying pharmacogenomics knowledge in the drug development process; assessing clinical validity, analytical validity and clinical utility; and integration of pharmacogenomics into clinical and public health practice. The full summary of the input from the agencies can be found at Tab 6 of your briefing book.

The first category was suggested by NIH, and though this will remain largely a private sector endeavor, primarily within the pharma industry, it's important for us to understand how pharmacogenomic knowledge will be used in drug development. The second category, the problem of how to develop evidence-based reviews, was highlighted by four agencies: CDC, CMS, HRSA, and NIH. Under integration, the

need to educate providers and consumers, as well as privacy and promoting wide access to clinical trials and new tests were noted by CDC, FDA, HRSA, and NIH.

In the public health arena, considerations of ethnic and racial variations and the effects of diverse populations, the potential use of pharmacogenomics for screening purposes, and the need to monitor pharmacogenomics impact were identified as important issues. Again, CDC, NIH and HRSA all contributed to these issues. Access and cost remain important concerns that will need to be considered and addressed. The need to understand the direct and indirect costs and potential for reduction of overall health care costs related to pharmacogenomics is important for us to try and understand in a little more depth. Adequate access was the focus from HRSA, while cost was highlighted by CDC, HRSA and NIH.

The feedback from the agencies largely parallels the agencies missions and will be very helpful. It was suggested that our discussion this afternoon would initially focus on an explicit statement of what we expect pharmacogenomics to do for people's health. We welcome more explicit suggestions from any of the speakers and any of the ex officios as we move forward in our discussion.

Additional issues that were identified through

other outreach efforts included barriers, and these additional outreach issues that we identified were done via our task force discussion, as well as some conference calls with key individuals within the private sector. We consulted with Bill Clarke, who is the chief technology officer and chief medical officer for GE Healthcare, as well as with Mara Aspinall, who is the president of Genzyme Genetics, and her colleagues at Genzyme.

The barriers that were identified by Bill Clarke and really echoed by the folks from Genzyme included that there are really no uniform reporting standards today for pharmacogenomic assays. There needs to be an appropriate approach for evaluation of the value of pharmacogenomic testing. There are issues of robust technology and reasonable cost that need to be addressed, and whether FDA approval will be required in order for reimbursement to take place for pharmacogenomic tests.

On that same strategy, there's really a lack of clear reimbursement paths forward in terms of particularly home-brew assays, and while there is a lot of data available on the correlation of genetic variation with different drugs, there's still not the body of data required to actually give good dosing guidelines for many of these drugs. So we're still one step away from being able to translate it into clinical practice.

The other barrier was really what is the catalytic event that's going to be required to move pharmacogenomics out of academia and into standard clinical practice? What is the driver here? Is it better medicine? Is it legal liability? Really, what are the issues that are going to make this happen? Because I think we have good evidence in several arenas for things where we understand the science, and yet the science hasn't really translated into a new standard of care in the practice of medicine.

We need further clarification from the regulatory agencies on what is actually needed to drive changes in drug labeling and how that's going to be managed.

Genzyme suggested some additional strategies to promote pharmacogenomics. They felt that pharmacogenomics was a paradigm shift and that all key constituencies within the health care system need to understand its role. Part of our programming today was to try and begin to bring together all of these different types of constituencies. We recognize that due to time limitations we were not able to have every single piece of the puzzle presented to us today and that some of these things will probably have to be deferred to our next meeting, but we were trying today at least to make a start in bringing

these issues forward.

The other strategy that Genzyme brought up was the need to encourage innovation with financial incentives. So what are the financial incentives that are needed in order to encourage companies, as well as physicians, to move forward in the practice of this new type of medicine?

Genzyme brought up a couple of other things that they were concerned about. They felt that there was a need to address both the home brew, the laboratory-developed tests, as well as FDA-approved tests. To my knowledge, there's only one FDA-approved test, which is the Roche AmpliChip for 2D6 and 2C19. Most of the work that's being done in this field today is with laboratory-developed tests, and we need to recognize that and find ways to address it.

The government, in their role as both a regulatory and a payer, needs to be looking at how they can put in place policies that would result in better drug efficacy and improved safety.

So the purpose of today's session is to really provide a common understanding of the fundamentals of pharmacogenomics and the state of the field today, to identify policy issues that will be critical to move this forward, and to determine if there's a specific role that

this committee can play in facilitating this translation into the practice of medicine. I want to remind the committee that our goal is to advise HHS. We can't solve all the problems of the field, but I think that there are a number of agencies within HHS that are involved in this field, and we need to assess whether we feel they've got everything well in hand or whether there are some specific recommendations that we'd like to make going forward for things they could do more actively or more cooperatively among the agencies.

So with that in mind, I'd like to give you a little bit of an outline of the session today. We're very pleased to have a panel of speakers who, I have to say, are all experts in their field, and we greatly appreciate their willingness to come and share their knowledge with this committee. We're going to start with the fundamentals. What the heck is pharmacogenetics and pharmacogenomics? We're going to hear from the public health perspective, the practice of medicine perspective from both the diagnostics and the pharma side of industry. In the afternoon we'll hear from the HHS agencies about their issues, and finally we'll have a talk on the ELSI issues.

At the end of this long session, I hope you're all taking notes during the session because we're going to

have a full committee discussion about really what we heard, what we would like to do as a committee moving forward, and the task force is looking for guidance from the committee on where you would like to see us move next so that we can be prepared if we need to do some specific activities in the interim between this meeting and the October meeting.

With that, I would like to introduce our first speaker, who really needs no introduction because he is, if I dare say it, the grandfather of pharmacogenetics. Dick Weinshilboum joins us today from the Mayo Medical School, where he is presently professor of molecular pharmacology and experimental therapeutics. He was intimately involved with the thiopurine methyltransferase research and actively teaches both pharmacology as well as pharmacogenetics within the Mayo institution.

DR. WEINSHILBOUM: First of all, let me thank the committee for the invitation. As someone who has been doing this sort of stuff for decades, to be introduced as -- I am a grandfather, but to be introduced that way is a little disheartening early in the morning.

(Laughter.)

DR. WEINSHILBOUM: So what I thought I might do to be helpful to the committee, and I think really our role here is to be helpful to you, is to do pretty much what I

did with a group of graduate students for this talk yesterday morning at about the same time. So I was asked to begin with some origins and concepts, in essence a quick overview of where we are.

Let me begin with a disclosure. I'm occasionally invited, although for years I wasn't -- all of a sudden I've become very popular since the FDA guidelines came out. So I'm invited to pharmaceutical and biotech companies, but Mayo is in the upper midwest where the Scandinavians settled and were quite a socialistic institution. So all of the honoraria fees do not come to me. They go back to Mayo Foundation to support our missions in research and education.

On a very serious note, there's a flipside to this. I've spent my entire life in an academic environment, and that's why it's so important that we have Eric Lai and Walter Koch here to give you an up-close and personal view from the for-profit industry side, because their view will be quite different than mine.

I should also, in the matter of a disclosure, point out that I currently have the honor to chair the National Institutes of Health Pharmacogenetics Research Network, the PGRN, with this little logo which you'll see down in the corner of my slides, since they paid for the slides, and each of these little starts represents one of

these centers. As of next week, Kathy Giacomini from UCSF will become the next chair of that group. The stars will move around a little bit, so I'll be back in Bethesda next week, where my wife says I should get a condo.

So let's begin, sort of Pharmacogenetics 101. You all know that what we're talking about is the study of the role of inheritance, that is who your mom and dad are, in essence, in variations among individuals and their response to any xenobiotic, including those that I as a practicing internist write a prescription for, the patient takes to the pharmacy, and takes the medication thinking that I know what I'm doing. So basically drugs are just a subset of xenobiotics, and we're talking about genetic variation in the drug response, in the chemical response phenotype.

In many ways this represents a confluence of two revolutions, that is the genomic revolution which everyone who reads Time magazine knows about, but as a matter of fact I feel very strongly as a pharmacologist that in the latter half of the 20th and the beginning of the 21st century there has been a parallel therapeutic revolution in which we have gone -- and I like to demonstrate this for my medical students in this fashion. This is the first edition of Goodman and Gilman's textbook, 1941. I was actually around then, but rumors

among the male medical students to the contrary, I was not reading G&G then. Here is the 10th edition. The books are the same size. There's virtually nothing in this book. That is, there is morphine and there's digitalis, there's aspirin and sulphur drugs. But no antibiotics, no antihypertensives, no antipsychotics, no antidepressants. Franklin Roosevelt was president of the United States and had hypertension, was treated with phenobarbital, which made his doctors feel better but didn't do much for his blood pressure.

So as a matter of fact, there has been a dramatic change in the therapeutic agents which we have available. I think it's been a quiet revolution, but as a matter of fact it's been earth-shaking. We talked about paradigm shifts in your introductory comments. Bring that together with the genomic revolution, and those are the ingredients that have created what we are talking about today and is the reason basically that we're sitting here, because the concepts of pharmacogenetics and pharmacogenomics really date back half a century. Every time I'm called up, as I was by Public Radio the day before yesterday, and they say Francis Collins thought this up, well, Francis is a wonderful man, but he didn't think this up. As a matter of fact, these concepts have been around for half a century, but they have been accelerated

dramatically by the technology that came out of the Genome Project.

So my definition of pharmacogenomics is the convergence of the advances in pharmacogenetics that have occurred over decades with the striking progress that has occurred in human genomics. You bring that volatile mix together and I think that's one of the reasons that we're sitting here.

The clinical goals are obvious, and in the introductory comments we mentioned avoiding adverse drug reactions, and I'll use an old chestnut, namely TPMT, to illustrate that in just a moment. But let's don't forget that we're also maximizing therapeutic efficacy, selecting those patients who might respond best to the drugs. Frankly, one of the impediments, and I'm speaking now from the view of the academic world, to the involvement of pharmacogenomics in the drug development process has been this issue of selecting responsive patients, which limits the markets for the drugs. Now, I'm sure I'll hear something quite different in just a moment, but we need to get the issues out and at least talk about them here.

The scientific goals are also obvious, the correlation of variation and DNA sequence or structure with variation in the drug response phenotype, the so-called genotype/phenotype correlation. Now, I never thought in my

lifetime, and I've been doing this stuff for over three decades, that I'd be standing here talking to you about DNA sequence. As a matter of fact, the postdocs in my lab, I walked in the other day on a Sunday and I said, okay, Ezekiel, how many base pairs did you sequence this weekend? He said 5 million. This is a mom and pop store, folks.

So when you stop and think about that, that's truly an amazing revolution that has occurred. Let's immediately say -- I mentioned that I'm an internist -- that all of us who write those prescriptions understand that genetics are only one factor that plays a role in individual variation in drug response. The patient's age, renal function alters rather significantly with advancing age. We are increasingly sensitive to the fact that males and females respond differently to drugs. Underlying disease and drug interaction all play a role. So this is only one factor, but it's one where objective information may now be brought to the physician, and the challenges which you mentioned in your introductory comments, how do we help the practicing physician to integrate this information into the therapeutic encounter, is going to be an interesting challenge.

Let's don't forget, because my medical students do, they focus on what does the drug do to the patient, but

the patient is doing a lot of things to the drug. That is, the drug must be absorbed, and we know the transporters play a role in this process, get to its site of action, interact with its targets, be metabolized and excreted. All of these processes, we now know, have very significant and clinically relevant genetic variation. Most of this field grew out of the field of drug metabolism, but that's only as a demonstration project because of pharmacokinetics we could gain insights into intact, unhomogenized human beings by looking at pharmacokinetic parameters and therefore look at drug metabolism.

I like to think of this as a scientific evolution analogous to the way in which we have approached the application of genetics to diagnostic medicine. Let's begin with some rather dramatic monogenic traits, and I'll show you some of those examples in just a moment. They were necessary to make the point, because I can't tell you how many years I would go around to departments of pharmacology talking about pharmacogenetics, and as soon as I'd say the words "allele" or "polymorphism," everyone's eyes would glaze over, their palms would get sweaty, and nobody would pay any attention.

Then they would tell me, why don't you get a nice inbred mouse because they won't show this yucky

variation. And I would say I'm studying the variation. So we had to make the point, and TPMT and CYP2D6, if they didn't exist, we would have to invent them, and I'll tell you about them in just a moment. But that will not be probably an example of the major way in which genetic variation will manifest itself. Increasingly, we're talking in terms of both PK and PD pathways, and I'll define those in just a moment, and increasingly adding genome-wide screens at the scientific level to gain insights into the myriad ways in which genomics can play a role in individual variation in drug response.

Pharmacokinetics -- and I'll just in the remainder of my comments talk about PK and PD -- are those factors that influence the final drug concentration at its target, predominantly transporters, drug metabolizing enzymes. Pharmacodynamics are those factors that influence the response of the target itself, not just the target but all the downstream signalling that comes from the target. We now know that although we might be able to make an end run around this, it's going to be awfully hard to make an end run around genetic variation in the pharmacodynamic pathways.

Now let's use a couple of what Eric turned to me and said I assume you're going to talk about the old chestnuts, and I said yes, sure, of course I will. So

let's use these two, and I like to use them because they're both well validated, and because in the draft pharmacogenomic guidance that the FDA put out in 2003, and I guess in March of these year these are no longer draft, they selected these two, thiopurine methyltransferase, TPMT or CYP2D6, as valid biomarkers, meaning they're old fashioned and we all know a great deal about them. So let's use TPMT as a prototypic example.

Here are the thiopurine drugs, 6-mercaptopurine, which was developed in what was then the Burroughs-Wellcome company by George Hitchings and Gertrude Ellen. They shared the Nobel Prize in 1988 in part for the development of these drugs which are a mainstay in the treatment of acute lymphoblastic leukemia of childhood, a disease that was uniformly fatal when I was in medical school, and today we cure 85 percent of these kids with drugs -- no surgery, no radiation therapy. That's what I mean when I say the therapeutic revolution was a quiet revolution. These drugs were also used as immune suppressants, azathioprine, which is just 6-mercaptopurine with amanadazol up here, which is cleaved off in vivo, and they're used in the treatment of inflammatory bowel disease.

Now, even the Mayo medical students who I teach know that these drugs are metabolized by xanthine

oxidase. George Hitchings and Gertrude Ellen knew that they also underwent a so-called phase II conjugation reaction where a methyl group was stuck on that sulphur. The metabolites were present in the urine. Twenty-five years ago, no one knew anything about the variation in the enzyme itself, but these are very powerful cytotoxic agents, and every now and then you would treat one of these children with leukemia and the drug would destroy the child's bone marrow, and the child would die from the drug therapy, not anything that anyone wanted, what we would have referred to in those days as an idiosyncratic reaction, which means we don't understand what the cause is.

This just shows you data which we published 25 years ago now on TPMT in the human red blood cell. In case I forget to say it, what you see here reflects the level of the enzyme activity in every human tissue, for reasons that will become clear when I show you the gene in just a moment. These are 298 randomly selected Northern European blood donors in Minnesota. There's an important reason why I say that, and I'll come back to it in just a moment. That is, everyone in Minnesota, except me, is named Anderson and Johanson and stuff like that.

But there's a scientific reason for bringing that up. Ninety percent of this population had high

activity, about 10 percent had intermediate activity, and this lady down here, whose daughter works at Apache Mall in Rochester, Minnesota, had zero enzyme activity. Rochester is a very strange town, folks. People will stop you when you're walking through the mall and ask you how your mom's enzyme activity is doing.

So using very, very sensitive molecular techniques developed by a monk in a monastery in what is today Brno in the Czech Republic -- this was before anyone had cloned much of anything. So we were using segregation analysis. If mommy is low and daddy is high, what are the kids? You could just as easily determine that this was a genetic trait using that approach. You can say that this woman has two copies of a gene for low activity, these people have two copies of an allele for high activity, and these are heterozygous with intermediate activity, and autosomal co-dominant trait, which is true for every tissue. This just shows you the consequences of having two copies of low. This was long after Lynn Leonard and I had described that if you have low TPMT activity, you are at serious risk for life-threatening myelosuppression.

This is a heart transplant patient in Germany treated with standard doses of azathioprine. Here's the white count. Here's the azathioprine dose. Notice that the white count drops, the drug is stopped; it goes up, the

drug is started. The white count goes down to zero, the drug is stopped. Started again. The patient died here with myelosuppression. They then measured the TPMT in the red blood cell. This patient genetically lacked the enzyme.

These cases, by the way, are not reported any longer. Do they occur? Tragically, yes, because I get many of the telephone calls. I got one just two weeks ago, again exactly the same situation.

So if you have low TPMT activity on a genetic basis, you're at greatly increased risk for thiopurine toxicity, which can be life-threatening. Mary Relling at St. Jude has demonstrated this is also a risk factor for secondary neoplasm. When we cure these kids for their primary neoplasm, Lynn Leonard in Sheffield has shown that high TPMT, you have decreased therapeutic efficacy for a life-threatening disease. At our place we have been doing the TPMT genotype, and then the phenotype study, since 1991. We do about 5,000 to 10,000 of these tests per year, about half on our own patients and about half referred in from physicians outside, and we are individualizing therapy. Clearly, if we see these people, we treat them with one-tenth to one-fifteenth the standard dose, and that's been our situation for about 15 years now.

The cDNA was cloned by Ron Honshal in our lab,

who is now at the FDA. The gene was cloned by Diane Otterness, who is out in California. Here's the gene itself. It is 10 exons, eight of which encode protein. On the short arm are chromosome 6. The blue area here is the part that encodes the protein. The most common variant allele in Caucasians, which we described in 1996, has two non-synonymous coding SNPs that change the encoded amino acid 1 on axon 7 and axon 10. If you have that variant, which is present -- this is not a mutation. This is a common polymorphism, the frequency is one out of every 20 copies of that allele in Northern European Caucasians -- then you are at very greatly increased risk for drug-induced toxicity if you're treated with standard doses of thiopurines.

By the way, that variant allele has never been described in anyone from Korea, Japan or China. That was the reason I made the point, and we're going to come back to this in my later presentation, and one of the reasons I was called by National Public Radio was to ask about BiDil. The hearings are today, so I think we'll be coming back talking about that. This is the variant that's found in East Asia. It just has the axon 10 variant at about a 2 percent frequency.

Because of the dramatic clinical consequences, and because it's relatively well validated, this was one of

the first examples that the Food and Drug Administration considered for possible inclusion of this information. Labelling had two public hearings. I testified at both of them. Felix Frueh is here. I saw him before we began. That was an interesting experience which I'm sure he'll describe in greater detail.

Let's move on to CYP2D6 to give another example. It's the same song, second verse. Interestingly, we published our first paper on TPMT in 1978. It was the assay that we knew we wanted to use for pharmacogenetic studies. It was almost at exactly the same time that the first paper on 2D6 was published. So these are old examples, folks, and that's why Eric asked me, oh no, am I going to have to hear about TPMT and 2D6 again? So this just shows you that cytochrome P4502D6 metabolizes 40 or 50 commonly used drugs, including beta blockers and antidepressants.

Here you're looking at a metabolic ratio for the antihypertensive dubresoquine, which was never introduced on the market in the United States. It undergoes 4-hydroxylation catalyzed by 2D6. Counter-intuitively, the way we have represented this, the way pharmacogeneticists do this is to show the metabolic ratio. These are the poor metabolizers up here. It's about 5 to 10 percent of a Caucasian European

population. Once again, I say that because there are ethnic differences in allele frequencies and types.

This group is the extensive metabolizers, and these low numbers are ultra-rapid metabolizers. That obviously is also -- or not so obviously but also of clinical importance.

This just shows you data from -- the previous slide came from the Karolinska, from Lief Battleson's lab. This is also from Lief Battleson's lab at the Karolinska, where they're looking at the tricyclic antidepressant nortriptyline, and what you're looking at is pharmacokinetics -- that is, plasma levels over time -- depending on the number of active CYP2D6 genes that you have. Most of us have two copies of that active gene. Here is our pharmacokinetic profile. By the way, this slide unites the two topics which are the least favorite of the male medical students. They find drug metabolism boring. They find pharmacokinetics terminally boring. Putting the two together here in one slide is amazing.

So you can see if you have two copies of a variant, you can either have gene deletion or you can have polymorphisms that result in no activity. You have a much higher peak plasma level and a much larger area under the curve. But look down here. This lady, who was herself a

nurse at the Karolinska, had 13 copies of the active gene. Look at her pharmacokinetic parameters. Now, her metabolites were way up there, way off scale. So these are active genes. This just shows you what can happen.

In most cases, CYP2D6 terminates the action of the drug. But for codeine, what it does is activate it by converting codeine to morphine. So if you are a poor metabolizer for 2D6, and that's 5 to 10 percent of the European population, you will not get the analgesic effect from codeine. But if you're an ultra-rapid metabolizer -- and this was a very recent case report in the New England Journal, December 30th, 2004. Sixty-two year old man hospitalized for pneumonia, treated with standard doses of codeine, right out of the PDR, as a cough suppressant. The next stop was the ICU because the patient stopped breathing. He had morphine levels 20 times the expected level. He was an ultra-rapid metabolizer.

I just show you this as a preview of Walter. I have no stock in any company, and certainly not in Walter's, but let me say that all that we're doing here is using this metabolic ratio to give us insight into what's going on at the level of the DNA. In today's world, and we'll be talking about this later, devices like the one which comes from Roche Diagnostics, give us direct insight into the DNA.

I finally want to give us a peak at the future. I feel obliged. I live in Minnesota. We're right next to Wisconsin. This is Karl Paul Link, the man who discovered warfarin, an amazing person. If you haven't read the story of the discoverer of warfarin and the farmer with the bucket of blood in the Wisconsin blizzard, go back and read it. They don't let you write articles like that anymore.

Warfarin can occur as an S and R antimere. The S is metabolized by CYP2C9. This just shows you that warfarin blocks the Vitamin K pathway which is required for the gamma-carboxylation of glutamic acid to make active clotting factors. The epoxide reductase shown in this little cycle here was only cloned just about a year ago. First let's look at the metabolism.

So now we're looking at the PK, the pharmacokinetic pathway, and there are common genetic polymorphisms for cytochrome P4502C9 in European populations. If you're homozygous for the *3 variant, you can see the clearance is much reduced as compared to the clearance of S-warfarin, which is really the most active portion of the warfarin. Here you can see what we see in the individuals who are homozygous for wild type 2C9. But look at that variance. Big variance.

Now we're looking at the Vitamin C cycle, and

it was in Nature, February 5th, 2004 that this target was first cloned. You would think we would have known about it before then, but we did not. I assigned this for our journal club. The people in my lab said wait a minute, we don't do warfarin stuff. Why are you assigning us this? I said because somebody is going to resequence this gene in about 10 minutes, and when they do, this will be used for pharmacogenetic research. Several groups did.

This is from the June 2nd, 2005 New England Journal. National Public Radio asked about this, too. So they're becoming very onto pharmacogenetics. That gene is called Vitamin K oxidoreductase C1, or VKORC1. The gene was resequenced. Ten common SNPs and 5 common haplotypes were identified. None of them were non-synonymous SNPs. They didn't change the encoded amino acid. So now we're moving on to the world of haplotypes, the combination of SNPs on a given allele. They divided their groups into low-dose and high-dose haplotypes.

Notice the mean maintenance doses of warfarin, about 2.7 for those who had two copies of the haplotype for low dose, and 6.2 for two copies of the high dose. This variant was responsible in their studies for about 30 percent of the variation in final warfarin dose, CYP2C9 about 10 percent. You begin to put those together and now you're beginning to talk about something that, if you're

prescribing warfarin, you might want to know about.

So the scientific evolution -- and I'll try to keep us on time -- was monogenic traits. Pathways were increasingly incorporating genome-wide screens and scans. Let's don't forget what the clinical goals are, not only avoiding adverse drug reactions but probably over time, more important, maximizing efficacy and selecting responsive patients. That has pharmacoeconomic implications which I'm sure you'll want to discuss later.

Let's don't forget the scientific goal, because as the science rolls forward, our ability to bring ever more complex, ever more complete information to the bedside is going to accelerate, and the vision, which we will never achieve -- I understand that. I'm a practicing physician. But the vision is very clear, to select the right drug at the right dose for every single patient that we see.

Thank you very much. I hope this is helpful.

(Applause.)

DR. WINN-DEEN: I think we have time for about five minutes worth of questions if the committee has any specific things they'd like to ask Dr. Weinshilboum. We'll have a second shot at him a little later in the session if you don't get all your questions answered.

Julio?

DR. LICINIO: Hi, Dick.

DR. WEINSHILBOUM: Good morning.

DR. LICINIO: Yes, good morning. Wonderful presentation again.

We had a discussion yesterday which I think you could elucidate in your presentation, which is that one of the things that strikes me about the field is that what you presented is very clear and incontrovertible. While we could question if someone has a gene for some disease, it gives a predisposition, they may or may not have the disease. These cases are pretty clear. If you don't have the enzyme, you're not going to metabolize the drug, period. So this is as clear-cut as you can get in terms of genetics.

If on the other side, the testing, which was a big topic of discussion here yesterday, is still controversial, for this it should not be, and yet it's not out there. So we had a discussion yesterday about these people putting these ads in the Internet and saying send your DNA here, we'll test it for you, and we'll do these tests, and there was a big discussion about how to regulate testing. But my view is that as long as there is a need, people are going to do it. If you don't allow it in this country, they're just going to send their sample to Canada or to England or to wherever.

Why, in your view -- I mean, I know it's beginning to catch up, and I actually cited yesterday your own institution as an example, where if you go for regular care you can get some of these things tested and get your treatment pharmacogenetically oriented. But it's not the mainstream of treatment yet, and it's so established, so old, so solid, why, if you just go to the academic medical center X, a good medical center in a good city, why don't they test for CYP2D6 before they give a drug that's metabolized by that enzyme? What's the delay? What's going on?

DR. WEINSHILBOUM: Well, of course, Julio is asking one of the many questions that I've asked over the years because I have been going around overdosing audiences on this sort of information, particularly for the more dramatic examples. For some of the well-established examples, and TPMT and CYP2D6 are used as examples because they are relatively straightforward and dramatic. That's why I said they're demonstration projects which if they did not exist, merely to make the point you'd have to invent them. Well, you didn't have to invent them. They're actually there, and some of us are fortunate to have been lucky enough to stumble across them early on.

Part of the difficulty is at the level of the practicing physician understanding this kind of information

and these concepts. We'll talk about that later and actually, Julio, I'll mention this later when I make my later presentation about practice of medicine. At our place, we have a genomics education program which focuses both on therapeutics and diagnostics, which we have funded by a private foundation about a million dollars a year merely to continually raise the consciousness of the physicians and educate them.

Now, physicians are intelligent and want to do what's best for their patients, but the vocabulary is a bit of a barrier here. We have to make things user friendly and easy for the physicians.

Number two, Julio is right with regard to in this age of information and the Internet that the patients are beginning to drive the process, and we need to be careful about not having inappropriate expectations on the basis of the patients. So patient education, as we'll mention in a moment, is also going to be an interesting challenge.

I get the opportunity to present at something called internal medicine reviews, which for the upper midwest means a lot of internists like myself come in and want to hear what's going on, and even dental reviews. At dental reviews, which are dentists from the upper midwest, they're telling me that their patients are coming in having

done just what Dr. Licinio said, having been tested over the Internet, and they all know their 2D6 genotype because they don't want to get Tylenol number 3 with codeine if they can't respond to it.

I found this fascinating, that dentists are now seeing this. So the patients may be ahead of the profession in some ways. There are a lot of other barriers that we'll have to talk about when we go into the further discussion, but I think this is a very great challenge, and you actually mentioned this in your introductory comments with regard to the barriers to the introduction of this science across what I refer to as the translational boundary.

DR. WINN-DEEN: Thanks.

We've got time for a quick one more, Ed.

DR. McCABE: You mentioned that I think it was TPMT, that there had been consideration for labelling by the FDA. Was that included in labelling, the pharmacogenetics?

DR. WEINSHILBOUM: There were two public hearings, and Felix Frueh is here, and we have representatives of the FDA, and I'm just this guy from Minnesota who was invited in to testify. It is my impression that the labelling has been changed to make information with regard to the existence of the genetic

polymorphism and the availability of testing -- there was no mandate for testing -- to make the physician aware of that information.

DR. WINN-DEEN: Okay, I'm sorry. We're going to try to keep on time, which means we have to move on to the next talk.

The next focus will be on the public health perspective, and speaking with us today is Robert Davis, who joins us from the Department of Epidemiology at the University of Washington, School of Public Health. He's currently on sabbatical in the CDC's Office of Genomics and Disease Prevention, and he's going to give us a little overview of where we are from the public health perspective.

DR. DAVIS: I will, as soon as I can find my talk.

First, thank you very much for inviting me here today. It's an honor to be here. As I was introduced, I'm actually a senior investigator at the Center for Health Studies at Group Health Cooperative Research Center in Seattle, Washington, and I'm also in the Department of Epidemiology. As a conflict of interest disclosure, I'm on sabbatical at the Office of Genomics at the Centers for Disease Control.

I want to start by showing our house, and this

was a celebration that occurred when the AmpliChip was licensed. We're big fans of the genomic revolution, and I came home and found my kids celebrating with my wife when the AmpliChip was licensed. I promptly turned to them and I said, "Simon, where is the evidence that the AmpliChip, when introduced to an institution, say the University of Washington, will actually improve patient outcomes?" And Simon promptly started crying, and Sophie threw the cake at me, and my wife stopped talking to me, and my department chair got mad at me. So I'm the bringer of bad news today, or the bringer of a sobering outlook, and I've already suffered the consequences, so there's nothing you can do to make it any worse.

But I just wanted to introduce that it was a tremendously exciting and uplifting talk when we heard about the cytochrome P450 AmpliChip and about its use and about the fantastic improvements that TPMT understanding has given us. But there's a big step between understanding how it works on the clinical level and understanding how it can be applied at the public health, sort of macro level, and that's what I want to walk you through today.

We have to get from here -- and these are my kids. They share my genes. I am the biggest fan of the genomic revolution there can be. I wanted to talk about how we get from this degree of excitement to an

understanding of how it actually works at the macro level, the public health level.

So let me go back to the start. As we've heard, the goal of public health approach to pharmacogenomics is really the same goal as the goals that we have when we're practicing clinicians, and that's the right drug to the right person at the right time. In 100 years, we'll be amazed that we used to start everybody who had asthma on albuterol because we're already discovering that that's probably not the best thing for quite a few of those people.

Wylie Burke and Ron Zimmer have published a really remarkable paper that talks about the needs to get from -- actually, is there a pointer here? I can sort of point like this.

DR. WEINSHILBOUM: I brought one.

DR. DAVIS: It's a great way to gauge how much coffee I've had.

But Wylie Burke and Ron Zimmer have really published a remarkably good paper that talks about the needs to go from the identification of gene/disease associations to the appropriate use of genetic testing. It really talks about evaluating these tests in terms of their clinical utility; that is, does it actually improve patient outcomes. It talks about studying how the tests are

actually applied in the health care delivery system, and then it talks about the statutory regulations that are needed to make sure that these tests are utilized in the right way.

I think genetic tests, by and large, are extremely similar -- or our approach to pharmacogenomics should be extremely similar to genetic tests. What I'm going to talk about is really trying to get to here and to here. To do that, what we really need is a system which I think is lacking in the United States today that guides us to produce the evidence, that guides us to talk about the best ways of integrating that evidence, and that helps us understand the long-term implications of what we do, particularly so that we move past the situation where people are still receiving telephone calls about the proper or improper use of therapeutics for leukemia. That is, in essence, why are we still, in the year 2005, receiving case reports of people who are not utilizing the evidence in the proper way?

The question is, how can we set up a system so that we are actually able to utilize this evidence in the right way? I consider that, actually, a public health approach.

So what's the real difference here? When drugs are being developed, we typically take them through Phase

I, II and III trials, where we go from small studies to progressively larger studies to look at response to medications and vaccines, safety and efficacy of medications and vaccines, and then we do clinical trials to, in essence, document the outcomes among patients and to expand the use of those medications in terms of larger patient populations and disease sets.

The public health approach is the clinical application of this bench research. It's the effectiveness in the real world, including the generalizability, and that's the modern ring of these real-world applications, to understand the full implications of what happens when we actually take this stuff and we try to apply it.

So here's an example that I think is perhaps not an old chestnut. I've probably got about a year that I could discuss it before it becomes an old chestnut. It's kind of a new chestnut. It has to do with increased evidence about beta-adrenergic agonists. They're the most commonly used medication for asthma treatment. As a practicing pediatrician, I've noticed that it produces adverse effects in some patients. Albuterol works wonderfully in most of my pediatric patients, but in some it's been clear to me as a practicing pediatrician that it doesn't have the same effect.

It turns out that polymorphisms of the beta2

adrenergic receptor plays a role in the responsiveness of patients, and patients homozygous for arginine, the B2AR16, in essence homozygous for arginine, respond differently -- i.e., poorly -- to the regular use of albuterol, and here's one reference. In fact, there are many others documenting this at the patient level. The basic science approach, then, is really addressing the evidence about how albuterol and genes work together to affect lung function.

I thought that maybe before I retired I would begin to see some of this type of information, and I think I saw that two years ago, and here we are already. It just sort of speaks to how rapidly this field is moving ahead.

The public health approach really says does our knowledge of this polymorphism affect measurable clinical outcomes, and does it lead to increased morbidity and mortality among treated asthmatics? Does the polymorphism lead to increased costs of health care and decreased quality of life among treated asthmatics? In other words, would our knowledge of that polymorphism lead to decreased morbidity and mortality, decreased costs of health care, and increased quality of life? So the public health approach really asks, given that albuterol and genes appear to work together to affect lung function, does it matter? Can we measure its effect?

So that's the first step. Then the public

health approach really expands even larger to say when you release this, when you license it and it begins to be used with everybody, and people are now being screened perhaps for this polymorphism before they're being put on albuterol, what happens when you study its effect in terms of the co-use of prednisone or fluticasone? What happens in the elderly, who may actually already suffer from diminished lung function? What happens in pediatrics, where asthma is actually probably somewhat of a different disease than asthma in adults? And what happens in different ethnic groups, who carry all sorts of other genes that may, in fact, actually modify the effect of the adrenergic receptor?

So, in essence, the public health approach would say we need to understand all of this in addition to understanding how the polymorphisms and albuterol work together in the global, macro sense. That's a pretty large charge for this committee. So how would we go about collecting information on measurable clinical outcomes in terms of morbidity and mortality in a diverse population set, including elderly and children and different ethnicities? There are really three major options that I could talk about today. One is observational studies, randomized clinical trials, and large practical trials. They all have different strengths and weaknesses,

and that's what I'm going to walk through now.

Now, it turns out that observational studies can basically be broken down into cohort or case-control studies, and this is in essence one step above the very compelling case reports that we heard from the previous speaker. Among asthmatics, you could basically say among those given albuterol or those not given albuterol, what's the rate of a good versus a bad outcome in persons given albuterol compared to people not given albuterol? Then if you stratify them according to their gene status, I basically set up how we would look at this in a cohort study in an observational setting.

Those cohort studies tend to be very large and very expensive, but they do give you very good information as to whether people on albuterol do better depending on their gene status. You could alternatively just simply nest a case-control study and pick a couple of hundred people who have good outcomes and a couple of hundred people with bad outcomes among those who have asthma and then look at the percent who have been on albuterol in terms of the proportions they make up of the good outcomes and the patients with bad outcomes, and then additionally stratify them according to their gene status, and once again you'd get back to the same place. You would actually have evidence that tells you whether or not albuterol

improves asthma outcomes according to your gene status.

The advantage of observational studies is that the data is actually easily available, and when I say easily available, I mean relatively. It's actually very hard, takes a long time, and it's very expensive, but it's out there already. We could actually begin to get this information today. As a matter of fact, people are getting this information today.

The comparison by gene group is relatively unbiased. That's the wonderful thing about genes, that apart from our typical suspects, confounders like smoking and alcohol, the nice thing about genes is that they distribute themselves in a fairly unbiased situation here, and we'd be able to get good information, good evidence as to the effectiveness of albuterol in different gene groups.

The disadvantage is that sample size limitations really come home to roost when you're stratifying additionally by elderly, by children, by other medications, by ethnic groups. So even somewhat large observational studies will run into limitations in terms of how much information they can give us.

Randomized clinical trials allow you to go out and, in fact, find a couple of hundred people who are homozygote and a couple of hundred people who are either heterozygote or homozygote for some other beta-adrenergic

receptor, and allow you to randomize albuterol among the two different groups of people, among the two different groups of gene strata. That would allow you to directly address whether or not albuterol works better among one or two -- am I shouting? I'm not shouting loud enough. I think that's the first time anyone has ever said that to me.

The nice thing about this is that you could additionally stratify according to other genes. So if you were interested in the gene interaction of beta2 adrenergic receptor with a different gene, you could additionally do, in essence, a 2x2 factorial design, or among this group you could additionally randomize people to albuterol and fluticasone and do a factorial design that way. So the nice thing about randomized clinical trials is they allow you to very directly address a very specific question with very high quality.

The disadvantage of a randomized clinical trial is that they typically enroll healthy patients and often limit it to those on monotherapy, either the drug or drug combinations that you're studying, and they have very limited generalizability. I hate to say that I'm 48 and I'm on three medications already. How that happened, I don't know. I'd like to blame somebody, but I think I can only blame my genes. So I would not be considered a

healthy patient for most of these trials, and most of these trials have limited generalizability to me, even though I'm a white male. What's wrong with this picture? I mean, most of the time this stuff is generalizable just to me, but most of this data, in fact, is not generalizable to me.

The nice thing about randomized clinical trials, as I've said already, is that you can stratify additionally by elderly, by pediatrics, by other medications, by the size requirements get very large.

So these limitations have really led to something I think is very exciting, which is the concept of large practical clinical trials with the objective to enroll many patients, over 100,000, in trials that are randomized at the patient or at the clinic and provider level. This allows for head-to-head comparisons of most commonly used medications. So it allows us to ask not only does statin A work better than statin B, but it also allows us to ask are there haplotypes whereby statin A works best for haplotype group A, whereas statin B works best for haplotype group B.

It not only allows you to enroll enough people to study very small differences that may actually have minor clinical impact but huge public health impacts, but it could also allow us to utilize the natural experiments among this large number of people. If you enroll 100,000,

30,000 of them are going to be "elderly" and 20,000 of them might be pediatrics, and that's still a fairly large sample size. You you can actually look at the drug effectiveness by gene status according to different risk groups; i.e., elderly and pediatrics. You could also look at other fairly common genetic polymorphisms to look at gene/gene interactions. Then you could look at the modifying influence of other medications.

So there's really a lot to be said for really strongly considering and recommending that we integrate genomics into large practical clinical trials. I think that's one of the more exciting things on the horizon.

The other thing that these large practical clinical trials do is they not only look at the drug effect but they look at the gene effect, and they also look at the system effect. That is, given that we know what's going on, the question is how well does the system respond to that information, and that's really an under-appreciated but real-world generalizability feature.

So what are the needs of the United States in terms of setting up a network that could actually address these issues? Well, in yellow in the subsequent slides, you'll see that I've outlined what I think we need for this kind of evidence of effectiveness to be created. We need clinical researchers, epidemiologists, biostatisticians and

trialists as a network of researchers.

I guess what I'm getting at is this is a full-time occupation to do these kinds of studies. This is nothing you can do with 10 percent of your FTE, because it really requires a complete mindset, a mind change, a paradigm shift in how you actually think about doing your studies and who you are going to talk to. So we need actually dedicated clinical researchers, dedicated epidemiologists, dedicated trialists that are looking at pharmacogenomics and pharmacogenomic tests.

We also need organizations that are willing to address this, because the problem here is that these types of issues can either be tremendously helpful to these organizations or they can show up on the front page of USA Today in a pejorative or a derogatory or a rather fearsome title about a large organization studying the genetic attributes of the population. So we really need to, I think, align ourselves with managed care organizations, Blue Cross/Blue Shield, United, Medicare, the VA, Medicaid, to talk about how we can actually network our researchers together with them to do these large practical clinical trials and large observational and randomized clinical trials.

IRBs will need to be brought up to speed, and many of them will require a tremendous degree of

reassurance that we will do the right thing for the right people at the right time. I'll talk later about the types of data standards that we'll need to develop to do these sorts of studies.

Now, I'm just going to briefly talk about this because I think Muin will talk about more of this later on today. But once we get this evidence, it will come in a big mish-mash that we call published medical evidence and that we all grapple with on a routine basis. So what we also need is a system somewhere around here that talks about a systematic analysis of drug and test effectiveness. This relies primarily on the format of systematic reviews and formal meta-analyses, and these incorporate evidence from randomized clinical trials, large practical trials, and observational studies.

I'm very pleased to say that there's already been movement here, where the EGAPP project, which evaluates the genomic applications, has already convened, and this committee knows quite a bit about this so I won't talk about this in any further detail.

Now, we have a question from one of the panelists, who asked why are we still not able to integrate this evidence, and I think that it's clear to say that the U.S. research enterprise has failed miserably in integrating evidence into clinical practice. Rob Califf

said this, and I'm just reiterating this opinion, but I actually believe that we really simply have not paid nearly enough attention to a scientific approach to integrating evidence into practice. The Cochran Collaboration in the United Kingdom has already begun for at least one decade leading the way toward the synthesis and collection of evidence in order to integrate it into practice. AHRQ launched their Translating Research Into Practice project, but we are still, as of June 2005, really on square one still in terms of any fundamental success in systematically integrating evidence into practice.

So let's assume that the evidence is strong, that knowing beta2 adrenergic receptor status among asthmatics improves outcomes. Let's say we actually do the studies that show that it actually makes a difference. What's the best way to get this evidence into practice? Well, still I think in the United States we are doing it the old way still. The old way was that if we could only educate doctors, this would solve the problem. I'm going to say something very politically incorrect. It's not a waste of time because it's necessary, and people get mad at me if I say it's a waste of time, but what we do when we educate doctors is we find out that doctors test better.

Well, that's a far cry from saying they

actually apply the evidence. In fact, Group Health has done a number of studies showing that if you educate doctors, they test better and their practice doesn't change a bit in terms of diabetic care. So I think that we can educate patients and the patients will have better knowledge, but if the doctor doesn't do it, I'm not sure that's really money well spent.

We could do academic detailing, and a number of us I'm sure have done studies on academic detailing. They tend to have high costs and temporary effects. Private detailing is not a bad idea, except that it's a directed change in terms of what gets done to the patient and it doesn't have a public health focus.

So I don't think that any of those are really the fundamental way we should be integrating evidence into practice. There is a new movement, though, which is long overdue, which is to perform randomized clinical trials or quasi-experimental trials as a means to test the best way to integrate evidence into care, and here's one example that I thought of, which is the usual care for asthmatics versus an electronic reminder within the electronic health record -- i.e., EPIC, that's being used in Kaiser now -- with automatic ordering of gene status based on diagnosis or prescribing behavior.

For an example, somebody comes in and you give

them the diagnosis of asthma, and the electronic medical record actually finds out that that's their first diagnosis ever in their electronic medical record. It would automatically order the beta2 adrenergic receptor, assuming that this evidence is strong that it affects clinical outcomes. I think that's a great idea. It would automatically order it and it could automatically write the right prescription in the right dose. It could do that, and as a matter of fact we're hoping to do a trial similar to that for warfarin at Group Health, where it's basically taken out of the physician's hands and it's put into the computer's hands, not completely but in essence it automatically does this so it's not dependent on me remembering to order the test and remembering to look at the test results before I write the prescription.

So what kinds of systems are necessary to get this evidence integrated into practice? Well, to do that kind of study, that actually requires a different kind of person. It doesn't really require an epidemiologist anymore. It requires health services researchers, and those are a different breed than your standard epidemiologist and trialists. It also requires substantial EMR development. It takes a lot of time to develop these sorts of pop-up screens in EPIC that could actually automatically order tests that are conditional on the

disease being diagnosed and that could automatically order medications. I'm not saying that's a bad thing. I'm just saying that we lack this right now. We are not doing that.

So finally, I'm going to talk about what I mean by surveillance. I've talked about how we could collect the evidence, how we could figure out how to integrate the evidence. I still don't think that's the full range of things that is incorporated by the public health approach. The public health approach also has always incorporated some degree of surveillance, and I think there are three types of surveillance that we would need to do.

One has to do with quality measures, one has to do with ethics, and one has to do with safety. What do I mean by quality measures? Well, there should be standard publications. Just like the MMWR shows the standard publication of how we're doing with vaccine coverage, I think that it would not be an unreasonable approach for us to say among subjects with asthma around the country, how many are being tested for this beta2 adrenergic effect? Again, I'm a little bit in fantasy land. I'm assuming that this data is now solid. But I'm saying that we should not be dependent on individual publications that sporadically get published. I think we should have a national system that says what percentage of asthmatics are being tested before they're being treated, and what percent

are being placed on appropriate medications conditional on their genetic results.

I think we also need to have some sort of surveillance mechanism set up so that we are on the outlook for genetic discrimination and exceptionalism, decreased access to service, and loss of insurance, and also the inappropriate use of tests. That is, these tests being used on the wrong population or incomplete counseling. I think it would be a horrible idea if we just sort of license these tests and then didn't have any institutionalized approach to conveying that information to the patient.

Then unintended outcomes, whether it be suicide once you understand your drug metabolizing effects -- I mean, things that we can't possibly conceive of will happen, and I think there has to be some sort of surveillance for unintended outcomes.

I also want to talk for one second about the safety model that I think is something we should really consider. In the vaccine model, we currently have a passive reporting system for unintended effects of vaccinations, and we also have a population-based data set called the VSD, the Vaccine Safety Data link, that puts together a population that looks at vaccine safety among 5 percent of the United States. I think the pharmaceutical

model has something similar with an adverse event reporting system that's passive in nature. The CERT projects and a couple of other projects perform a function for population-based collaborative projects to look at medication safety.

I think in the future, hopefully, we will have a registry of these adverse event reports, people who have unintended effects after vaccinations, and it will be easy -- i.e., possible -- where we will get buccal swabs for DNA among those patients, and we will get a candidate gene generation approach. That is, we'll begin to form a registry of people who have unintended effects, and these will allow us to then study new candidate genes, or perhaps even old candidate genes, for their role in predisposing certain people to adverse effects following vaccinations. There's no reason why we can't do the same thing with a registry of adverse effects in the pharmaceutical arena.

Here for a surveillance system, we need safety researchers. Again, those are actually different than epidemiologists and health services researchers, as well as ethics researchers, people who are specially trained to actually grapple with these very troublesome issues.

Finally, I want to talk about the development of the electronic health record. Everything I've talked about today has assumed the availability of data in

electronic format to collect the evidence, to conduct trials of integrating evidence into health care, to provide information that guides and monitors clinical care, either pop-up alerts when you're prescribing medication, pop-up alerts that may pop up when family history is collected, or pop-up alerts that pop up when high-risk conditions are noted.

In fact, none of this exists today, and there is a tremendous need to develop this type of electronic health record. Research actually has to be done in each one of these five areas, how we collect the information, how we process the information, how the data is actually structured in our data files so we can actually study it, and then the security and transmission of that data. It's actually sort of stunning to think that when I used to put in R01s or whatnot, we actually had to address these de novo each and every time. We do not have a dominant Microsoft industry here. Right now we're still at the intersection where most electronic health records are de novo, home-grown systems, even the larger players of the clinical arena.

So you can see that I guess what I'm saying is that we need a systematic approach to create the automated files, electronic medical records, the networks of providers who are willing and able to grapple with

collecting the evidence of effectiveness, networks of researchers who are willing and able to do studies of how to integrate the evidence into clinical care, and willing and able networks and researchers who are able to do the surveillance that I think will be necessary for pharmacogenomics.

To create this system will take a lot of work and a lot of money, and it's not clear who is going to actually lead that charge. To create the system, I think that funding could come from these players. FDA, the CDC, AHRQ, NIH, pharma and insurers I think would all have a role for creating such a system that would allow this to occur. I think that there's also a role for legislation and standards such that the FDA and the CDC and insurers could mandate some of these things. This is clearly out of my field, though, and I don't really want to address this.

I do want to leave you with one thought. Again, I am the biggest fan of the ability to do this type of work. I think that some of you might have been thinking, boy, this guy really lives in the land of fairy tales. Where does he get this information from? Where does he get his ideas from? Well, this is, in fact, where I get my ideas from, but there are no challenges, there are only solutions. I actually think that everything I've told you today is a challenge, but

it's something that we actually have within our power to solve.

Thank you very much.

(Applause.)

DR. WINN-DEEN: So I want to thank you for being extremely responsive to our charge of please tell us what the issues are and things that we could potentially consider as a committee for areas where we could maybe make some real task force kind of recommendations.

Are there questions from the committee for Dr. Davis?

Ed?

DR. McCABE: What you designed for us was an infrastructure which doesn't exist at this time. The first speaker mentioned that there's the likelihood that this may be driven by litigation, and I teach about pharmacogenetics to our medical students, and I maintain that the diagnostics will be driven by litigation. So that's going to happen much more rapidly, I think, than we will have time to develop the infrastructure that you've discussed.

So how would you develop a rapid response when the medical legal industry recognizes that there is a large vein of gold out there that they hadn't recognized before and now create the new cottage industry against this?

DR. DAVIS: That's a great question. I think

there are two things that can happen. One is there is this Pharmacogenetics Research Network. I think I've gotten the name close enough. That's a wonderful network, one that I'm actually very jealous about. But what really sort of struck me is that there is no network like that for what I was just describing.

There is a network for what I was just describing for vaccines, and it was created because in the late '80s there were only three vaccine companies still left in the United States producing vaccines, and the liability that they were facing in the court system, the total dollar amount actually exceeded their total net assets for all the vaccine companies. In response, the CDC actually formed the Vaccine Safety Data Link process that actually now does exactly -- not exactly but pretty much what I've shown you on 5 percent of the United States.

So we have shown the capability of setting up these networks. We have something in response to these litigation concerns. The CERT networks were formed, I believe, in a joint effort by the FDA and AHRQ specifically to look at issues of patient safety, and I think that to a large extent they actually have the researchers and the networks that would be able to address many of these issues.

Why aren't we doing it? Honestly, it's a

matter of money. I think there needs to be a substantial allocation of resources. How about if I stop there? I don't want to start moaning about the small amount of funding that we're able to get for some of these studies. But they are substantially less than the amount we need to actually do this in a systematic way.

DR. WINN-DEEN: I wanted to sort of follow up on that question. You described a system of large population-based clinical trials. I really enjoyed your outline, but as I started to think about if you had to make 100,000-patient clinical trial to answer every pharmacogenetic question that might be posed, what the cost of that is to the health care system. I'm not going to say which part of the system, whether it's the U.S. government or private that should pay for that, but how do we even begin to grapple with the thought of doing that for all of the drugs that are out there? Do you have any thoughts on how one might prioritize which things you would start with?

DR. DAVIS: Would no suffice?

(Laughter.)

DR. DAVIS: That was the honest answer, but you flew me up here. So just simply to say that I think what I see coming is genetic testing and pharmacogenomics is two things. One is it's really caught the public's imagination, and these sorts of things are being offered to

patients already; and it has sort of the stunning ability to bankrupt the system, to either bankrupt the system or to dramatically improve health care. I think if you look at it that way, then actually the cost of these studies is not as much as one might think.

I think a lot of the cost is setting up the infrastructure. I mean, most of these patients in the large clinical trials are being seen already and they are being prescribed medication already. The technology to run their gene chips and to collect the information is already there. It's a matter of plugging those pieces together and funding that network to exist, and you then have to actually set up a group of people who are far wiser and far more experienced than I to prioritize that.

I say that with my pediatric heart shrinking, because who gets left out in those priority-setting committees? The priority is usually driven by either morbidity and mortality or cost. Those are usually middle-aged to elderly people who are beginning to die of congestive heart failure, stroke, heart attacks, and those are the things where the need is the greatest to do the studies. But I think the priority setting needs to also look at gender-specific effects, look at pediatrics, the very elderly, and whatnot. I should have just stopped with no. How's that?

DR. WINN-DEEN: Is there some agency within the government that you would see taking the lead in trying to develop such an overarching plan?

DR. DAVIS: I've actually wondered about that a lot because we don't really have a single agency that sort of has public health as its mantle. I think there is a very clear role for the FDA, a very clear role for AHRQ, and actually for what I'm talking about there's a very clear role for the CDC, although this would expand its mandate, and there's obviously the conflict of interest I have in saying that, where I'm doing my sabbatical. I think NHGRI and NIH could play a very strong role as well. I think there actually needs to be an amalgamation of those efforts.

DR. WINN-DEEN: Ed?

DR. McCABE: So I'll follow up with a question to Tim, because I think one of the expenses is the sequencing. If we can get the testing down, if we can get sequencing down and its cost -- I know there was an RFA to decrease the price of sequencing, and I was wondering what the anticipated trajectory is to get us to the thousand-dollar genome, knowing that it's a guess.

MR. LESHAN: Right. We're looking at the next 10 years as our focus and we're trying to get it down to that level. Whether or not we'll be able to will really

depend on how well we can develop that technology. Based on the progress that we've made over the last 10 years, we think we can get there, but there's still a whole lot of work to be done in order to do that. I think you're right, that if we can reduce that cost, that will greatly enhance this.

But there's also the issue about people's receptivity to this. I think the public is very interested in it. But at the same time, I think we do have this problem, an issue that's been around for a long time that Dr. Weinshilboum talked about, how do we break the barrier within the academic and the physician community to make sure that this is something that people really want to invest in and will participate in.

DR. McCABE: And a question to Sherrie, then, in follow-up. It would seem that VA would have a population in which to begin to pilot this. Is there any discussion of this in the VA population?

DR. HANS: Yes.

(Laughter.)

DR. HANS: You're absolutely correct that at the conceptual level the VA has the necessary patient population, has the necessary information technology infrastructure, has the necessary research infrastructure and delivery system to be able to do something like

that. It is a matter of the additional costs of running such a large-scale research program under current budgets.

DR. DAVIS: Could I just follow up, if I might. One of the things I've really noticed is that there's a lot of people really beginning to talk about this seriously because they understand, I think, the costs of continuing to do not only business as usual but that the perceived business as usual within five years will be even magnified dramatically. So I've been really heartened to see people at CMS and the VA and the managed care organizations trying to climb on board the train. Unfortunately, we have train cars scattered around. We just haven't hooked them up and gotten them going yet.

I was up at AHIP not too long ago, America's Health Insurance Plans. They're very interested in these concepts. So I think there are a lot of very interested partners. It's just a matter of putting people together in the proper context.

DR. WINN-DEEN: We're going to take two more questions, and then we're going to go to break. First Julio, and then Francis.

DR. LICINIO: One question related to what you presented, which was very interesting, about large studies that you need to validate this. The issue is who is going

to fund those? Because if you go to a more naturalistic setting, like a health care organization or something out there in the real world, the patients are on multiple drugs, and if you're trying to look at the effect of one drug, you really have to get more of a research type of study. Ideally for what you're proposing, it should be for drugs that are established, not trying to look at new drugs that are just coming to the market.

So the drug companies are usually not willing to go to the expense to do this kind of study for a drug that's already out there and is selling well and possibly at the end of patent. NIH was the exception, or NIGMS. The categorical institutes should then be a little reluctant to do this kind of large study just for pharmacogenetics because the cost is very high and they don't see the sample collection being worth the cost of several R01s.

So do you have any ideas for this kind of a conundrum?

DR. DAVIS: Well, I agree with you. I think there are a lot of reasons why people won't participate. In terms of who you mentioned, I think this work is going to have to come from people who are already paying the bill -- i.e., CMS and other insurers -- where they're actually currently picking up the cost, and there's

really no good evidence that certain of these medications work in the diverse situations. It is that the medications are actually being used.

So I think that it's kind of a perverse incentive, but it's one that's very real and very recognized. So I think in reality that's what we're looking for. What we're looking at now, can we align other things to make that more palatable. I think in terms of some statutory requirements and legislation that would require some of these studies to be done, and the cost could be shared a little bit, I think it's somewhat naive for me to say it but I think that's actually a realistic and probably a fairly, in the long term, beneficial thought.

DR. WINN-DEEN: Francis?

DR. CHESLEY: Thanks. I just wanted to amplify the dialogue we're having around cost and suggest that I believe that the tipping point here will likely occur when a strong business case can be made. As you've related, we really need infrastructure for the research, and a key component of that research is really going to be cost-effectiveness research, as well as the effectiveness research to be able to demonstrate to those who pay that there's a business case to be made, and therefore it makes sound business sense to take this approach. I think at

that point, all the various players will come together, federal and non-federal as well.

DR. DAVIS: You know, could I just respond real quick, which is that a lot of times we think of these cost-effectiveness studies as being a home run. But, in fact, I think what they will actually show is that there's a tremendous amount of waste, and that's not nearly as sexy, but I think that's actually what we're dealing with, and that's the business case that needs to be made.

DR. WINN-DEEN: Sam?

DR. SHEKAR: Just one quick point. There's another trend that's going on in health care, as we know, which is the tremendous growth in the electronic health infrastructure, the underpinnings of health care delivery. Since so much of what you have discussed relies upon fairly immediate and fairly transparent transmission of data back and forth, the costs that are borne through an electronic health infrastructure underpinning may in fact be covered through that type of support. Therefore, as a suggestion for a future speaker, it may be interesting to know what's going on through the Department, through the Office of Dr. David Brailer and some of the work that's being done to support growth of electronic health infrastructure across the medical care industry and health care industry. I just made that as a suggestion.

DR. WINN-DEEN: On that theme this morning, as I was getting ready to come down here, there was an interview with Frist and Clinton on bipartisan support for the bill that is before Congress right now to get funding for this program, and I think it might be worth getting someone from the judicial side as well, or the Congressional side, to give us a briefing on where that is as well.

I think we'll stop here and take a 15-minute break and come back for the continuation of the session promptly at 10:20.

DR. WILLARD: At 10:20 to the minute.

(Recess.)

DR. WILLARD: While we're waiting to begin, let me acknowledge Sandra Howard, who is joining us today from planning and evaluation at HHS. Thank you for being here and we look forward to your participation.

DR. HOWARD: Yes, thank you so much. I'm very pleased to be here. I do work in the Office of the Secretary. My office provides analytic policy support to the Secretary, who is very interested in the issue of personalized medicine, among other aspects of this particular project. My office also provides analytic support to some of the advisory committees to the Secretary, and if we can assist you in your deliberations,

we certainly would be happy to look into that. We've already been discussing this with Sarah and other staff. Thank you.

DR. WILLARD: Terrific. Thank you very much for being here.

Just a word. Everyone here who is taking advantage of Reed's absence, he did tell me the only thing he didn't want me to do today is to embarrass him. So please protect me and we'll try to keep on time as we go forward.

Emily?

DR. WINN-DEEN: So we're now ready for Weinshilboum Part 2. Now he's going to focus a little bit more on his role as a physician and talk to us about pharmacogenomics in the practice of medicine.

DR. WEINSHILBOUM: And what I'd like to do now, and I've now got a lavaliere and I've got a really fancy laser here, is to move beyond the sort of Pharmacogenetics 101 and begin to talk about the issues which we appropriately have already begun to talk about; that is, the translation of this information into the clinic. But I think we need to step back, and I've called this "Challenges and Opportunities." Dr. Davis had something similar.

As I thought about how to organize this, I

think it's important to talk about it in terms of the science, and I've divided it into basic and translational science, drug development and regulatory science, and ethical, legal and social science, about which I as a pharmacologist am clearly a novice. But I think it's important to put up a diagram like this which we already have implicitly talked about, and that is eventually what we want to get to is the therapeutic encounter between the physician and the patient when either the physician writes the prescription or, as Dr. Davis said, HAL the computer writes the prescription, whatever we end up with so that the patient has the right drug at the right dose.

In general, those of us in academic centers tend to think in terms of academic medical centers, like Mayo or Duke or whatever your personal one happens to be, and a relationship with our funding agency -- it can be American Heart, NIH, et cetera -- and that we will be able to influence this in some fashion.

That's a short-sided approach because, frankly, drug development in the United States since the Second World War has focused on the pharmaceutical biotechnology industry, and just as the NIH is the place that predominantly those of us in academic centers look to, we need to think in terms of regulatory agencies, and particularly the Food and Drug Administration.

Now, interestingly, the amount of interchange between these groups -- that is, between, say, the NIH and the FDA, speaking totally as a novice, so just as I made the point initially that I spent my life in an academic medical center, I clearly know nothing about this area other than what I found as a tourist dropping in to give a lecture every now and then. But it struck me that these two agencies didn't talk to each other that much in the past. What you're going to hear is that that dialogue is also important, and we're moving forward with regard to those kinds of interactions. That's already been mentioned in previous presentations.

So let me begin by pointing out that although our focus has been on translational pharmacogenomics, Dr. Long from the NIH is here, and she would point out that NIGMS has been supporting our research for 30 years, and clearly we need the basic pharmacogenomic research in order to get to the translational research, and they feed off of each other. I think it's important to make that point because Dr. Davis was talking about putting his teams together.

Frankly, we have found for our teams, which include molecular epidemiologists, population scientists, clinical investigators, that having basic scientists involved is critically important, because what happens is

the basic science runs right by what you're doing. It says goodbye to it and runs right by it. So we need to be sure that the latest developments are incorporated in this, and the whole team really includes all aspects of health care research.

I want to come back to the scientific goal because we were just talking about the National Human Genomic Research Institute and what they can offer, and obviously our understanding of the genome keeps changing right beneath our very feet. So the nature of sequence and structure differences in DNA that can have practical implications at the translational interface keeps changing. This is a slide that I keep adding to with regard to the nature of the sorts of genetic variation that will be important and is important in pharmacogenomics.

Obviously, the SNPs, the single nucleotide polymorphisms, the insertions/deletions, VNTRs. Gene deletion and duplication I already mentioned with regard to CYP2D6. Increasingly, we are finding large segmental duplications, and I'll actually show you an example in just one second. So the nature of the kinds of assays we have to do keeps changing, and that, Dr. Davis, is why I said you need the basic scientists sitting right there, in person, in the flesh, at the table, because your assays will be out of data mañana. Gene variation resulting in

alternative splicing. Whole new areas of genomic science are opening up, and epigenetic or what I like to call pharmaco-epigenetic variation.

I'll show you just this one example. What this is showing you is on chromosome 16, a duplication of 145,000 base pairs, one of the genes we were studying. The idea of the Genome Project being "complete" is an interesting and ever-changing target, but this area has one of our genes that is 99.9 percent identical, duplicated right in the middle of this duplication of this big chunk of DNA. Well, that really messed up our genotype. The comment was made, what about sequencing? Well, sequencing, even if you're using dye primer sequencing, if you've got instead of two copies of that allele, four copies, and you're trying to interpret your sequence traces, that's a real mess. I won't bore you with the details other than to say the science is changing out there, and we need to remember that the basic science is going to drive this process, too.

At the NIH -- and I put this within the context of the NIH Roadmap. So the director of the NIH and the NIH has gone through this strategic planning exercise in which they have given it the usual strategic planning catchy phrases, but the concepts are pretty simple. New Pathways to Discovery means biology is very complicated, and no one

has the expertise to know all aspects of it, so you need the kinds of teams that Dr. Davis was talking about at both the basic and translational level.

The Research Teams of the Future means that you're going to have to organize the way in which we gain the new knowledge and test the knowledge in new and different ways. Now, I've never done any knockout mice, but if I could do a human knockout, there's really only one gene I want to knock out, the gene for the human ego structure, because, frankly, the biggest barrier to putting these sorts of groups together is who is in charge here, and we need to find ways that we can adequately reward team and social interactions in ways that our current system frankly discourages.

Finally, Reengineering the Clinical Enterprise basically is the need for multi-center, multi-group organizations because of just what Dr. Davis was talking about. The power calculations are going to kill you, and no place -- the Mayo Clinic is a big place, but we know that we have to team up with other institutions in order to be able to have adequate numbers of patients to test these hypotheses and determine how we want to move forward.

What has happened as a result of -- and I got in a little trouble with Tim about my comment about Francis Collins not thinking up pharmacogenomics. But what's

happened as a result of the dramatic changes that have occurred in genomic science is that whereas the examples of TPMT and CYP2D6 began with phenotype and with armies of postdoctoral fellows shoulder to shoulder across the world marching out, they purified the protein and cloned the cDNA and cloned the gene -- I even told you the names of some of them -- got the polymorphism, and that took 15 or 20 years, in today's world we type "NCBI" into our web browser and then you've got the gene sequence. That was what Dr. Honshal spent a year and a half of his life to get.

So now we can begin with genotype and go back to phenotype, and one of the complementary strategies that's being used in this area is to very rapidly determine gene sequence variation in individuals of differing ethnicity. Once you have the common variation in gene sequence, then to do the functional genomics to determine which of that variation is functionally significant, and then the really hard part which Dr. Davis was talking about, to determine which of the common variation that's functionally significant is of clinical importance. Those are among the challenges. This is not the only way to do it. Genotype to phenotype and phenotype to genotype are complementary approaches.

Let's take a different example. I made an interesting observation myself when I put these examples

together. 2D6, TPMT, warfarin, 2C9, VCORC1. I said where has this information come from? There's an important point here, and I'm challenging Walter and Eric because all of this information, all of these chestnuts have come from academic medical centers. They have not come from industry. The challenge, Eric, for industry is to find ways that we can partner with our mutual strengths in order to be sure that in the future industry is making -- I'm being a little provocative here, and that's unusual for me, but let me do it anyway -- that industry is making these kinds of contributions.

So the irinotecan example. Irinotecan is an antineoplastic agent, a camptothecin derivative. It inhibits topoisomerase I, and its toxicities are predominantly diarrhea and myelosuppression. This diarrhea is not just something that you take a little Imodium for. This is life-threatening diarrhea.

Here's the way that, now going back to boring drug metabolism -- irinotecan itself is a pro-drug. It's metabolized by cardoxylesterase to form SN38, which is the active drug, which is itself glucuronide conjugated by UDP glucuronisil transferase, and that gene -- I have to show these gene structures because I love them. This is a really nice gene that I love to tell the graduate students about. It has a whole bunch of upstream exons that are

then alternatively spliced in to conserve four downstream exons, and then you get the substrate specificity depending on which of these you set in.

Well, the one that metabolizes irinotecan is UGT1A1. That is also responsible for bilirubin metabolism and for Gilbert's syndrome, not disease but syndrome. We now know that that's predominantly due to variable number 10 and repeat in the ta-ta box. If you have seven ta's, you have a lower level of activity. This is in the promoter. If you have six, which most people do, you have a higher level in people who are homozygous for seven, like myself. Every time I go in for my physical exam, I'm told by the intern or resident who is doing the exam, well, your unconjugated bilirubin is up a little bit, and it always is when I'm fasting. That doesn't make any difference in most settings, but with irinotecan, it makes a big difference because that's the isoform that metabolizes irinotecan, and if I'm ever treated with that drug, which I hope I never need to be, I know that I will need a somewhat different dose, a lower dose of the drug.

This is to get us to the pathways. It's also to do something else. Here's irinotecan. This is from the pharmacogenomics knowledge base, PharmGKB, which is sponsored by the pharmacogenetics research network that I mentioned, and what we're doing is putting a bunch of

pathways there. All the little squares that are sort of this purple color are drugs that are metabolized. All the little egg-shaped things are genes encoding proteins that either metabolize the drug or transport the drug, and now this begins to give you some idea of the degree of complexity that we will find ourselves dealing with with most drugs, where the metabolic and transport pathways look like an explosion in a spaghetti factory.

So you're going to find that this will become extremely complicated, and the examples that we've used are examples of simplicity. Where the world is going to take us, the real world is going to be much more complex than that. I showed you that because I wanted to be sure that I brought to your attention the fact that the NIH is sponsoring this knowledge base, PharmGKB, where all of the data from the network, and we hope from outside the network, will eventually come together in one place, genotypes and phenotypes. That kind of a database is a tremendous challenge. To try to combine genotype and phenotype, it makes GenBank, with all due respect, look fairly straightforward and simple.

So I want to talk about pathways. Having talked to medical students and graduate students forever, I've learned that reiteration is an important part of the pedagogical science, so let's go back to TPMT and let's

talk about thiopurine metabolism and metabolic activation pathway, because azathioprine is a pro-drug that's converted in vivo to 6-mercaptopurine, which can be methylated or oxidized. That's kind of what I showed you a moment ago. But 6-mercaptopurine is itself a pro-drug that undergoes a series of metabolic activation steps to form 6 nucleotides which are incorporated into DNA, and that's a major mechanism, the major mechanism probably, for the cytotoxic effects of these drugs.

I show you this because this is kind of a moo cow/bow wow pathway, really. It's much more complicated than this, but I'm showing you the very simplified pathway. When we first published our data on TPMT, I will tell you that everyone knows that this is the major metabolic pathway. This is actually a minor pathway. I thought about bringing along the line from the reviewer for Cancer Research that said these dumb pharmacologists aren't smart enough to understand that this minor pathway couldn't possibly influence individual variations in response to these drugs.

Now, everybody has those sort of letters. I didn't bring it along. What was going on at that time was Lynn Leonard at Sheffield had demonstrated that by measuring 6-thioguanine nucleotides, she could predict who was going to get toxic on these drugs. She met me at an

international meeting and she said, Dick, what I can't figure out is we treat these kids with exactly the same dose of exactly the same drug. Some of them will have very high 6-thioguanine nucleotide levels and some of them won't. I said, Lynn, maybe it's because this pathway genetically, if it's impaired, you pump more of the drug down here and you're going to have higher 6-thioguanine nucleotide levels. So she sent us blood samples from 95 consecutive children in the U.K. who are in the UKAL, the United Kingdom Acute Lymphoblastic Leukemia trial.

We measured the enzyme activity, she measured the 6-thioguanine nucleotide levels. When you got up here to 600 to 800, that's when you begin to have myelotoxicity, and these are the heterozygous individuals. She also had samples -- these are data we published in 1989 -- samples from individuals treated with standard doses of these drugs who developed life-threatening toxicity. Half of them died. She sent us those samples and a group of controls. These were patients with dermatologic disease being treated with azathioprine. Notice we're up in the thousands of picomils for the active metabolite. This person was 26 days after the drug was stopped and he was still above any of the controls on the same dose of the drug.

When we published this, we said if this can be

confirmed, we can predict and prevent this toxicity, and indeed it's been confirmed, as I mentioned, over and over and over again. But that's to make the point that pathway analysis is extremely complicated, and what you think a priori, just because something is a major pathway, like the xanthine oxase, doesn't mean that's going to swing the variation. So the translational lessons for TPMT, among others, are the importance of having an intermediate phenotype like the 6-thioguanine nucleotide levels. Kids with leukemia are treated with a large number of cytotoxic agents. There are a variety of reasons why they are going to become myelosuppressed. If they have a viral infection while they're on these agents, they will have myelosuppression. But by having the active metabolite, we can sort out those in which it was the TPMT that was the problem.

In addition, it emphasizes the difficulty of pathway analysis. So when we design these studies, the mega-study, the 100,000-patient study, we need to understand that it's going to be extremely difficult to fish out what a given genetic variation might be doing of importance.

This is just to make the point that the modified central dogma is not gene goes to mRNA goes to protein goes to metabolite, but that we now have genomics,

metabolomics, et cetera, and that means that the assays that we have available will have to be very different kinds of assays. So the clinical assays will involve phenotypes, and by that I mean the endpoint, myelosuppression, or the intermediate phenotypes, and those intermediate phenotypes may well be a metabolomic signature. So it may be measuring 10,000 metabolites and using informatics to fish a signature out which at first we won't even understand. But we need to know that during the discovery phase we'll be looking at all kinds of phenotypes between the DNA and what we see in the patient. It's going to become very interesting, but I think we're going to need those different phenotypes.

At the clinical level we'll be measuring not just SNPs but also haplotypes, and eventually Tim was already talking about 3 billion nucleotides, and I'll be interested in how our doctors at the Mayo Clinic deal with that when their patients come in with it. Obviously, we'll be talking with Walter in just a moment with regard to the development and validation of these tests, significant challenges which you know a great deal more about than I do.

This is just to make the same point I made before. Walter will be talking about it, and I knew he was going to be here, so I used his device as an example. The

scientific evolution here, let's think about what I've been saying and what we all know, and Dr. Long, who is in the audience, will be saying. We've gone from phenotype to genotype to a complementary genotype to phenotype, which frankly has accelerated the process 10-fold at least. So we resequence these genes, do the functional genomics, and before we even have the paper off on the resequencing data, we'll be dealing with our clinicians in the breast cancer clinic because they have the DNA to test hypotheses.

So the basic science crosstalk with the clinical science, in theory we ought to be breaking down those barriers, and with the right organizational structure, and with the diminished ego structure, we can actually get there. We've gone from monogenic traits -- clearly, that irinotecan pathway was there to say we need to be thinking polygenically, and we've gone from single genes and proteins to entire pathways, from single polymorphisms to haplotypes, genome-wide screens, and Tim will eventually give us all 3 billion nucleotides, and from the mom and pop store approach, which is what I've done through most of my career, to high-throughput platforms and groups. We've already talked about all of this. I'm just reiterating themes that Dr. Davis introduced.

With regard to drug development regulatory science, I feel obliged to put this up so poor Eric can

respond to it. This is not my comment. It's from "Surviving the Blockbuster Syndrome" in Science last year talking about pharmacogenomics and that there has been some skepticism with regard to segregating out different patient populations who respond.

Now, when I do my clinical work, I work in a hypertension clinic, even the Mayo medical students, God love them, know that it's beta blocker, diuretics, ACE inhibitors and calcium channel blockers. That's not the question. The question is for whom? Which one will respond? There we're not talking about life-threatening situations all the time, but we're talking about churning the system. So they keep coming back and, oh, it didn't work, and what are we going to do, even if we have the nurses doing it. We know that about half the patients won't respond to any of those drugs.

And that brings us back to this little diagram that I showed at the beginning. Clearly, with regard to the drug development process, the role of the Food and Drug Administration and the regulatory science becomes absolutely critical, and I made a joke about this at the beginning, but as a matter of fact it was not a joke. It was true. I have noticed that since Larry Lesko and Janet Woodcock have taken an interest in pharmacogenomics, and I've got one of their papers here, and we'll be hearing

from Felix about this later on today from the Food and Drug Administration, that since the FDA has been interested in this area, the pharmaceutical industry's interest has been increased.

There are tremendous differences among companies. Please, you can't generalize. But as a matter of fact, there was and remains some resistance to thinking about issues of segmentation of the market as a result of knowing at the front end which patients will and will not respond to a given class or specific drug agent.

At the translational science, we already talked about this. The involvement of this science in the drug development process is already going on. I know that. It is increasing. What that says is that all the examples I've given you -- thiopurines, irinotecan, warfarin for God sake, that's the 1930s -- these are all examples of drugs that were out on the market and academic science studied them and came to the conclusion that there were large genetic variations in their side effects or in their therapeutic efficacy.

Eventually, a great deal of this science will be built right into the drug development process. That has very significant regulatory and economic implications which I'm not qualified to deal with but which I'm sure we need to address.

Clinical trials are going on. Type "clinicaltrials.gov" into your web browser and go and look at the clinical trials, tens of thousands of them, and how many of them have pharmacogenomics built into them at the front end. Remember, you've already spent the money -- this is the point that Dr. Davis was making -- to create the infrastructure, to recruit the patients, to get the clinical data together, and you're drawing blood samples to send them off for an SMA-12 or whatever that's called in this day and age. So why don't we make DNA a part of that so that you can either prospectively or retrospectively go back and ask the questions Dr. Davis wants us to ask?

Part of the Roadmap was public/private partnerships. Within the Pharmacogenetics Research Network, we have been grappling with that. There are very significant issues of intellectual property and proprietary interests which stand as barriers, and we might as well just put all these issues out on the table so we can talk about them in the course of the day.

So we need to find ways that we can not just talk about this but actually find ways to deal with the unique problems of each side so we can deal with it.

Finally, legal, social and ethical issues. You know much more about this than I do. Confidentiality is just as big an issue here as it is with all other areas of

DNA testing, insurance perhaps a little less so because nobody knows, although we have tried, what TPMT is there for. It's found in bacteria, but we don't have any disease that if you are like that lady whose daughter works at Apache Mall and comes up and asks me about mom's enzyme, who has zero TPMT, we don't know that this means you're at risk for any disease. If we ever find that out, then this becomes an issue. But for many of these variants, that's less of a problem here, although it's still a problem.

Finally, what do I mean by "therapeutic activism"? This is not like BRCA1 or 2. If I find that a patient is homozygous for low TPMT, I want to lower the dose of the thiopurine. I can do something right then, either use the drug or don't use the drug, lower the dose or raise the dose so that in this situation there isn't therapeutic nihilism. If there's ever going to be a place where there's therapeutic activism, it is in the area of pharmacogenomics.

Finally, the issue that was raised just a few moments ago. This is from the New York Times October 10, 2004, "The Genome in Black, White and Gray," and what was the focus? It was entirely on pharmacogenomics. The issue related to the hearings today on BiDil, the drug that is being evaluated for the possibility of being approved for only one ethnic group, for African Americans, is being

discussed right here. I heard Francis Collins interviewed on Public Radio about that and heard his comments, which is that this is undoubtedly -- it's not skin color that's the issue but it's the underlying genetic variation, which showed these striking differences that I mentioned.

This keeps coming up. This is 2001 in the New England Journal of Medicine, where there were articles about ethnic differences and response to angiotensin-converting enzymes, and two editorials taking the kinds of diametrically opposed points of view that this committee knows much more about than I do. Here we are in 2003, New England Journal of Medicine, and it was deja vu all over again. We were having exactly the same discussion, and I come back to this just to point out that this common variant which is found in Caucasian Americans is not found in Asians.

When I was a visiting professor at the National University of Singapore, where the population is 80 percent Chinese, they said, Dr. Weinshilboum, this is a problem we see only with these European kids. What's the deal here anyway? They actually have developed the testing to use for Europeans. They clearly were devoted hematologists and oncologists that came to Minnesota in February to learn the techniques.

Finally, this issue of health care professional

educational. I heard what Dr. Davis said. The implication was pretty clear, and I will have to say that in a review that Li Wae Wong and I wrote in Nature's review of drug discovery, we said that this would be an important part of what we need to do. We were roundly pilloried by the sociologists at Cold Spring Harbor. I continue to believe, because what I've seen is, at our place the gastroenterologists, who see a thousand new inflammatory bowel disease patients per year, have totally embraced TPMT; that in hematology/oncology, the resistance is basically one that in that community toxicity is their business. Push the patients to toxicity.

So we need to realize that there are sociology differences within medical subspecialties, too. But if gastroenterologists are educable, I think there's hope for everybody.

(Laughter.)

DR. WEINSHILBOUM: Finally, I want to end where I began, by pointing out that this is only one factor among many factors that influence individual variation in drug response. The clinical goals are ones that no one can argue with. No physician wants to harm his or her patient. We all want to maximize efficacy of these drugs that come out of the therapeutic revolution, and it would be much, much cheaper if, at the front end, we could select

the responsive patients. Genetic inheritance is only one factor in the drug response phenotype, but the pace of our understanding is increasing dramatically, and the goal has already been demonstrated. We have examples out there that make it very clear that this will benefit our patients.

So the vision remains the same. Thank you very much. I hope I haven't gotten us too far off time.

(Applause.)

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 labelling 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.

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.)

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.

We now have our public comment session. As Reed Tuckson noted yesterday, one of our critical functions at each meeting is to serve as a public forum for deliberations on the whole range of health and societal issues that are raised by the development and use of genetic and genomic technologies. We set aside time each meeting and each day to hear from the public, and that's what we'll do now.

We have two speakers, and in the interest of our full schedule and the fact that we're tight on that schedule, I'd ask the commentators to keep their comments to five minutes, and if you have written comments, to please give us a copy of those so they can be entered into the permanent record.

Our first speaker is JoAnne Glisson from the American Clinical Laboratory Association.

If you would just come to the front, there's an open seat there. Welcome. Thank you for joining us.

MS. GLISSON: Thank you for having me.

ACLA is an association of independent clinical laboratories, national, regional and local laboratories. Our members include large reference labs and

small focused, esoteric labs. Independent laboratories and the laboratory-developed tests they develop and perform represent a key constituency in the development of this exciting new technology. We look forward to working with the committee as you continue your consideration of the issues associated with pharmacogenomics and its promise.

Thank you.

DR. WILLARD: Thank you. I appreciate your brevity.

Any questions or comments from the members of the committee?

DR. WINN-DEEN: I just want to make a comment on behalf of the group that tried to put the program together today. We didn't in any way mean to slight the reference laboratories that are doing lab-developed tests, and we recognize the valuable role that you're playing in this field. There just simply wasn't enough time on today's program to hear from all constituencies. We certainly would like to reserve the right to call on you for a future meeting.

MS. GLISSON: Thank you.

DR. WILLARD: Other comments from the committee?

(No response.)

DR. WILLARD: If not, thank you very much.

Our second speaker is Robert Yocher, who is vice president of regulatory affairs at Genzyme.

Welcome and thank you for joining us.

MR. YOCHER: Thank you. Thank you for the opportunity to comment on the exciting topic of pharmacogenomics.

We at Genzyme believe we are uniquely positioned to discuss this as a biotechnology company and who develops unique therapeutic products for unmet medical needs; and also as a laboratory service provider of genetic tests and clinical pathology.

The age of pharmacogenomics has started, but it's at its earliest stages, and like all science in its early formative years, the process is truly iterative. While there has been a handful of notable successes, for the drug companies in the pipeline now, it's really only the earliest few drops out of the pipeline. Most of the fruits of our efforts will not be realized for seven to ten years from now.

However, the agreement on the systems and the understanding of what the requirements are for the realization of targeted therapeutics which are now defined by pharmacogenomic testing, need to be in place now. Therefore, Genzyme believes the following are necessary strategies to understand the realization of the

full potential of pharmacogenomics.

First, we believe there needs to be a broad coordinated effort necessary integrating pharmacogenomics as this is a paradigm shift. All of key constituencies within the health care system need to understand the role of pharmacogenomics. There should be education of physicians and other providers to get them on board and thinking about it. There needs to be education of payers. Education is necessary on a number of levels for the foundation of pharmacogenomics as a concept, as a benefit to patients, and benefits to payers.

More importantly to this committee, there needs to be education and coordination of agencies throughout the HHS, FDA for the drug and test development, CDC and CMS for laboratory services, CMS for adequate payment, CDC for education, and NIH for the design of experiments and the new statistical approaches that will be necessary to lead these development technologies.

It's critical that the efforts between the agencies are coordinated, especially as new rules and recommendations are created. We cannot have new rules in one agency which are not consistent with the other agencies. For example, for biomarkers deemed valid by FDA, it should also be accepted by CMS as valid. There should not be two levels of evidence required.

Some other examples. There needs to be a shift in thinking about population means evidence-based medicine to targeted populations and cohort outcomes. The whole classic drug approach has been on centrist, large populations, and now we're looking at truly just the outliers. So there needs to be new statistical methodologies developed.

For instance, a prospective analysis of retrospectively collected samples in biobanks, and validation of these biomarkers. At the recent DIA/FDA meeting, NIH and FDA had a quite interesting discussion and came to no agreement on the process of how to do that. Terminology must also be agreed upon in organizations. Dr. Janet Woodcock stated in her presentation to the DIA and FDA workshop on April 11th of this year that further exploration of the concept of the framework is needed, and reassessment of the ideas of validation, and perhaps even adopting new nomenclature for validation.

We also believe that the government needs to pay to encourage innovation. Innovation is critical to moving the health care system forward. With the fast pace of medicine today, laboratory-developed tests are considered the state of the art diagnostic tests and are often the way that innovation occurs in the laboratory. In

many cases, manufacturers will not seek FDA approval through 510(k)s or PMAs for these products or devices because the routes are either not economically viable because the populations are too small, or especially since the technology is changing so rapidly and the pipeline is so long that by the time you get your test approved, the technology has passed you by, as was mentioned this morning.

For drug manufacturers, it's important to provide incentives such as label extensions or exclusivity for drugs associated with new pharmacogenomic tests to justify the additional development of cost and timelines. But in doing so, the regulatory pathways must be clear, predictable, and easy to implement. For pharmacogenomics to work, we believe that drug manufacturers must understand and recognize the benefit of creation of drugs that will be more targeted to the right patient for the populations, and therefore show better efficacy and safety.

We need to bolster the support of the current multiple approaches to diagnostic access, especially inclusion of laboratory development tests which right at this moment are not discussed in the early FDA models.

We have submitted more details in writing to this committee, but we've covered many of those topics this

morning, and we stand here ready to help assist you and volunteer in your efforts going forward.

DR. WILLARD: Thank you very much.

Questions from the committee, or comments?

DR. WINN-DEEN: Are you going to make your written comments available to us?

MR. YOCHER: They have been provided already.

DR. WINN-DEEN: Okay.

DR. WILLARD: Thank you very much. Appreciate that.

We are now at our lunch break. An announcement first for those who will be headed to the airport at the end of the afternoon. You should sign up for airport transportation at the registration desk to facilitate getting out in a timely manner.

For the lunch break, committee members and ex officios, the lunches that we ordered will be just outside, as they were yesterday. For members of the public, lunch is available in the hotel restaurant, as well as other restaurants in the area.

We will reconvene promptly at 1:30 p.m. and continue the session on pharmacogenetics. Thank you very much.

(Whereupon, at 12:27 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m.)

AFTERNOON SESSION (1:30 p.m.)

DR. WINN-DEEN: We're going to ask everyone to come in and take their seats so we can start the afternoon session. We have a lot of material left to cover, and we want to try to make sure we stay on time with this session as well.

The first part of the afternoon session we're going to hear a series of three short presentations representing the different agencies within Health and Human Services that are involved in work with pharmacogenomics.

Our first speaker is Dr. Rochelle Long, who is the branch chief with NIGMS, and she currently has oversight of the Pharmacogenomics Research Network and knowledge base, and so I think is in a unique position, having looked at all the applications that have come in, as well as working with all the funded researchers within the Network, to talk to us a little bit about the state of the art in that part of the world.

Rochelle?

DR. LONG: Thank you. I thank the organizers for inviting me. I'm the first of three panelists, as I understand, talking about research that is supported within the Department of Health and Human Services, and I'll be specifically talking to you about NIH, the National Institutes of Health, which is comprised of multiple

institutes. So I'll be giving you a survey of all the work supported by all the institutes, and then moving on to tell you a bit about the Pharmacogenetics Research Network, with which I'm personally involved.

What I did was start at the CRISP, which is the Computer Retrieval of Information on Scientific Projects, looked up and found over 400 different awards supported that have as their key phrases pharmacogenetics or pharmacogenomics. For today's talk, I will be just talking about extramural grants to the community outside of NIH. I will not be concentrating on the intramural program at all.

The green ones are basically training mechanisms, 40 career awards, 24 institutional training grants, and five fellowships. So this shows that people are thinking about pharmacogenetics/genomics when they comprise their training programs. The sort of peachy/orange area shows that there are 70 different cooperative agreements that list as key phrases pharmacogenetics/pharmacogenomics, and that's a relatively large proportion of 400. This includes some of the large multi-million dollar awards through the Pharmacogenetics Network, but also clinical trials, any time they're collecting materials from people and actually planning to do pharmacogenetic/genomic studies.

There also are 40 large centers and program

projects that tend to be concentrated at a single institution to delve into a scientific program, as well as two facilities and centers. There are nearly 200 individual research grants. Normally this is the bread and butter of the awards made from NIH, especially from my institute, the National Institute of General Medical Sciences. So I think the relatively large proportion of these large cooperative groups shows how it takes multidisciplinary teams and large facilities to approach problems in pharmacogenetics/genomics.

There also are a few small business awards, and again a relatively large number of conference grants where people want to discuss the topic.

As I mentioned, there are many institutes at NIH, and many of the categorical disease-oriented institutes are conducting large-scale clinical trials in their disease areas, identifying the genetic contributions to complex diseases. Many are banking DNA samples for subsequent analysis. This is one thing, by the way, that is not done as a network through the Pharmacogenetics Network. They're not banking them as a group in general, but I'll get back to that.

Almost all large efforts are promoting sharing tools for researchers to enable all researchers to do better quality research, and also promoting data-sharing

activities. This is definitely an activity that came to the fore in recent years at NIH, the idea being if federal government funds are being used to support the work, the results should be shared subject to privacy or HIPAA-type concerns because they're many times derived from patients or individuals, yet dating sharing is a concept that NIH wants to promote.

When I surveyed the different institutes, the National Institute of Mental Health specifically mentioned their STAR*D trial, Sequence Treatment Alternatives to Relieve Depression. Those samples are undergoing analysis for genetic predictors of who might respond to different drugs used to treat depression. They also strongly promote tissue repositories, and they do in fact have oversight for many different mental health disorders, collecting materials for subsequent human genetic studies.

The National Institute of Child Health and Human Development supports the Pediatric Pharmacology Research Units. They are clinical in nature, and they do include limited pharmacogenetic studies in some components at some sites.

The National Heart, Lung and Blood Institute is one of our major co-participants in the Pharmacogenetics Research Network. They've funded a significant number of multi-million dollar awards themselves over the last couple

of years. They also have had a large program called Programs in Genomic Applications, or PGAs, that support tools for researchers to use, be they clones, be they mice, be they statistical methods. But again, the emphasis is on tools and getting that out there for researchers across the nation, or even internationally to do studies.

The Heart, Lung and Blood Institute also supports sequencing services available for researchers. These are often sequencing, resequencing and genotyping services at this time, and they also support individual research grants. This is important to recognize because not all good research takes place at good universities on the east or west coast of the United States. Again, I come from NIGMS, and research grants to individuals do matter a lot.

The National Cancer Institute, as you might suspect, has multiple large adult and child clinical trial networks ongoing. They are beginning to think more proactively about planning to do pharmacogenetic analysis of samples, and I expect their greater involvement in the Pharmacogenetics Network with the next renewal. They also have a cooperative human tissue network. They also bank samples, and they also support individual research grants.

The National Institute of Diabetes, Digestive and Kidney Disorders also, again, has several clinical

trial groups particularly studying diabetes as a disease, and they have the drug-induced liver injury network of researchers setting protocols to collect materials from people who have experienced severe drug-induced liver injuries.

The National Institute of Aging supports clinical trials for Apo-E alleles and Alzheimer's correlations, sort of a classic predictor for complex disease, at least one component of it. The Human Genome Research Institute you probably recognize, supports the HapMap Project, using SNP blocks as a tool to look at the genetic contributions that contribute to variation in responses to drugs, and also vaccines and compounds in the environment. The big effort in the HapMap is collecting and identifying the SNP blocks correctly so that investigators can go on to do these sorts of studies.

The Human Genome Institute is also the center at NIH for the Roadmap Initiative on molecular libraries and developing sets of compounds that probe molecular space.

NIDA, the National Institute of Drug Abuse, also has several tissue and cell repositories. They make services available to researchers. For example, they're part of the Microarray Consortium available through what's called the Neuroscience Blueprint or group of NIH

institutes that come together to raise the research level for all.

The National Institute of General Medical Sciences, where I am based, historically has funded individual awards, most often studying drug-metabolizing enzymes because these enzyme systems are common to metabolizing many different classes of drugs. Therefore, it would be common for drug use to treat heart disease or cancer or depression, so it makes sense that the General Medical Sciences would want to support this research.

Starting around 2000, we started the Pharmacogenetics Research Network. Now, this is the way that the Pharmacogenetics Research Network looked from approximately 2001 to 2004. At this time there were six institutes participating. This initiative is undergoing renewal, and as of this summer it will come out for the next five years, starting in 2005. I'm pleased to say that we now will have nine institutes and offices contributing, so it's really becoming a trans-NIH initiative.

As I mentioned, historically NIGMS has supported research in the drug metabolism transporter area. You heard Dick Weinshilboum speak earlier. He has one of the pharmacogenetics awards to look at Phase II drug metabolizing enzymes. Another longstanding grantee of ours is Kathy Giacomini, who looks at the membrane transporters.

I'll point out that each of these groups was charged with putting together an interdisciplinary team. So here you see somebody from pharmaceutical sciences paired with somebody from a genetics background, and the very best groups that competed through this initiative brought people with pharmacological and people with genetics/genomics backgrounds together, along with people who knew statistics, along with people who could look at samples from clinical studies. You need large teams to do this kind of research.

Besides working in the metabolism and transport area, we have had groups looking in the cancer area both at breast cancer and at colorectal cancer, and at leukemia in children. Howard McLeod also works in the colorectal cancer area. We had a number of groups, as I mentioned -- NHLBI was a good supporter of ours right from the start. These researchers are looking at both cardiovascular and pulmonary diseases, looking at compounds or drugs that lower cholesterol levels in the blood, looking at anti-arrhythmic agents, looking at anti-hypertensive agents, as well as looking at drugs used to treat asthma.

It's interesting that many of the investigators coming from this side of things, again the historical NIGMS side of things, proposed what I would tend to call

genotype-to-phenotype studies. They had proteins, they had families of genes, they had families of proteins of interest, they were looking at variation, and they were trying to find out what that meant functionally.

Interestingly, when we had the first competition for the Network, a lot of people also came who had very interesting patient samples. So they saw people in their research clinical situations that responded differently to drugs, and they wanted to look at the genetic contributions to that effect. So I call these more of the genotype-to-phenotype type of studies, where they're trying to find the underlying genotype or types or haplotypes that go with their clinical observations.

The Network is united by PharmGKB, which is a knowledge base. I'll tell you a little bit about that in a moment. PharmG stands for pharmacogenetics or genomics. KB, knowledge base, meaning they are trying to interpret what the functional implications, what the clinical implications, what the medical decisionmaking points ultimately might be for predicting responses to drugs. But I must emphasize that PharmGKB was and still is conceived as a research tool. It is not yet a place that a common practicing physician can just log right in and figure out which drug to give to that patient. We're not there yet. If I leave you with no other thought than this,

keep in mind that there's a lot of research that needs to be done to accurately predict what the genetic contributions to predicting drug responses are.

We also supported a local informatics award that helped these groups get started to put their research results into PharmGKB, and we supported an award that specifically looked at the implications of pharmacogenetic/genomic studies for minority populations.

This is PharmGKB. This is a pretty recent slide. It shows you that any researcher can come to it, can browse through genes, can look at primary data, can look at pathway pictures -- you saw one of these earlier with Dick Weinshilboum's talk -- can enter simple queries, and they can start to pull up data. As soon as data become human data, you do actually have to have a password to access the site. For example, you need to have a valid research purpose. It's not hard to get a password. You just have to describe your research program.

I also want to emphasize that none of the information here is individually identifying. If it gets down to a granular level, that it's a person with red hair in Chicago with a certain sort of rare cancer who came into a certain study at a certain time, no. So a lot of thought has gone into this to ensure that it is ethically and legally compliant in all the most modern and appropriate

ways.

The Pharmacogenetics Research Network at the present moment, their primary emphasis is on conducting cutting-edge research. You will see their papers from their individual lab groups published in both basic and clinical areas and journals. They are really working on establishing the knowledge base PharmGKB and actively depositing their data sets for genotypes and phenotypes and correlations between the two. They're working to develop pathway displays that can very easily pictorially display pathways of drug clearance and mechanisms. There are almost no drugs that I can think of that you take that just encounter one single gene as they go through the body, one single protein. It's that spaghetti diagram concept again, trying to represent research knowledge.

I do want to emphasize that this is open for scientific community submissions of data. So it's not a network-only tool. It's available to all researchers.

I think this group is still learning as a network. Early on they worked to devise policies. For example, what should you put in an informed consent for somebody whose research data ultimately will show up on a website, and is that different than just a scientific publication? They worked to develop intellectual property policies that were not encumbering. In other words, they

were asked to deposit their data relatively early on, but the strategy developed was actually to encourage provisional patent applications, because people want what is important and meaningful to be able to be commercialized, and yet that doesn't mean the research results can't be shared with others.

They are developing principles, looking at ways and comparing ways to do clinical study designs, looking at statistical analysis and ways to do more and more efficient experiments, and this is a very interesting and active area of the Network.

I'd like to point out to you that another aspect of the Network is for them to share their work with everybody in the research community. They are working right now on authoring a series of four white papers, the first one being an overview where they will discuss what are the cutting-edge problems, issues, barriers, obstacles to do pharmacogenetic studies, and have some recommendations in that paper.

The second paper is actually looking at pharmacogenetic testing and for research purposes what needs to be done, what are the considerations and, by the way, how will this fit into an ethical framework, how will this fit into a regulatory framework. But the emphasis for this group is, again, research, getting good, meaningful

results.

The third paper is actually going to deal with guidelines for educating professionals in the area of pharmacogenetics/genomics. That would include physicians, but that also might include pharmacists or others who are part of the medical care team.

Each of these papers ultimately will be targeted to the appropriate journal to get the word out to the community that should be hearing some of this thought and discussion process.

The fourth white paper tentatively is in the area of doing association studies in pharmacogenetics/genomics and what is unique and different than, say, simply doing studies that might concentrate less on drugs and predicting drug effects. I've seen draft papers, I've seen draft outlines. I really expect them to be hitting the streets in good journals probably over the next couple of months or so.

This network has also worked to generate and donate sample sets to the repository. I want to particularly credit Julio for some of this work, collecting materials from individuals from Hmong Chinese communities and from Mexican Americans in greater Los Angeles. There was extensive community consultation that took place and a real effort on getting samples right and having people know

they're going to be used for research purposes, and understanding they might not personally benefit but that ultimately better work could be done in the field because of it.

Finally, many members of the Network are members who do testify sometimes in front of FDA hearings. They have the knowledge, they have conducted the studies, and I feel that their work fundamentally contributes to some of the efforts at the FDA to change labels for drugs on the market and will continue beyond as they discuss ways they might interact.

So I will conclude my talk just by pointing out that it was our institute that commissioned and actually had two publications that you have as brochures out at the table. One is called "Medicines for You," the other called "Genes and Populations." These were developed to actually encourage people to understand the purposes of research and help them make decisions about joining research studies. They were just done as thoroughly as my institute thought it was possible to do. They're available free. I encourage you to take copies and go back and request more if you'd like them for any purpose.

That concludes my talk. I would be happy to take questions or delay them to the panel, however the organizers think is appropriate. Thank you.

DR. WINN-DEEN: We're going to have the three HHS group talks, and then we'll have a sort of open Q&A to all of you at the end.

Next on our list is Felix Frueh, who we met informally earlier today. We called him up to answer some questions on FDA. He's going to talk to us about the specific efforts within FDA to develop guidance documents in this area.

We apologize in advance for putting you on the spot for all things related to FDA and CDER, but you're the chosen victim, I guess, or the sacrificial lamb.

DR. FRUEH: Well, I would like to thank the committee for giving me the opportunity to present an update on FDA's guidances as they relate to pharmacogenomics.

It was funny. I was three days ago presenting at a targeted therapeutics summit, and the person that introduced me had a graphic of sort of all the stakeholders who have an interest in pharmacogenomics shown in a circle. At the bottom, with the writing upside-down, were the regulators. Then I saw Dick today showing a slide again where the FDA was all the way at the bottom. I was quite surprised, actually, that Eric then show the slide where the regulators were on the top. So I think we're making progress.

I'd like to give you a little bit of an update on what's going on. The role of the regulators. Pharmacogenomics was identified in the critical path initiative at the FDA as one of the key opportunities on the critical path to new medical products. What we need to realize is that this is really a play of two partners. It's the drug developers, and it's the device companies or the creators of devices that need to work together. So pharmacogenomics combines drugs, drug therapy, with diagnostics, and the regulation of both need to adequately reflect this thinking.

I think FDA made it very clear over the past couple of years that we take pharmacogenomics seriously, and we have put forward a series of guidances that illustrate the current thinking that we have in the field, and I would like to go into this. This wasn't meant to be read. This was just to illustrate that we have a website up that deals with genomics at the FDA at which you'll find all the information, the guidances and additional background information that we currently have. The talk is going to be split into basically three sections. I'll talk on the pharmacogenomic data submission guidance that was mentioned earlier. We'll talk about two device guidances. Then I would like to combine these two aspects into drug test co-development guidance, or a concept paper

as it is now, that was also addressed earlier today.

Earlier in March of this year, after about an 18-month gestation period, guidance for pharmacogenomic data submissions was published, and we've gotten since a very good response from industry to it. We continue to receive comments to the guidance which are very useful.

Why is this guidance important? The guidance does a couple of things. It illustrates the FDA approach to review of genomic information, so it should facilitate review decisions. It's a guide to drug development. It empowers the FDA to make drug development more efficient, and we provide several news ways for how to interact with the FDA. It's a means for fostering targeted therapy. It's also a new communication tool. It's an encouragement to share information on a voluntary basis for the first time with the FDA, and we have again gotten very good feedback on that, and I will go into that in a minute.

It's also an outreach to stakeholders that have expressed great interest and support in this guidance. So it really was a guidance that wasn't just showing up somewhere on an FDA website, but it actually has made headlines also in the lay press. So it was a very powerful tool for us to start communication with stakeholders that otherwise wouldn't have gotten involved in that dialogue.

The guidance introduces a classification of

genomic biomarkers, as mentioned before. It clarifies what type of genomic data needs to be submitted. It introduces a new voluntary submission pathway, and it encourages industry to use it. So it's not a guidance on just a voluntary part, but it really shows how genomic information can be conveyed to the FDA and, if one desires to do so, on a voluntary basis for a certain type of data.

It introduces a new agency-wide review group, the Interdisciplinary Pharmacogenomics Review Group, and it clarifies how the FDA deals with the data.

The guidance does not provide information on how to validate genomic biomarkers. It does also not provide information on how to use genomic biomarkers. We limited the guidance with intention to genomics at this point, although if you read the guidance and you replace the word "pharmacogenomics" with "proteomics" or "metabolomics," I think many of the concepts, if not all, would still apply.

I mentioned that the guidance addresses not just voluntary data but also requires data submissions, which is the main focus of it. Most importantly for industry is that it does not create new processes for the review of data submissions. So it uses the existing framework that we have and puts the genomic data in that existing framework.

The voluntary data submission pathway is a submission pathway for what we call exploratory data, regardless of whether or not that is part of an existing or an active investigational new drug application or a new drug application. It's intended to build expertise and the foundation for developing scientifically sound regulatory policies. So we want to lure them with these submissions.

It creates a forum for scientific discussions with the FDA outside of the regular review process. The data that we discuss in that voluntary forum is not being used for regulatory decisions. So it's really an interaction between the scientists at the FDA and the scientists at the industry or at the company without the regulatory overhead that usually persists in FDA-sponsored interactions.

We received the first submission in March of '04. We have about a dozen submissions received since. Several more have been announced. So I would say the program is well underway and it's been successfully started. We have an evaluation of pretty complex raw data, such as microarray data, that we are engaging in, and the dialogue along with that evaluation has been critical to understand and learn what they're doing.

I think the success is illustrated also by the fact that the two companies that submitted the first two

voluntary submissions are actually coming back -- one of them already has come back, the other one has announced -- with a follow-up submission. They've been doing some work in the meantime and they want to get our input again.

It's also been an outreach already into other geographic areas. We've had the first meeting with the European regulatory agency in May of this year, and the Europeans as well as Japan have published pharmacogenomic guidances. The interest definitely is growing.

CDRH has issued a guidance on the instrumentation for clinical multiplex test systems. We're moving now to the device arena, which is a device -- and the definition here is coming from the guidance -- a device that is intended to measure and sort multiple signals generated by an assay from a clinical sample. It's used to the specific assay to measure multiple similar analytes that establish a single indicated diagnosis. So it's really targeted at what we've been hearing a lot about, the microarray field, and for giving a specific example, the AmpliChip.

Now, these technologies are a two-component system. So the second CDRH guidance talks about the actual device and not just the reader, and this specific guidance goes into detailing and providing information on such devices that are intended for use in testing DNA to

identify the presence or absence of a human genotypic marker. The device itself then is used in an aid in determining the treatment choice and individualizing treatment dose for therapeutics.

We've seen that before. The point I want to make here is that this really for the first time has set a new paradigm in how FDA is looking at such devices, because these are multiplex devices, these are highly complex devices, and we no longer have the option to just look at every single data point itself but we need to look at it in a combination, and with the complexity comes a new challenge on how to review these devices.

For the three bullet points, we've heard a lot about them this morning, so I don't need to go into the detail of that.

Now, if you want to put it all together, we need a strategy to combine devices and drug development process, and in April of this year we published a drug/test co-development concept paper. The comment period for it is still open, and we're planning on issuing a draft guidance on this later this year.

What this concept paper does is really put into perspective a couple of things. If we're talking about biomarkers, we have in the basic research arena the identification of the target, the target validation, and

then we move that biomarker along the drug development pathway all the way to what is hopefully an approval. The critical aspects are that early in the process we consider the label based on the marker status, and we visit that often during the development pathway so that we have a label that reflects what we actually see in clinical trials. So that clearly becomes a strategic issue for the company developing tests and drugs simultaneously, and we touched a little bit on this earlier this morning.

What is critical in this process is that this is an interaction between the device area, CDRH, and the drug development area, CDER or CBER. This again puts in perspective what is going on during the drug development process and provides tools and information to exchange opportunities between sponsors and the FDA, and if we're talking about the strategy for how to do these things, I think it's critical to overlay these so that we have a smooth process for how to develop drug/test combinations.

The voluntary submission process is a process that can be used throughout the entire drug development pipeline to discuss novel and exploratory findings that perhaps at some point might actually help in the area here to identify novel biomarkers and characterize them.

The benefits of this approach are, I think, obvious to us. We can use it for patient

stratification. So that's an efficacy as well as a safety issue. We can use it for enrichment purposes in clinical trials. The labeling becomes a critical component of it, and it can be crucial for a company to bring the product to the market. I think the example of Herceptin really illustrates that only in the presence of a targeted therapy, the product could be approved. It has the potential to save drugs from being withdrawn from the market, and it can also potentially rescue candidate drugs that otherwise would be stopped in the drug development process.

Strategy, competitive advantages, timing, cost, availability of alternative therapies, the platform choice, and the complexity of the platform itself are all critical issues that need to be addressed during the process. Ultimately, whatever is coming to the market needs to be clinically useful. Otherwise, why develop it in the first place? Often that's actually the bottleneck. So showing the clinical usefulness for the drug/test device at the end is critical.

In summary, the FDA encourages the use of pharmacogenomics and provides a series of tools, such as the guidance documents, meeting opportunities to support the translation of pharmacogenomics into clinical practice. The combination of drug therapy and the use of

devices is critical, and we are developing our guidances with this in mind. Pharmacogenomic data submission guidance, the one that was issued in March of this year, has been well received and is currently being successfully implemented, and regulatory agencies around the world are interested in pharmacogenomics, and I think it's fair to say that the U.S. FDA is really leading the way on how to do this.

I would like to thank my colleagues in CDER, CBER, CDRH, and in particular Drs. Janet Woodcock, Robert Temple, Larry Lesko, and Steve Gutman, all of whom have been really visionary and critical in making all this happen. This is the address for the website where you can find all these documents in writing. At the end, I put up a couple of questions for the committee for perhaps the discussion that we have at the end of this series of talks.

Thank you very much.

(Applause.)

DR. WINN-DEEN: Thank you.

Finally, we'll hear from Muin Khoury, whom most of you know very well. He's our representative on this committee from CDC, and he's going to give us an update on the EGAPP project.

DR. KHOURY: Thank you, Emily.

I guess being the last speaker in a long list

of speakers, probably by now everything that needed to be said has been said.

I have to apologize to some members of the committee because you've heard about EGAPP before, but there are some new members, and the context is pharmacogenomics, and we've made some progress on the initiative. It seems that the word "EGAPP" keeps coming up, so I wanted to tell you actually what EGAPP is or is not and see how it would work in the context of pharmacogenomics and have some discussion about this.

All these points have been made before, but we can run through them very quickly. It is a public health issue because potentially it can affect a lot of people, so public health worries about the population's health. The potential for targeting prevention efforts and avoiding side effects. We heard this morning that about 100,000 people die yearly from adverse side effects. So clearly, it's a population-relevant issue.

The need for evidence-based transition from research to practice. You heard Dr. Davis this morning talk about that transitional translation, if you will. Implementation and access has a big thing to do with respect to access to the right services and the right tools, providing public education, et cetera. So pharmacogenomics does provide a potential for early

application of genomics to population health. I may be a bit biased here, but I think pharmacogenomics is moving probably more quickly than other fields of genomic applications, with the exception of the world of single-gene disorders, which is fairly well established.

Now, at the CDC we have a role in protecting the public from bad things, like infectious disease outbreaks, but we also want to use whatever technology is available to improve the public's health, and we do a lot of activities that Dr. Davis mentioned this morning under the rubric of surveillance. So, for example, when the BRCA1 direct-to-consumer advertisement campaign happened in four cities, we did a survey in four cities that we talked about briefly yesterday. We also have our finger on the pulse with respect to the potential public health implications and impact of genetic tests in general.

So a couple of years ago some of us did this paper for Genetics in Medicine. It seems now a long time ago. There were only 751 genetic tests at that time, and we deemed at the time that a very small fraction had immediate public health implications or impact, and there were no pharmacogenomic tests, at least in that database.

So I wanted to describe to you a bit where we are with EGAPP and how we got here. Sometimes it feels like an uphill sort of struggle here to get to where we

are. On the right-hand side you have all these committees that have been meeting over the last few years that have been essentially, in one way or another, asking for HHS and CDC in particular to do something in this area. Our responses over the last few years are represented on the left-hand side. Early on, after the NIH/DOD task force report by Tony Holtzman, et al., we put together a number of interagency HHS data working groups to figure out what kind of data are needed to make that transition from research to practice, and how to monitor the impact in terms of postmarket surveillance.

After the SACGT report in 2000, we started the ACE project. I don't have time to go through this, but it laid the foundation for the kinds of questions that we could query all genetic tests, from soup to nuts, from the analytic performance in the lab all the way to the ethical issues. Most recently, this year, early last year, we started the EGAPP initiative, which we hoped would be a more sustainable effort, because we've learned a lot collectively both at CDC and in collaboration with our HHS agencies as well, and in consultation with a lot of folks from academia and the private sector.

So at this point we are launching into this three-year model project whose goal is to establish and evaluate a sustainable, systematic evidence-based process

for assessing genetic tests and other applications of genomic technology in transition from research to practice. So you can see that pharmacogenomics is squarely in here.

You've seen this complex diagram when Dr. Linda Battey from our office presented this, maybe not last time but the time before. But to cut a long story short here, the basic infrastructure behind the EGAPP is an EGAPP working group -- that's the circle in the middle -- which is a non-federal multidisciplinary independent working group that interacts with stakeholders, and there is a wide variety of them, from health care providers all the way to regulation labs, industry, et cetera, and requests evidence-based reviews that are done essentially by evidence-based centers, and these evidence-based reviews identify gaps in our knowledge, and some of these, depending on what is returned back to that committee, they would do deliberations, they would disseminate recommendations and reports to audiences.

The two immediate target audiences for us are consumers and providers. This is not a regulatory process by any stretch but more of a voluntary, sort of educational leveraging process. For those few tests that will emerge, we could refer them for more direct appraisal by the U.S. Preventive Services Task Force and the Community Preventive

Services Task Force that are housed at AHRQ and CDC respectively.

Those two committees, those existing task forces that have been sustainable and have demonstrated their usefulness over time, have not been taking on too many genetic tests. I mean, they have a lot of applications in medicine and public health they're taking on. They've been reluctant to take on genetic tests for two reasons. One, again, the volume of the load. The second is that the framework for evaluating genetic tests hasn't -- they use the medical model of immediate clinical benefits to persons, and for most of them, I'm told by members of different committees, that they would return uncertain or incomplete evidence for most genetic tests that exist right now, and we don't want that to happen necessarily. We want essentially to describe what we know and what we don't know, and then leverage and do the pilot projects and data collection projects that would allow us to essentially round out our knowledge so that we can move genomic applications faster in practice.

So, in other words, we don't want this to be necessarily a bottleneck that says don't do this, but this is what we know, this is what we don't know. In order to do what's right, more research needs to be in this area.

So the EGAPP planning objectives were to work

to implement the previous recommendations for actions from the previous committees, the tremendous knowledge that's been gained from the ACCE model project, which I can answer questions about if you have, the existing processes that already exist for evaluation and appraisal, health technologies from the various groups, and the international experience, because the U.K., Canada and other groups have a lot of efforts underway. We want to create a transparent process, announcing and reporting the process, developing and publishing the methods, and provide clear linkage between evidence and conclusions/recommendations.

We want to develop and disseminate information that's useful to health care providers and consumers, and secondarily to policymakers and the payers and purchasers, and in appropriate and practical formats. So a key objective of this process, which is only a three-year experiment right now, is to evaluate and develop hopefully a sustainable process.

So what have we done so far? In January of this year we held an expert meeting on evidence-based reviews of genomic applications where we had 21 invited participants from around the world, and people from evidence-based medicine, health care, genomics, epidemiology, ethics, et cetera. We considered existing and potential methods for systematic evaluation of genetic

tests and genomic applications.

We had established the working group, this independent non-federal working group, after broad solicitation and nominations in February and March, with great response from both professional organizations and individuals. We have an interagency steering committee represented by the membership here, an alphabet soup of the federal government, and we did a full review. The process was completed late in March.

The EGAPP working group is represented here. Let me just tell you that we have a world-class slate of wonderful people here. The committee is chaired by Al Berg, the chairman of the Department of Community Medicine from the University of Washington, who was the ex-chair of the U.S. Preventive Services Task Force. Not only do we have the ex-chair of the Task Force, but we have the current chair of that Task Force, Ned Calonge, from the Colorado Department of Public Health. These are all self-nominated people. We didn't have to twist anybody's arm. We have geneticists, we have ethicists, we have evidence-based people, we have clinicians, we have laboratorians, and we have economists and public health people.

So the working group was established. We had our first meeting May 18-19, a few weeks ago, and

immediately that group went to work. They are scheduled to meet three or four times a year over a period of three years. They've formed three subcommittees to decide on potential topics that they want to take on with respect to evidence-based reviews.

Now, notice that the federal government has no real influence on them. There are lots of stakeholders that can suggest topics, and we can take pharmacogenomics to their table, and I suspect, having heard some of the discussion that occurred in May, that they might want to tackle at least one or two pharmacogenomic tests.

The second subcommittee is working on finalizing the analytic framework, which was started in the January meeting, and that's very important. They have a subcommittee that's working on outcomes to be considered. But because most of the U.S. Preventive Services model is a health outcome model, whereas in genetics and genomic applications, in addition to health outcomes they might want to consider patient and family-related outcomes and some of the ELSI issues that usual technology doesn't have.

The second meeting will be July 18 and 19 in Atlanta.

What was also done already is we want to begin -- they decided as a matter of priority with respect to the

application of genomics is to look at the ones that are recognized as common and important, like screening tests, those that are used in clinical scenarios to guide interventions, like diagnostic workup, treatment, prevention, including pharmacogenomic tests, tests with potential public health impact, and move the focus towards prevention.

Some of the less likely candidates are newborn screening because there are existing processes in the federal government; namely, a second advisory committee on heritable disorders that is actually tackling newborn screening head-on. In the world of single-gene disorders there is a separate process led by the Office of Rare Diseases at NIH and the CDC folks to deal with rare diseases.

The conducting of evidence-based reviews on topics selected by the working group would be essentially started in July, and the evidence-based processes will start in August and September. Throughout the last few months we've been engaging lots of stakeholders, with emphasis on providers and consumers. The contractor that's working with us, RTI, has done preliminary survey and research on the stakeholders list, that keeps growing. We have feedback in terms of newsletters. The first newsletter appeared on May 6th. And active solicitations

for years 2 and 3 is going on. This really has been so far a model partnership with our sister agencies. I can say that with no reservations.

One of the things that we want to do is, depending on the gaps in knowledge that are found, we want to influence the funding process and conduct pilot data collection studies, first retrospectively to look at available data, and some of the ideas of networks and all of these things can be leveraged that you heard about throughout the day, from the Pharmacogenetics Research Network and other efforts that NIH and others have. What we are also doing is developing and implementing a comprehensive evaluation plan that not only evaluates the process but the products, and the impact and value to the health community.

So there are two overall types of products, both from the working groups. Their published methods will be out there, the criteria and prioritized list of topics, the approved evidence-based reviews, the conclusions and recommendations and lessons learned. From the project overall, we want to obviously disseminate the working group products and the targeted information and messages, but also derive information from stakeholders on the value and impact of this process, and then data from the pilot studies.

So again, I whipped through this very quickly, and because of the lack of time I think I'm going to leave you with this image of sort of an interactive process that I think is going to be tackling pharmacogenomics as one of its early things. One thing to leave with you is that this is sort of a step in a long-term process that I'm hoping the public sector and the private sector and academia will come together in trying to apply to pharmacogenomics and other genomic applications. Thank you.

(Applause.)

DR. WINN-DEEN: Thanks, Muin, for that update.

Because these talks have run a little longer than we had budgeted, what I'd like to do is maybe take one or two questions while our next speaker is getting set up for her talk. If I can put you on the spot, Dr. Deverka, to come up and get your slides going. Then we'll take Q&A for all four members of the afternoon panel immediately after her talk.

Is there anybody that has an urgent question you'd like to address to the HHS agency speakers at this point?

Kevin?

DR. FITZGERALD: Just a quick one. Particularly in the FDA presentation, but also in some of the other ones, when you're talking about clinical

benefit or therapeutic benefit or something like that, is there a specific definition that is used to apply to that? And I guess in part I'm thinking of something like recombinant human growth hormone for children who are projected to be of a certain height or less, and I know that was very controversial. I presume when we get into this kind of thing, more of those controversies are going to come up. So is there a definition that you're using, or a threshold?

DR. FRUEH: There's no generally applicable definition. I think the definition is looked at on a case by case basis. I mean, you're looking at the outcome, at the benefit/risk ratio every time you're approving a drug, for example. So you're really basing it on an estimate on what at this present time makes the most sense to approve a drug or not. So I think that applies for co-development situations as well as for the regular drug application process as we have it today.

DR. WINN-DEEN: Did you have a question or a comment?

DR. LICINIO: A suggestion.

DR. WINN-DEEN: Okay.

DR. LICINIO: Which is actually to Rochelle, and I should have said this to you before, which is that at the NIH, the National Center for Research Resources has

this large program of GCRCs, some of which, just a couple I think, have pharmacogenetics cores. Do you think there's any movement at that level to increase pharmacogenetics within the context of patient-oriented research?

DR. LONG: I think to coordinate with other groups that are doing activities in the same area makes good scientific sense. Insofar as those efforts are possible, we are trying to identify different groups and coordinate them. For example, in the research grant applications you're asked to define who else is doing something at your institution, and reviewers look to see have you formed the right teams and maximized your potential to do good quality research studies. Beyond that, it's a matter of networking, getting the right people together, and if there's benefit to both, they usually do want to start talking.

DR. WINN-DEEN: We'll pause in the Q&A for the agencies right now.

I'd like to introduce Patricia Deverka, who is joining us from Duke's Institute for Genome Science and Policy, where she's a fellow in the Center for Genome Ethics, Law and Policy. She's going to talk to us about some of the ELSI issues that we might want to consider as we look at the field of pharmacogenomics.

DR. DEVERKA: Thank you, Dr. Winn-Deen.

I'm very pleased to be here today, and I thought I might preface my remarks with a brief personal story. I was really gratified to hear Dr. Davis this morning talking about the need for large observational studies and practical clinical trials to be conducted to more clearly study the association between beta-adrenergic receptor polymorphisms and asthma treatment outcomes. I agree strongly with that proposal and actually put together an outline for such a large observational study when I was working at a large pharmaceutical benefits management company, MEDCO.

About four years ago, MEDCO had asked me to evaluate this new emerging field of pharmacogenomics and what it might mean for MEDCO's client base and its business model. As part of that evaluation, I visited a number of small start-up companies that were working on pharmacogenomics both in an attempt for me to learn more about the science, as well as to understand how new pharmacogenomic tests would be brought to market.

It was clear that what was missing was strong evidence that it was worth doing pharmacogenetic testing in a real-world sense, and it seemed to me at the time that MEDCO would be a good real-world laboratory to efficiently study an emerging area in pharmacogenomics, and asthma was a disease that was highly relevant to MEDCO's

clients. They are essentially pharmaceutical benefit plan sponsors, and they're primarily comprised of large employers, managed care organizations and insurers.

So I proposed this study. It took advantage of the fact that MEDCO has access to the drug claims data on millions of individuals, and access to medical claims data. I took advantage of the fact that I'm a health services researcher, and I thought that we could use that to identify people who both had a diagnosis of asthma and were exposed to albuterol, a short-acting beta agonist, as well as other drugs, and then very efficiently we could follow them forward in the claims data to see how many times folks with a certain genotype had evidence of an asthma exacerbation.

What you can see is missing there is where would I get the genotypic information from, right? So the claims data are great, but you never have genotypic information. So what we actually proposed, and we went through a long process to be sure this could be done ethically, was that we would invite eligible patients to participate in the study. If they gave us informed consent, we would actually mail a buccal swab to them, and they would swab their cheek and mail it back, and then we would do the genetic analysis, integrate that information with the claims data, and be able to track asthma outcomes

on thousands of patients very efficiently.

Well, I also thought that asthma was very relevant because a lot of payers are very concerned that asthma treatment is expensive and, in fact, purchase asthma disease management programs regularly in an effort to improve asthma outcomes. So I shopped the study around to a handful of MEDCO's most forward-looking clients, and I did this over a couple of years, and, I've got to tell you, I was turned down by everybody. It was not that they didn't agree that the science was compelling, and it's not that they weren't interested in improving asthma outcomes, and it was not because they had to pay anything to participate. They didn't.

They primarily said no because of their perception of the ethical, legal and policy problems associated with inviting their members to participate in such a study. So since I was a passionate supporter and remain a passionate supporter of the field, I decided to pursue formal training to see if these concerns were well founded and, if so, what could be done to develop practical policies that would address these concerns while simultaneously advancing the science. So hopefully that provides a little bit of context for my remarks today.

A couple of the folks today said that pharmacogenomic testing represents a paradigm shift in

health care. I want to beg to differ. I don't actually think it's a paradigm shift, and I think that's good because if it's not a paradigm shift, then we have lots of tools and experience available to us, as well as ethical rationales for any policies that we would develop.

The idea of stratifying patients on the basis of risk factors is not new. Certainly we know that people with elevated cholesterol, elevated blood pressure and who smoke are at increased risk of cardiovascular disease relative to folks who don't. In fact, we have for years tested women with breast cancer to see if their tumors were ER-positive or ER-negative, and that would modify treatment accordingly.

I actually think that some of the excitement about pharmacogenomics is due to the fact that it's really the first functional technology to come from what has been an enormous public and private investment in the Human Genome Project, and I think some of the concerns and the idea that we actually need a novel framework to deal with these ethical, legal and policy issues comes from the fact that pharmacogenomics brings three controversial areas together.

Firstly is genetic testing. I won't belabor the point, but clearly with the sad history of eugenics in the United States and people's concerns that flow from

that, that's one reason why genetic testing is a sensitive issue. The idea that somehow DNA is special, is uniquely predictive, the idea of genetic determinism floats through all of these discussions, and I think the pharmacogenomics challenges, the traditional approach to genetic testing for disease susceptibility, predominantly in the past for rare disorders, because people are thinking that we're going to have to do pharmacogenomic testing in primary care settings where genetic testing is not being done today and people aren't sure that we can just pour the same models into the primary care setting that have really been done so well in a handful of experts.

Drug exposure is very common. About 70 to 80 percent of people who have access to prescription drug benefits fill at least one drug prescription a year.

I think the other issue is managed care as a significant actor. They're sort of characterized by their cost containment focus, and I think that's why people don't trust them, and here I don't just mean private payers but also public payers like CMS. Clearly, with the Medicare prescription drug benefit, they're going to be a big player in this field of personalized prescribing, and with their cost containment focus, their traditional approaches of managed care, like creating restricted formularies or using therapeutic substitution, really runs counter to the ideas

of personalized prescribing. So people are concerned that these may be barriers to market entry for pharmacogenomics in the most appropriate way.

Then finally we have the pharmaceutical industry. I think it goes without saying that right now especially they have a rather poor public image. I think people don't trust them predominantly because of their concerns that they haven't been transparent about the safety issues of some of their drugs, that they haven't published fully all clinical trials, that there may be concerns over the high prices being charged for drugs.

What we are not sure about is whether they can be trusted to do the right thing with pharmacogenomics, or are they going to cherry pick certain aspects of the field in order to address their pipeline and profitability problems.

So what I'd like to do for you today is to really break my talk into three areas, and the last one I'll spend very little time on. Being definitely the last speaker, I think I can skip over a lot of the points I was going to make. So I think there are a number of ethical, legal and policy issues on the research front, and that could be either with new drugs or with existing drugs. I think there's a whole series of issues in clinical practice, and then finally postmarketing surveillance,

postmarketing surveillance about the performance of the test as well as the drugs that are associated with those tests. But I'd say here I'm not going to go into a lot of detail because I believe the current system would require major redesign and large investments to do that in the near term.

So what are the concerns in clinical research? What I tried to do today is to provide you a fairly detailed list or a comprehensive list of what the issues are, but I'm only going to go into a couple of them in detail for purposes of illustration, and I chose ones that I thought you might be most interested in.

So one I'm going to talk a little bit more about is informed consent in the era of DNA banking. Informed consent is the primary mechanism by which we protect human subjects in the research setting, and people have argued that we need to modify our framework for informed consent with the notion that we're going to be creating these large biorepositories.

There's a whole series of privacy and confidentiality concerns. The degree of concern varies with the degree of anonymization. So if the data are identifiable versus coded versus permanently anonymized, clearly our concern about these issues differs. What are the procedures to limit unauthorized disclosures? It's

very common now to use sort of trusted intermediaries that are essentially the gatekeeper between the supply of the information from patients, and ultimately the researchers, and the information is coded.

Then the potential for discrimination. Here I specifically mean that folks have described that maybe pharmacogenetic testing would reveal a group of patients that would not respond to a drug, and if that was potentially the only drug to treat a serious condition, that could be very problematic because a lot of people might be concerned that you would be more expensive because you have essentially a more serious or untreatable form of the disease.

Harms to families. This should say harms to individuals, families or groups. Collateral information. What I mean by that is whenever you do pharmacogenetic tests, you just don't learn about that. You also can oftentimes learn about disease susceptibility. For example, when you test the Apo-E4 gene, it gives information about how someone would respond to statin therapy in an effort to lower cholesterol, but that also can give information about susceptibility about Alzheimer's disease.

Then finally, another category would be race-related information. I am going to go into a little bit of

detail since BiDil has frequently been linked to the field of pharmacogenomics, and a number of our speakers have talked about that today.

The whole idea of stratifying individuals, particularly with pharmacogenetic tests, has made people be concerned that we would create new orphan drugs, and I am going to go into that one a little bit more in detail because that is a bit unique to the field. Then we certainly have heard that one of the benefits of pharmacogenomics is that you can essentially do smaller, faster clinical trials and speed drugs to market if you essentially select people for trials on the basis of their pharmacogenetic profiles. That, folks have argued, might result in having less safety data by the time the product comes to market. We certainly know that doctors don't always prescribe according to labeling. So when the drug is on the market and people who don't have that genetic profile get the drug, we don't have any real information about the safety issues.

Then finally, a big, big topic, and I won't really go into it today, is do we have the right incentive structure? Clearly, intellectual property issues are critical. People are mostly concerned about patent bottlenecks. That's due to a number of different entities holding patents on various genetic markers, thereby driving

up the cost of having to obtain multiple licenses to develop a test, and ultimately translating into tests that are quite expensive.

Then the focus by the pharmaceutical industry I would argue is predominantly on new drugs, not necessarily to study marketed drugs, whether they're branded or generic. Today more than 50 percent of all prescriptions written in the United States are for generic drugs. Those companies have no resources to do pharmacogenetic studies, and I would say the pharmaceutical industry has no financial incentive to do that. So from a public health perspective, what can we do to alter the incentives to encourage that kind of research?

As I said, I'll spend a little bit of time on biorepositories. Everyone talked today about the importance of linking genotypic and phenotypic information, and we know these are being done on a mass scale, and they're different because the folks that are collecting the sample may ultimately not be doing the research. You're not asking for informed consent for a single study. You probably have an unspecified number of future studies, and you can't specify, since you don't know what the studies are in the future, who the investigators may be. There's sort of the expectation that a number of different groups would try to take advantage of these biorepositories.

So that's sort of taking the informed consent discussion away from the traditional emphasis on trying to protect subjects from physical harms to protecting subjects from primarily what are informational harms. What facilitates this type of research would be things like blanket consent, where you say yes, you can use my specimen for any future use. But from an ethical perspective, it might not really be considered sufficient to meet the standards of informed consent because that's maybe too broad. There has to be some balance with asking people to consent to various types of studies while recognizing that it's extremely difficult to ever have to go back, contact patients and ask them to consent to different studies.

I'd say that the exclusive focus on the individual research subject, which is how informed consent documents are structured today -- they talk about risks and benefits to the individual -- I think that's arbitrary from an ethical point of view, and practically speaking we should actually be speaking about risks and harms to groups, which can lead to the potential for group harms even if you anonymize the sample. So, for example, if you found out that for a serious disease, Native Americans were particularly not responsive to the only drug that treated that disease -- I'm making the example quite extreme -- that there could be a potential for group harms that would

be stigmatizing to that group to have that information be out there.

There's clearly a lot of debate that the research participants have to have some measure of control over the research that's done with their stored tissue, and frequently what's done is that folks are asked to give a tiered consent where they sort of say what types of studies they would be willing to have their samples be used for, any type of study or any type of cancer study, or just a breast cancer study.

There is certainly a lot of discussion about the fact that these biorepositories, studies can go on for many, many years, and do the investigators have a duty to contact participants years after a study is complete if the study reveals important results that could impact the person's ability to use certain drugs. Right now the general practice is that you almost never recontact people, the argument being that the results of the study are not validated and you're actually doing more harm than good by giving people information that really shouldn't be acted upon. But people are saying that that really may evolve here and we would have a duty to contact participants.

Really what's done now is in many cases to separate the informed consent for collection and storage of tissue samples for pharmacogenetic testing from

participation in clinical trials. So you can say no to one, yes to the other. That's done I think for practical reasons, because people are concerned that IRBs may hold up the start of the study over ethical concerns of the DNA testing and the biobanking procedures, but also I think it's legitimate from an ethical standpoint because they really are different things.

I think what we're trying to do is to strive toward the appropriate balance between fostering pharmacogenomics research while ensuring the ethical treatment of human subjects, and we heard today how the Pharmacogenetics Research Network is trying to address this issue. I'm aware of the National Cancer Institute having a workshop next week talking about how they should harmonize practices for biorepositories that the NCI fosters, and I think that will be the key, will we be able to harmonize the approaches used for biorepositories.

Let's spend a little time on the concept of race. There's no precise biological or genetic definition. Sort of the prevailing thinking from a social perspective is that race is really a social construct, it's not biologically defined. But we know from research that certain pharmacogenetic variants are more common with some ethical and racial groups than others. We certainly heard that today. And there have been published studies

demonstrating differences in response to conventional treatments across various racial groups.

Now, a lot of people debate the scientific validity of these studies because they say that self-identified race is a very imprecise way and that you can get a lot of noise. When people say, for example, that they're African American, that can really mean a lot of different things. But now people are talking about BiDil and the fact that there's an advisory board today and it will be the first ethnic drug targeting a racial group.

There's actually no genetic, at this point at least, information about the underlying genotypes that may or may not explain why African American's appear to do better with BiDil. That hasn't been done. It's simply been on the phenotypic self-identified race that they're saying that BiDil works for African Americans. I think that pharmacogenomics could actually resolve some of these problems because they would say it's better to genotype than to ask people what the race would be.

So the potential harms from this type of research is that we're going to be reinforcing notions that racial differences have a genetic basis. People are quite concerned about that. Statements about how a drug works in a particular population are not going to be valid in genetically different populations because we've heard that

there are important differences in the distribution of genetic variants depending on where the study is done.

I think from a practical standpoint drugs could be marketed to particular racial groups in a misleading manner. You could either give the impression that all members of that group would benefit, so all African Americans would benefit from BiDil, or you'd give the impression that this particular drug, like BiDil, is more effective than other non-racially-defined medicine, and we know that's not true.

A theoretical concern. If certain genotypes are linked to poor medication response more commonly in certain racial minorities, that group could be stigmatized by the implication that they're more difficult or more expensive to treat. I think ultimately people will think that physicians will take a shortcut and use race rather than genotype as the basis for drug selection.

Then I said I would talk a little bit about orphan genotypes. You can have two kinds. You can either find out through pharmacogenetic data that a particular drug is unlikely to be safe or effective for a particular genotypic subgroup of a general population or of a disease group. So these people are the difficult-to-treat subgroup that we don't really classify that way today. Or it might reveal that a disease that was formerly thought of as large

and attractive from a commercial perspective is really composed of genotypic subgroups of individuals with the disease and no one of those subgroups is large enough to attract commercial investment. So you've sort of created disease orphans, genotypically defined.

That is the potential concern, that drugs will not be developed for these genetically-defined subgroups. I think this is really a theoretical concern. Firstly, what's not attractive to a large pharmaceutical company because of their size and scale and their commitments to Wall Street might be very attractive to a small start-up company, where they don't need to make billions of dollars. I think that the ethical concerns arise really if there's no other safe and effective treatment available for the disease. If there are alternatives, then we don't really have orphans.

That was really my second point. It's unlikely that the subgroup is going to be so small that they would never attract investment, although it's possible. Clearly, we must work in the context where we're dealing with serious diseases and the drug that works well for the majority population must provide substantial benefit. I think if those conditions are met, and that's a pretty high bar, then we would have ethical concerns, and folks have talked about modifying the existing orphan drug law to

essentially address this issue. But I think it's too early to say if we really need to do that or if this is going to be a problem.

So here are some of the issues in clinical practice. We've heard this all morning, so I won't get into it. I'm concerned that pharmacogenomics is coming into the marketplace without adequate validation. There will be suboptimal access to and use of pharmacogenomic testing, and that's for a couple of reasons, one because professionals such as pharmacists and physicians have huge knowledge gaps about genetics and the difficulty of interpreting probablistic information, as well as payers. I mean, when I would talk to payers, people would be extremely excited if they could have a scientific rationale for denying people access to a drug. But I think the nuances of where the cut points should be, where is the threshold for actually saying I'm justified in denying you access to this drug on the basis of your pharmacogenetic test, that's where it's difficult.

When are physicians obligated to offer a pharmacogenetic test? We heard today that they couldn't even go that far with TPMT on the label. They didn't create it as a mandatory thing. When are they actually obligated to follow these test results? So they come back and say you have a 30 percent chance of response. Is that

too low to offer a treatment to someone? What if it's the last treatment that's possible for them? That might be very appropriate.

Then I think a lot of folks have said the field is going to advance if we focus on liability, and it's not just liability for physicians but for pharmacists and pharmaceutical companies. Really, their liability derives from negligence theory. Here, physicians and pharmacists would be negligent because they didn't offer what had become a reasonable standard of care, and pharmaceutical companies would be liable because they did not actually disclose a potentially knowable safety problem with their drug. So I think that that is a major issue. I'm not an attorney. I've gone to the limits of my ability there, but I think it is important to understand that that is a real possibility, but I think it requires that pharmacogenetic testing be viewed as the standard of care.

Folks are saying do you actually need informed consent for pharmacogenetic testing in clinical practice? Should we be thinking of this more like a cholesterol test, where nobody gets your informed consent, or should it be viewed as disease predisposition testing, like saying what your risk is for Alzheimer's disease? I think those are sort of two extremes of a continuum, and at least initially we'll probably be somewhere in the middle

where we'll give some information talking about how we're going to actually use this information to guide therapy. But because a test is linked to an FDA-approved drug and the doctor has already made the decision to prescribe a treatment, I actually think that pharmacogenetic testing will not be that controversial, because I think that people will really view it as therapeutic drug monitoring to titrate the dose.

Inappropriate uses of pharmacogenetic testing. These are all direct marketing. I know you all covered that yesterday, but I might just be a little bit controversial and give you some examples where I think it might be appropriate for consumers to be able to do their own pharmacogenetic testing directly without going through a physician. Then the secondary information problem that can product psychosocial harms. We've talked about this before. There's also the concern that you learn not just other bad things about the individual but that you could also learn bad things about their family members, that they're more difficult to treat or that they have a certain risk disease predisposition, or that their current disease might be a more progressive form.

Discriminatory uses. I know that everyone is in support of the non-discrimination legislation without really any strong evidence of discrimination of occurring

in the marketplace. I think folks have felt like that sort of legislation is necessary to help people feel comfortable about getting genetic testing.

Then I'm concerned about higher drug costs leading to barriers to access. We heard that Herceptin was over a billion dollars. Well, I've done a lot of cost effectiveness analyses in my day, and one of the reasons Herceptin could be over a billion dollars is because it's very expensive. Pharmaceutical companies may say, even though they can develop the drug faster and more cheaply, I don't necessarily think they'll pass those savings on to the consumer, that they actually will be able to say on the basis that I'm delivering greater value to this patient subgroup, I can justify a higher price. So I think that higher drug costs are likely what we would see in the near term.

Then we talked about this, that there is a real problem if we have rapid and unmanaged introduction of genetic tests into the marketplace. I would just say here that predictive values of pharmacogenomic tests are likely in many cases to be too low to be clinically useful. Almost all of the genetic studies that have been done have been retrospective, when you know the outcome, looking back and saying what's the genotype, and I think that you need to do prospective studies, which are rarely,

if almost never, done to understand what is the positive and negative predictive value of these studies in this population. So we're going to get all excited about pharmacogenomics and potentially shift our resources away from more effective ways of improving public health. And I think we've talked about the other points.

So payers I think have a lot of insight. These are the hopes that they have about how pharmacogenomics might be used in the real world. They're hoping that there will actually be decreased health care costs, for all the reasons that are listed here. But they're also concerned that in reality, like every other new technology that ever gets entered into the marketplace, it will actually be cost increasing. It will be more cost effective, but it will not be cost saving. So you'll pay more and you'll get more, but you will not save money, and that's for a number of reasons.

I've already given the reason for higher drug prices. It's going to cost money if we have special privacy safeguards for genetic information. There are clear concerns that patents could be extended if you combine the drug and the test together in a specific use. Right now we're not paying for many of these tests today, and if we do broad population screening, those are going to add up over time.

This is just a little bit how they might think about pharmacogenomic testing. You know this. The first point is self-evident. Whether it becomes an important element of clinical practice depends on whether and how it is reimbursed. But I think we really need to think about pharmacogenomics. It's not actually worse than anything we're doing today. So today we're having tiered formularies, we're passing more costs on to the consumer, we're asking them to pay more out of pocket, we have step therapy, we have prior authorization. It seems to me that from an ethical standpoint, pharmacogenomics is clearly on par, if not superior, to these other approaches because it does tailor the drug to the individual.

It's clearly ethical desirable not to give someone a drug that you have evidence that would show that it's unsafe or ineffective. It's also ethical at the group level, because there's a stewardship obligation by payers for managing what are collective and scarce resources. That would be health care dollars. I think that's really difficult to operationalize in clinical practice because of the probablistic, not binary, nature of the results.

So where do you put the cut points? I would argue that the cut points are going to change depending on the disease, depending on the severity of the side effect

or the likelihood of response, and predominantly because of the cost. Where I have heard that payers are interested in using this is in the area of biotech drugs, where that's the fastest growing component of drug spending currently, and that they're very worried about that that will break the bank and that pharmacogenomic tests would be a way to sort of rationally put people into either receiving it or not receiving it, because a lot of times these biotech drugs are for very serious conditions.

So that's the longstanding new technology tension that always has existed between what's rational at the policy level versus what's rational at the individual level. I might say I want everything that could possibly benefit me, but we can't necessarily expect society or my employer to pay for it. I think, though, that all of this is predicated on assuming that these tests are really reliable and predictive, and of course you always need an allowance for an appeals process.

Finally, I thought I might be a little provocative and say when might direct-to-consumer access to pharmacogenomic testing be permissible? The blanket statement, like they should never do genetic testing direct to consumer -- well, you have to have the science be good. So you need appropriate standards of analytic and clinical validity, and of course you need to convey the

results in an accurate and understandable manner. But a lot of the smaller start-up companies that are operating in this space, they know that. They know that for people to buy their product, because they do cost hundreds of dollars -- you can go to some of these websites and get your panel done, but it's going to cost you about a thousand dollars.

I think that when the test contains information about response to over-the-counter drugs, which it would -- we heard it gives information about all drugs, and certainly even xenobiotics, so dietary regimens and other things are going to be affected -- how can we ethically say you can have access to a drug over the counter but you can't have access to the test that tells you how you might respond to that drug over the counter?

So, for example, if we actually found out, and people suspect that maybe NSAIDs are not really safer than COX2 inhibitors -- they simply haven't been studied in the long term. And let's assume that there could be a test to say who is at increased risk for the cardiovascular side effects associated with NSAIDs. It seems quite appropriate to me that we would allow a test like that over the counter.

I think also when the individual has insurance coverage for the drug but not for the test, I think that's another appropriate setting, and again that's quite

plausible. When individuals are concerned about discrimination or stigmatization, so they want to go around the system because they're afraid that their employer or their insurer would get access to the results when they're paying for them.

So I think a lot of this idea that you need a separate framework for the ethical, legal and policy issues in pharmacogenomics really kind of comes down to this slide. Is it special or unique relative to other medical technologies? You can kind of tell my bias, that I would think no, but I think it's important that I share with you the reasons why people have said yes, that DNA is uniquely identifying. We all know that from "CSI" and trials. The permanency of the sample, that these things can live in banks for years and years and years and years, and even in immortal cell lines.

There's a huge amount of information, and that's scary to people. It's uniquely predictive. People have described it as a future diary, as well as the paternalistic view that the science is very complex, so we have to treat it differently, and then the issues about the concerns about stigmatization by race or ethnicity because of the likelihood of genetic variability in those groups being different.

But I think that we should really think about

pharmacogenomics as a prescribing tool. It's just helping physicians decide the best intervention. I think you can practically separate them from disease susceptibility results. You're certainly not going to give out a microarray to a physician. You're going to have to give something that's much more digestible. So I think we can keep the disease susceptibility stuff out, with some important exceptions.

I think it's really important for us to acknowledge that genetic variation is only one factor impacting drug response, and we've heard about that, because if you don't, you're kind of reinforcing all the bad ideas of genetic determinism, essentialism, and exceptionalism, and I think ultimately we'll make patients less willing to be tested. So far we've really had not strong evidence of genetic discrimination for disease susceptibility genetic tests. I'd argue that it's even less likely for pharmacogenetic tests for the reasons that I've talked about.

So I would say in conclusion that pharmacogenomics really just highlights the need to resolve what have been longstanding problems about how do we integrate new technologies into clinical practice. There's lack of information across a number of areas. We've heard about that today. I think we need to think about how much

political will we have to support changes in these areas.

One thing I didn't talk about, but it's clear that the information technology that's going to be necessary to support this is going to be huge, and people are moving to standardization in that area, and there's been a lot of investment, but that's clearly an enabling piece.

As a society, we've had cost effectiveness data out there for years and years and years. In my experience, payers still decide on price. We don't necessarily understand cost effectiveness information, and we haven't made explicit the values that have to be built into any cost effectiveness analysis when you decide what costs count and which don't.

So let me end there. Thank you.

(Applause.)

DR. WINN-DEEN: Thanks very much.

I'd like to move right to Q&A because we're really running short on time here. So are there any pressing questions for any of the folks on the panel?

Julio?

DR. LICINIO: I had one question. It was a very interesting presentation. This panel has a long history of our discussing issues related to genetic testing but which are not unique to this panel. There is a whole

literature and line of thinking around that which has a lot to do with privacy and right to know and all of that. So let's say in a consent document, unless it's very clearly specified that the person wants to be contacted in the future, you don't contact. When in doubt, you don't over-expose the person to the information, because you're talking about genetic susceptibility, which may or may not happen, to a disease that they may or may not have, and some people don't want to know. For most diseases in this case, there is no cure, and I think they would (inaudible).

In the case of pharmacogenetics, I see this very differently because you're talking about the drugs that the person may be exposed to. So let's say in terms of the ethics of the testing, if you do it for research purposes, that person was not considered in the consent, should be recontacted, and you know for a fact that a person has a variant of a gene that can cause adverse reactions to a drug or can result in no effect to treatment that could be for cancer, for example, where if they don't respond they can die, or they should have chosen another treatment, is it ethical not to give the person the information when there is no clarity about that, or even when the person says "I don't want to know about my genes in general," but if you know something that another person is going to contract, you know that they have a mutation

that something bad is going to happen, how ethical or unethical is it?

In other words, do you use the same standard of ethics as for genetic testing, or should the standards here be different?

DR. DEVERKA: I think it's important to always allow folks the option not to be recontacted, and I know that's common practice with some genetic testing for disease susceptibility. I think you're right, that pharmacogenetics is different. I'm trying to imagine a scenario. I guess it would be that you would have information that would affect their outcome where there would be no other treatment, for example, for a serious condition like cancer. I think that you have to respect their decision.

In fact, in most cases people don't even really have a means of recontacting folks. Either the samples are permanently anonymized and there's not a mechanism to do that -- so I think from an ethical standpoint, I would say that I would follow their wishes in the informed consent.

DR. WINN-DEEN: Tim?

MR. LESHAN: Thank you for your presentation. I thought it was very good. I just had a point of clarification, and one point I didn't say earlier is that Rochelle couldn't cover everything, but we are

doing some ELSI research at the Genome Institute to look at some of these issues as well.

But you talked about the higher cost of implementing some of the privacy standards, and I'm not aware of any data that shows that. I wonder if you could talk about that a little bit more.

DR. DEVERKA: Well, folks have certainly talked about the cost of implementing HIPAA, right? I mean, people have complained about that a lot. That graphic that I gave was really just sort of a hypothetical, what are all the potential sources of increased cost, as well as what are all the cost offsets that would decrease overall health care costs. So I'm not aware of any specific studies that talk about the cost of protecting genetic information. It's just sort of logical to me to think that if we're somehow treating that information differently, that it will have a cost associated with it.

DR. WINN-DEEN: Kevin?

DR. FITZGERALD: I know you were trying to go back and forth and balance yourself here between is it a paradigmatic shift, isn't it, what's the impact going to be or not. So how do you see the way forward for a development of this technology and an emphasis on the importance of this technology while at the same time avoiding the genetic reductionism, essentialism,

determinism and all those other things that cash out from this sort of naturally in people's minds when they hear about all the power of this technology?

DR. DEVERKA: Well, in addition to what I already said, we have sort of a framework already for evaluating new technologies. It's got a lot of deficiencies, but I don't think we're well served by putting this in a special, separate bucket.

I just lost my train of thought. Sorry. Can you say your question again? About how we're going to advance it when people think it's --

DR. FITZGERALD: Right. It seems to be, and not just from empirical evidence but also when one looks at its various frameworks, if you push this and hype this or just even talk about the potential for this, that it's going to be interpreted, absorbed or seen by many people as furthering a genetic essentialism, reductionism, determinism sort of thing.

DR. DEVERKA: Well, I think one major step is the vocabulary. I think that people have talked about not using the word "genetics" when we talk about these medicine response profiles. I think if we said to a patient I would like to do a test that would help me guide what drug is best for you, I think that that has a completely different connotation than we want to do a test to see if you're at

risk for getting a really bad disease in the future, and I think people understand that difference.

So I think one big thing that we could do is pay attention to the vocabulary, and that's sort of my remarks in the clinical setting. I think in the research setting, our ethical obligations are to disclose all of the potential risks, which unfortunately, I think in today's environment, do contain some of the potential risks for discrimination or stigmatization, and that we need to disclose that and allow them to make an informed decision about that.

DR. WINN-DEEN: I had a couple of FDA-oriented questions. So I'll splat them out here on the floor and let whichever of you guys from FDA wants to respond.

I think we heard a comment this morning from the folks that are involved in developing laboratory-developed tests that they would like to see some recognition from FDA that those tests have some status in terms of if the biomarker is validated, that a test developed in a home-brew kind of situation could still be used in pharmacogenetics, why or why not. Currently it seems, from the comments that we heard this morning on TPMT and in the white paper on companion diagnostics, that there's really no formal recognition or utilization of that mechanism by FDA as a way to provide pharmacogenetic

services.

DR. HACKETT: If you're talking about the biomarker as described in the guidance document, and you're talking analytical only, and there's no clinical validation, so you get an answer but that won't tell you what the possibility is of being responsive to the drug or developing a toxic reaction, that's a problem there. If you go ahead and develop the test, then you can go ahead and probably get it marketed. That's the simple answer.

DR. WINN-DEEN: Okay. So let's take TPMT as an example, where we have, I think, clear evidence that there is something there, but FDA did fall short. While they said tests are available, they didn't really acknowledge that the only way those tests are available today is through laboratory-developed tests. Is there a requirement that we move to an IVD assay before we can have something that's formally recognized in FDA labeling as a pharmacogenetic test?

DR. HACKETT: Other than a biomarker, yes. If you want something beyond that, then you have to go through the regular approval process.

DR. WINN-DEEN: Are you talking about the ability to make a clinical utility claim?

DR. HACKETT: It's still like a research product. It's not an FDA-approved product.

DR. WINN-DEEN: You're saying that a test result produced by a CLIA-certified laboratory is a research product?

DR. HACKETT: No, the test itself is research. It's not an FDA-approved test. CLIA, again, is also only analytical result. It's not clinical validity. Does that help?

DR. WINN-DEEN: it raises concerns.

DR. HACKETT: The test is not FDA approved, and the only way you can get that approval is to go through the process.

DR. WINN-DEEN: No, that I clearly understand. But I'm talking about in the practice of medicine, does that mean that we can't recommend that in a practice guideline or in a drug label, a test for this entity be performed? I mean, it seems like for gleevac, we recommend BCR analysis be performed, and to my knowledge there's no IVD BCR assay out there.

DR. HACKETT: Do you want to try that one for labeling?

DR. FRUEH: I think there are two separate issues here. One is a combination product or a co-developed product where a test is required in order for the drug to be used. Those tests need to be FDA approved. Beyond that, in many, many drug labels, probably

100 or more, we point to pharmacogenomic information, and that's particularly in the area of short metabolism. I think TPMT, irinotecan, are two extreme examples where we actually went and we visited the label because of the toxicities that are associated with it.

If you're looking at 2D6 polymorphisms, for example, in drugs for depression and so forth, where it's well known that the drug is heavily influenced but it's not toxicity that is immediate, the recommendation is just not there yet. This has also been addressed earlier. A lot of this information has come forward over the past few years and the drug actually is a lot older. So we don't yet see it in the label. But the development in recommending that the test is being done is definitely going to be part of the label, and there is no problem in putting that in the label, even in the absence of an FDA-approved test.

DR. WINN-DEEN: Other questions for this group of speakers?

(No response.)

DR. WINN-DEEN: Thank you very much for your presentations.

We're going to take a 15-minute break -- sorry, 10 minutes -- and resume promptly at 3:15.

(Recess.)

DR. WINN-DEEN: On to discussion. I personally

have a lot of notes from today's session. So I guess what I'd like to do is see if we can figure out if there are some particular areas -- well, two or three things that I think we should work on. One is are there some things that we heard today that just stimulate us to want to hear more about any particular subjects, and if so, do we need to try and ask staff to put together a Part 3 to this program? We had Part 1 this morning, Part 2 this afternoon. Do we need another half-day or so of information gathering and education?

The other is can we try and bin some of these things into different areas? Are there research issues? Are there ELSI issues? Are there consent issues? Into some kind of logical groups that we then could tackle in trying to make some kind of a summary report of where things are, and then some specific recommendations for what this committee would like to see happen in the area of pharmacogenetics. I think we have some people who want to say something.

DR. WILLARD: Let me take the chairman of the day prerogative to try to frame this the same way we dealt with large population studies yesterday, which is to get the committee to focus on what kind of direction can it give to the task force so that the Task Force on Pharmacogenomics can make best use of its time between now

and the October meeting.

The real issue, as I was listening today, is for the committee to decide are there still issues and gaps where we feel none of the existing groups are tackling them and/or where we simply lack information. It's going to take some discipline to keep our discussions along that track. There are many interesting and chewy questions around pharmacogenomics, but some of them may well, we decide, be under control and are well attended to by existing groups, in which case we don't have much to do except pay attention to that and monitor that as time goes on.

So I think if we can focus our discussion on how best to recommend to the task force so that they, with a little more leisure, can decide exactly what needs to be done, and then have that task force come back to the full committee in October with some specific ideas, much as we're doing for large population studies.

DR. WINN-DEEN: People still have their hands up, so we'll go Kevin, Agnes, Cynthia, and Deb. So we have four people in the queue here.

DR. FITZGERALD: As a member of the task force, a couple of other things that I'd like to be able to see to get input. I think one of the things I'd like to pursue a little bit that did come up, and I'm not sure that the

people that we had were set to answer, I'd like to get some more perhaps of the financial side from industry as to what their parameters are on some of these issues. In particular, we heard the desire for partnership with academia, with government and that sort of thing. I just want to get a better sense of how that would flesh out, that partnership.

Also, I'm just wondering where the judiciary is on this. That's a group we haven't heard from, even in the genetic discrimination sort of thing. How do they see this cashing out?

DR. WINN-DEEN: You mean are they waiting for the lawsuits to come?

DR. FITZGERALD: I'm just wondering. I'm just wondering what's their perspective on all this, what do they see as the red flags and things like that, that we're just not hearing. I don't know, I haven't heard any of that yet. So I'm just wondering if it's possible to get somebody in October to speak to us on that.

DR. WINN-DEEN: Okay. On the financial aspects, we also really didn't hear from insurers. Is there some interest in trying to hear from insurers as well?

DR. FITZGERALD: Right, yes. I think we'd have to have that whole -- I don't know if it would have to be

somebody necessarily from each industry, but somebody who has that information or studies that information.

DR. WINN-DEEN: Right. Okay.

Agnes?

MS. MASNY: I think Sam Shekar had brought this up earlier, about the electronic health infrastructure. I think that would be something we would need to hear a little bit more on both for the area of pharmacogenetics, and I'm sure it's going to have impact for the whole area of personal genetic information that we should be more up to date on.

The second area that I just have a question on is that for the task force for the large population studies, is there an overlap with what we're looking at in the pharmacogenetic studies in populations, possibly large populations, with the large population study that you're examining for our group?

DR. WINN-DEEN: Hunt, do you want to just take that?

DR. WILLARD: Well, there certainly are some questions that will be in common to those two groups, and there's also substantial overlap I think between those two task forces. So I think we just all need to be mindful of that as we go forward, but it's a good point.

DR. WINN-DEEN: Cindy?

MS. BERRY: Because I work with Congress, I tend to have to oversimplify things. So maybe this is too simple for this group, but I was listening to everything that people were saying, and I divided the remarks into kind of a flow chart. Over here was research, the pharmacogenetics, the research needs. Then once you get the research going and you've got some conclusions and all that, then the question was how do you integrate that into practice. So those were sort of two main issues.

Leaving aside the integrating into clinical practice, it seems to me that there are big, big gaps in the research that is being done or that has yet to be done. So I divided that further, research with regard to existing drugs, drugs that have already been approved, they've received FDA approval, so what do you do there? Who does that research? Is it the pharmaceutical companies? Do they have to go back and do some research on their own product that's already been approved? Is it academia? Is it government? And how do you coordinate those? I think we heard a little bit about that earlier today. There's got to be some mechanism to coordinate those things. Is there a systematic way of conducting pharmacogenetics research on existing drugs? In other words, that it's not ad hoc. It's not some guy at Vanderbilt decides all of a sudden I'm going to go look at

this, and then maybe one pharmaceutical company says, well, maybe we'll go back and look at our drug. There's got to be some more systematic way to do it. So how do you coordinate that?

Then the other box is, of course, pipeline drugs. In that case, it seems to me that the burden would fall on the company itself because they're the ones that are inventing the product. I mean, nobody else has access to that. So if it's a pharmaceutical company, how do you get them to do that level of research? Do you have a mandate? Does FDA require it, or is it more an incentive-based system?

It seems to me there are lots of different questions and sub-questions in addition to ethical questions that we can put under each one of those, but that was my attempt at kind of simplifying what we heard today, the things that we're going to be faced with. So I don't know who else we need to hear from as far as that goes. I think we got a good base of it, but I'd like for us as a group to contemplate what can we advise the Secretary to do so that we can really encourage this kind of research both in existing drugs and then in pipeline drugs, and who is the best entity or industry or sector to do that.

DR. WINN-DEEN: And I would add even under "approved drugs," there's two bins. One is where you know

the biomarker, and one where you don't know the biomarker but you know there's some kind of adverse events that you'd like to know the biomarker for. I think those are two different bins as well within that group. So I think the task force could definitely consider trying to make a flow chart and come up with some tentative outline of who might be best suited to do that to throw out on the table for discussion at the next meeting.

Debra, did you have some more commentary?

DR. LEONARD: Yes, about what we'd like more information on, and this kind of ties in with the framework that Cindy just presented, which was very nice.

I do believe that Japan has mandated that all existing drugs be evaluated for pharmacogenetic impact on the Japanese population, and maybe it would be useful to hear how they are doing that and how it's funded and what they're actually looking at. I don't know a lot of details about it. I believe Nakamura is one of the major researchers involved in that process with the Japanese FDA equivalent. I don't even know what that organization is called.

DR. WINN-DEEN: The Japanese Health Ministry.

DR. LEONARD: But like with the biobanks, that we heard from other people doing this, it might be interesting. I don't know if there are other ethnic groups

or populations where this sort of thing is being done, but at least in Japan it is.

Then the second thing is with the FDA presentation, there was information that several submissions of pharmacogenetic information have been done. Are you willing to share what the FDA is learning from that process, and when? Because one of the things is, with drugs in development, Cindy, you were saying is there an FDA requirement for the pharmacogenetics. I think that's where FDA is moving. So can you give us an idea of what you're learning and what your timeline is to be thinking about making this part of the FDA approval process rather than a friendly submission of information? I don't know that you have to do it now, but maybe that's something that could be done in the future.

DR. FRUEH: I'd be happy to present you all these answers. Actually, I just put a presentation together for that very reason, because it's now one year since we started to get these submissions, and we have learned quite a bit. We're certainly not at the point where we're going to move it into a required type of submission, simply because the data is too complex and we need to make sure we create the appropriate policies and guidelines for that. But we are moving in that direction, that's no doubt. I'm happy to share at any point what we

have learned and what we are doing with that information as you deem it appropriate.

DR. LEONARD: Because maybe that would be useful to hear about next time. Maybe drugs in development, there's a process in place that will move in the right direction for drugs in development through the FDA. We may be able to say move it along faster or get more resources if you need more resources, or whatever. But I think one of the major issues is with the existing drugs and with the book that was shown by Dick. It's not a small task for the existing drugs.

DR. WINN-DEEN: I personally am still struggling with what do you really have to do to get something in a drug label. I'll probably keep asking you guys that question because it's not really clear to me still.

DR. LEONARD: It's not clear to me, either. I think that that's a very important thing to be clarified. If death doesn't do it, I'm not sure what does.

DR. WINN-DEEN: Tim?

MR. LESHAN: One quick addition. You might also want to talk with the Personalized Medical Coalition and get their perspective on some of these issues, as they're grappling with all the policy issues as they relate to personalized medicine.

DR. WINN-DEEN: One thing that was brought up to me during the break is that there apparently are differing standards for informed consent and what you're allowed to do with bank samples if you're a government agency versus if you're a private entity trying to do basically exactly the same research but under a different hat. Is there someone we can get from the human protection group that can clarify that for us, what's going on, why there's a double standard, if there is a double standard?

MS. CARR: Can you clarify? Where did you hear that there's this double standard? Did somebody say that today?

DR. WINN-DEEN: Yes.

MS. CARR: Who said that?

DR. WINN-DEEN: So you're volunteering. Do you want to come up and just make your comment to the committee, express your concern?

MR. YOCHER: Yes. The government agencies, which are going to actually have a workshop on biobanks next week, participate under a different set of regulations, 45 CFR Part 46. Industry has to operate under a different set, 21 CFR, Parts 50 and 56. Where trusted third parties are used to hold the keys to trace back to source documents, that system is allowed in the government. What's happened in industry is a part of FDA,

called the Bio Research Monitoring Group, has said this is not allowed because they reserve the right to go back to the source documents, and without having to go through a trusted third party.

This has been an issue for quite some time, and we think since we're trying to do public and private consortiums working together on pharmacogenomics, we can't have two standards.

MS. CARR: Thank you for clarifying that. I now understand what you're talking about. I thought you were talking about a different standard for government agencies, but what you're referring to is the different set of regulations that govern HHS-funded research. It's true that the common rule and FDA regulations do have a different approach to research involving human tissues, and even the definition of a human subject is different, the allowance for a waiver of consent is different, and actually NIH, through its program, the Clinical Research Policy, Analysis, and Coordination Program, an initiative of the NIH Roadmap, is actually very interested in this problem.

We've talked with FDA. Joe Hackett's colleagues in his center I think are certainly looking at this issue, and I don't know if Joe can speak to it any further, but I think there is a consciousness at FDA of the

fact that they have a different approach is an issue, and it's certainly a concern for NIH.

If you're referring to the workshop that NCI is sponsoring, I'm sure that will be an issue. I know there's also a group -- PRIMER has a tissue working group that's very concerned about this, too, and also may be making some recommendations about it as well.

MR. YOCHER: Thank you.

DR. WINN-DEEN: It certainly seems to me that if we're going to talk about doing public/private partnerships, that we have to be able to operate under one set of ground rules where all agencies are accepting of a set of ground rules that works for everyone. So I would like to see us talk about that a little bit more and see if in our role as an advisor to the Secretary there's anything that can be done to mediate normalization of things between agencies within HHS.

Other comments and concerns? Kevin.

DR. FITZGERALD: Just one other thing, and we can talk about it again in the task force, but it's something that kept coming up, and somewhat tangentially, during the various presentations is this idea of benefit and the therapeutic things that are going to be done, the clinical usefulness, that sort of stuff. At the end, one of the reasons I asked the question of the ethics

presentation -- and her answer was you've got to get good language. That reminds me of the thing we face today, even, say, in Phase I clinical trials, where you have wonderful informed consent forms, and yet the patients still walk away certain that this is going to benefit them in some therapeutic way, in spite of the fact that this is a Phase I trial. It's called therapeutic misconception.

My fear is there's going to be a huge therapeutic misconception surrounding this sort of technology and it's going to be very difficult to get really good understanding out in the public. Some people who are very good at that sort of thing are some of the sociologists who have been starting to study this thing about risk awareness and different ways of conceptualizing risk and all that sort of thing. So that might be another area we might want to look at.

DR. WINN-DEEN: So you're talking about sort of the public perceptions of risk/benefit?

DR. FITZGERALD: Well, it's a little more complicated than just public perceptions. Different groups have different filters, different heuristic structures, different ways they interpret the very same words and the very same data and the very same material. How does one, then, address that sort of situation? It's one I'm sure the genetic counselors see all the time when people come in

and they have to deal with this constantly. But it's also something a lot of sociologists have begun to look at in a more systematic way.

DR. WINN-DEEN: Agnes?

MS. MASNY: This comment relates not so much to a gap but just something for the task force to keep in mind. If we're going to be putting a document together or resolutions, whatever, that we include a section about the education for health professionals in this area. That was brought up many, many times for physicians, pharmacologists, nurses, other health care providers. I think it would just be something the task force has to make note of.

DR. WINN-DEEN: Yes, I actually made note of that in a larger context, because I think we heard from several people that education is not sufficient to create clinical implementation, and I would like to really explore what's going on with the clinical implementation piece both for things that already exist, whether there's a good body of evidence, what is really happening that's keeping that from happening, as well as is there some mechanism that we could propose going forward for best practices. When you get to the point where you have all the evidence, how do you turn evidence into implementation for better health care, and what are the steps you have to go through on that

implementation side?

So I think most of the work that's been done to date has focused on how do you get to the evidence, and we've seen a couple of examples where even with evidence, we're not seeing full uptake. I think Eric Lai's little chart, where he compared HER2 and Herceptin with TPMT testing with 2D6 testing, all of which are "valid biomarkers" where we know what they mean, we're still seeing this variation in uptake, and we need to understand that a little better.

Deb?

DR. LEONARD: Just several points, two quick ones and then a question, I think for Tim.

We heard several times also today about gene patents and the impact that this was going to have on restricting the development of broader pharmacogenetic testing, and I know we're dealing with gene patents separately, but maybe we can remember this as we're hearing the report of the NAS task force that's going to have a report coming out this July, that hopefully we will get before our next meeting.

One point --

DR. WINN-DEEN: Can I just say something on that? Sarah, or whoever is going to be organizing this, since we're going to be having some kind of a report on

that report, I assume, before the next meeting, can we ask whoever is doing that to talk about it both in the general as well as in the pharmacogenetics context?

Sorry. Go ahead with your other point.

DR. LEONARD: That's okay.

The second point is that one statement kind of struck me, which is that when there's FDA approval, then CMS should pay. We just finished a coverage and reimbursement document, and I don't know that that's in there anywhere, but it did seem like a logical connection between the two agencies. I don't know whether it exists. Don't worry, staff, we're not going to go changing the coverage and reimbursement document. But it was something to think about, I think, in the context of coverage and reimbursement and pharmacogenetics.

My third question is really in the model of the NCI cancer -- they're not core facilities, but they're basically resource facilities that are set up to help with certain types of cancer analyses that are done across many different kinds of research. What would it take to have the same sort of resource developed to support pharmacogenetic analysis of patients from clinical trials in a more centralized way? It could come out of the Pharmacogenetics Research Network. In fact, Dick said that they had applied for this and it wasn't funded. But it

seems like that would be something, since they already have data analysis and statistical analysis and many resources within that network, that if there could be a type of laboratory created -- and I don't know what mechanisms would be needed, but could you speak to that a little bit, Tim?

MR. LESHAN: I'm not sure I can speak very specifically to that. We provide a lot of the basic resources for genomics research through bioinformatics research that we fund and that we do intramurally in our institute, as well as just the power of the convener on these kinds of things and having workshops to try to provide the basic kind of information for people so they can better understand these things. But I think it would require a proposal of someone to present to our institute as to how they think we should propose providing those resources. I think it's something we would definitely consider, but I don't think I know the best mechanism at this point. There may be others, Rochelle or whoever.

DR. WINN-DEEN: Hunt?

DR. WILLARD: Just to clarify, there are such cores that are out there. NHLBI supports major sequencing cores, which were mentioned in Rochelle's talk, where people can submit projects for gene resequencing, and pharmacogenetics would certainly fall under that. To me,

it's not a core resource issue. Genotyping is dirt cheap and can be done in a thousand-plus cores and facilities around the country. So I don't think it's access to technology that's holding up any of these studies. It's a conceptual block to pulling together the large studies at the translational end, but getting the data out of labs I don't think is a major road block.

DR. WINN-DEEN: Sandra?

DR. LEONARD: I disagree.

Oh, I'm sorry. Go ahead.

DR. HOWARD: On the point that you had made earlier, I think you might want to hear from CMS themselves about the effect of FDA approval on their reimbursement policies. As you know, they have responsibility for the elderly and disabled population, and there's recently been a drug benefit added. You might want to hear from them about how these technologies may then impact their responsibilities toward these populations, and also their responsibilities in the area of cost containment, because they do have some responsibilities in that area. They don't address the totality of the population, but I know that insurers, that payers in general kind of look to them to see what decisions they've made about that in the populations that they address.

But they also have the other program, Medicaid,

in partnership with the states. They don't make coverage determinations the same way, but certainly these technologies are going to impact upon those populations. So you might want to hear from them as well on that.

DR. WINN-DEEN: Deb, did you have a follow-up to your previous comment, or something new?

DR. LEONARD: I disagree, Hunt, because I think that a general sequencing facility or genotyping facility isn't going to have the pharmacogenetic information and pharmacologic information to say to an investigator who wants to investigate different responses to asthma drugs or antidepressants or whatever, you might want to look at these or help with designing what genotyping or resequencing you would choose to do, because I think many of these projects may come out of clinicians who don't have the genetics knowledge and the genomics knowledge, the statistical information, the bioinformatics information.

So to have a more focused pharmacogenetics type of core, rather than the generic sequencing kind of core, might facilitate this research.

DR. WILLARD: Then we're disagreeing only on what to call it, because to me, then, it ceases to be a core if you're really wanting it to be driven intellectually and conceptually by this core where

physicians and clinicians around the country might be able to offer cohorts of patients, and from that would derive pharmacogenetics conclusions and data. So to me, that's different from a "core," but whatever we call it, then I might agree there's a need for such a thing.

DR. WINN-DEEN: I think a lot of the pharmGKB labs actually had a component where they both collected clinical samples that were well characterized as well as had to provide a mechanism for doing whatever resequencing or genotyping needed to be done on those. So I think within the individual awardees of those grants, there is that expertise, and it's a mixed expertise. So you've got clinicians as well as the high-throughput genotyping and sequencing support team to know how to sequence.

DR. LEONARD: But in talking with Dick afterwards, he was saying he had made a proposal for this type of thing that could integrate with various clinical trials that would be ongoing so that you could evaluate the specimens pharmacogenetically and use the resources within the Pharmacogenetics Research Network, and that was not funded.

DR. WINN-DEEN: Okay, I'm going to let Julio talk because he's in this network, and he also has a question. So you get the floor on both counts right now.

DR. LICINIO: The thing is that what you're

referring to -- and I don't know if Dick is still here, but the network that was put together, it's not that it was not funded. It was part of a roadmap RFA for translational centers, and the whole RFA was canceled. So it's not that it was not funded as a specific project. The whole initiative kind of disappeared.

But I actually just very recently, a couple of weeks ago, wrote an editorial about this, because I think the point which you're bringing up, which is very important, we should consider maybe now or in future meetings. I think this field, having worked in it for a while, if you look at it very carefully, there are some people who do outstanding work on both sides, and I'm not talking about those. But where you see the biggest deficiencies are these people who work on the genetic side and have more of a genetic background.

The clinical material they just call samples. So as an example, years back I was asked to consult in order to do a collaboration with a company, and they asked me to calculate the cost of doing a pharmacogenetics trial that would result in blood samples that should be analyzed. They said the cost per sample is too high. If you do genetics research, I can go out there and get 1,000 schizophrenic patients for a study. I can get the samples in one day. Just go to a few large state

hospitals and you can collect 1,000 people in a day.

But you cannot, for pharmacogenetics -- you have to screen the people, and then treat them and observe the results of treatment in a controlled way, which is extremely expensive. The people who do the genetics side, they don't understand the clinical issues, they don't appreciate the clinical issues, and they don't accept the cost, which is extremely high.

So you often see -- as the editor of two journals, I see this all the time. You see very sophisticated genetics on clinical samples that are of very questionable value. So in my own PharmGKB study, to get the first 120 patients into my study, I had to screen 2,111 people, because if you're studying the pharmacogenetics of a drug, ideally the person should have that disease and nothing else and be taking that drug and nothing else. So if you're studying the pharmacogenetics of an antidepressant, you don't want a depressed person who is also diabetic and taking insulin at the same time, because if they change, you don't know what's changing.

Out there in the real world, when you talk about the common and complex diseases, it's very rare to find a person who has that disease, only that disease, nothing else, and is willing to take that one drug and nothing else, does not have back pain, is not taking a ton

of natural supplements, is not taking this and that thing. So the geneticists, they fail on that side.

The clinicians, they fail on the side of -- some of them who have more clinical backgrounds, they collect very good samples and they have very good trials with samples collected, and they don't know the first thing about the genetics, and that's maybe where this thing could be helpful. Then they just test a few polymorphisms here and there. They do things that don't have enough power. They do a lot of tests in a sample that's insufficient.

So what I see often are people coming from the clinical side, the pharmacologist side, without a knowledge of genetics, and people coming from the genetics side without the knowledge of the pharmacology. So maybe some type of interface between -- the Pharmacogenetics Network is wonderful, but it is relatively circumscribed to those people who are in the network. But the (inaudible) doesn't really at this point -- I know it's a goal for the future -- it doesn't reach to the clinician out there or the clinical researcher out there, and a lot of geneticists are not in the network. The network is not driven by geneticists.

So it should be important maybe for this panel to try to kind of bring those two communities together

through a core facility, through some type of mechanism to integrate these two sides, because that's where the divorce happens.

DR. WINN-DEEN: Thanks. I think that's a really great idea, and we'll try and see if we can figure out a way to make some kind of task force recommendation.

Hunt, and then Alan.

DR. WILLARD: One point on that, and then another one following up on Pat Deverka's talk. I think Dr. Davis this morning made a very rational and impassioned plea to figure out how to do translational pharmacogenomics that is linked somehow to health outcomes. That is, as Julio points out, a very different kind of science that people who are trying to do the basic science in a laboratory, and it may be that these networks, which are valuable certainly for one area of science, don't necessarily completely bridge that gap, and the task force may want to look more closely at the mechanisms that would specifically lead to addressing not the basic science but, assume the basic science is there, how do you then take those discoveries and that knowledge base and push that through with a series of studies that would deal not only with clinical analysis but the pharmacoeconomics, the health system design and financing, et cetera, because there are a whole number of different avenues that would

need to come into play in order for there to be "success" and adoption of this or any other technological advance in the practice of medicine.

The other two things that I jotted down during Pat Deverka's talk that the task force might want to look at, which I'm not sure we or other groups have taken up, at least fully -- one was the issue of genetic exceptionalism again. This we dealt with two years ago, I believe, but it comes back up specifically in this context that I think is very relevant as she presented the issue of pharmacogenomics. I mean, is this really a truly new beast that everyone is going to have to figure out a way to deal with, or is there a way to slip this into existing paradigms, regulatory or otherwise? That seems to me is a reasonable task force question.

The other one is race and genomics and a follow-up related to whatever is happening today with the BiDil advisory committee meeting, but there may be other examples as well. There certainly will be other examples coming down the pike, and to address that from the standpoint of are there gaps in knowledge and what would the Secretary need to know about those issues where we might be able to be of some help.

DR. WINN-DEEN: Do you think it would be useful to hear a short synopsis of what actually happened today,

whichever way it goes?

DR. WILLARD: That probably depends on what actually happened today.

DR. WINN-DEEN: Well, I mean whether it was approved or not approved, is there a lesson to be learned there? I mean as a potential topic for the October updates.

DR. WILLARD: Let the task force do what the task force will do. I think it depends on what happened today, what was recommended, and what other kinds of examples may well come along. I'm sure there will be plenty of opinions on whatever they did.

DR. WINN-DEEN: Alan?

DR. GUTTMACHER: Yes, thanks. I just wanted to rejoin the discussion that Debra and Julio and Hunt and some others were having, just to sort of state the obvious. The example of pharmacogenomics in this area of interdisciplinary research is a very edifying one but far from a unique one. It really crystallizes, I think, what is the challenge to the NIH, and not just to NIH but to academia, to private industry, et cetera, to think about how we do research in an era when nobody has the degree of knowledge in enough areas to be able to do the research anymore.

I think the PharmGKB network was a wonderful

example of how to move into that area. It's not sufficient to do all of pharmacogenomics, and certainly NIH continues to deal with this, realizes it's a very fluid area and needs to come up with new models for doing it, but it's not just the funders that need to do it. It's not just the NIH among the funders. It's all the funders, but it's not just the funders. It also challenges academic institutions, and many are obviously trying to do this, how you come up with ways of putting this together.

It's further a challenge and perhaps an opportunity in this area since obviously this gets to an area of translational research where there are private industries that are interested in the knowledge gained here and how one creates interfaces with private industry as well. It's obviously interested in this kind of information. There are no, I think, easy answers to this, but everyone involved recognizes the fact that they don't have the answers yet. So any advice the committee could offer -- I wouldn't just look at the funders. I'd look at them, but I'd look at other kinds of changes we might make in the way we approach these things.

DR. WINN-DEEN: Right. So I think part of our focus on funders might have to do with our charge to deal with HHS and not stray too much from our mandate to be a group that makes recommendations to the Secretary. But we

certainly could talk about how HHS agencies can do outreach and work jointly with non-HHS entities, whether they're public or private, to move forward.

Other commentary? I think the task force has plenty of meat. We'll do our best to put together a program that's organized.

Sarah has some comments.

MS. CARR: Actually, it's more of a question. Does the committee want to talk or give any further guidance to the task force about the long-range goal here? It sounds like you're not ready to begin writing any kind of report. You're still exploring and needing to put together additional presentations and fact-finding for the October meeting but not ready to think about the product that will come out of all of this yet.

DR. WINN-DEEN: Well, I'm hoping that we will come out with some recommendations, but I'm not sure if we'll come out with a big book like Coverage and Reimbursement that within it has embedded recommendations, or whether the work product will be more like our letters to the Secretary on education and discrimination that just points out some specific things. I think this subject is so complex in many ways that you may have to have some white paper, at least, that frames the issue and then talks about the specific recommendations.

MS. CARR: Well, would the committee like to give the task force the latitude to think about what form -- I guess that's inherent in this, but I think it would be good for the task force to think about that early on.

DR. WINN-DEEN: Is there anybody that has any objection to an open thought process at this point for how we might convey whatever recommendations?

(No response.)

DR. WINN-DEEN: Okay, good. I'm seeing everybody in agreement that we can have some latitude.

Agnes?

MS. MASNY: When you mentioned about the white paper, one of the speakers, and I can't remember which one, had mentioned that there were four white papers that were published in this area.

DR. WINN-DEEN: Rochelle Long, NIGMS.

MS. MASNY: It would be very helpful if those could be made available to the committee.

DR. WINN-DEEN: We'll get hold of those when they come, as they come.

I want to thank everybody who participated in this session from the speaking side, and all the people on the task force who participated in getting us this far, in particular Fay Shamanski, who did all the work of organizing everybody to actually be here and put the

program together. I certainly appreciate having everybody's help and believe in the Shaker saying of many hands make light work. It really does make a difference to have a lot of people participating. We thank all of you for your participation and look forward to additional input and discussion.

Did you have one more thing for the task force before we close this part?

MS. CARR: Actually, no. I was more responding to Debra. The translational research centers' RFA or PA that was canceled, I think they had a meeting a couple of weeks ago to think about what to do instead of that, I think. So we could hear from them. That could be something else you might want to do, and maybe the NIH Roadmap in general might be something that might be of use to hear about, if only for the task force or the full committee maybe.

DR. WINN-DEEN: Okay. I'm turning it back over to Hunt for the next steps and closing remarks.

DR. WILLARD: Thank you to Emily and the task force. That was a terrific, albeit exhausting, day. My thanks to the speakers as well. I think we never fail to learn something, and today we actually learned an enormous amount, and I thank you all for that.

It falls on me simply to announce our next

meeting is October 19th and 20th, and at least currently is scheduled to be held here again according to my notes. The meeting dates for next year are in your table folders, for those who like to plan your long-range calendars.

I think all of us want to both recognize and thank and say goodbye to Barbara and Joan, this being your last meeting. Ed has already totally forgotten he was ever on this committee, I'm sure.

(Laughter.)

DR. WILLARD: His 12 hours have passed.

But you've been terrific participants, and we will miss you and wish you well in your retirement.

Any other business?

DR. LEONARD: Sarah, are the meeting dates set for going out?

MS. CARR: For 2006? They were supposed to be, but we're having to work on them. We haven't found sites for those meetings yet, so we're holding off on setting them in stone yet. But we hope to do it very soon because we know your calendars will fill up soon.

DR. LEONARD: Could you send out at least tentative dates that we could hold?

MS. CARR: Could we do that? Yes, we can certainly do that.

DR. WILLARD: March, June and October.

(Laughter.)

MS. CARR: Don't put anything on those months.

DR. WILLARD: Suzanne?

DR. FEETHAM: A theme that has been going through the whole work of SACGHS, and certainly these last two days, is access. I'm bringing it up separately from the pharmacogenomics because it really is underlying everything we've been talking about. In talking with Tim, I know a fair amount of studies have been funded through the ELSI regarding access. What we don't know is if they have solid evidence to report about that. But that's something I'd like us to think about for a future meeting and have our colleagues do the homework to know whether they're at a point where they'd want to be presenting that. But I think that's just critically important, underlying all of the work we're doing, and if the science is moving along in that area, it would behoove us to know what the state of the science is.

DR. WILLARD: Thank you for that. Access, of course, is one of those overarching issues we identified early on, and we do need to keep coming back to it. So I appreciate that.

Agnes?

MS. MASNY: Not that I want any more work, but just the beautiful chart that we put up regarding the

timeline of all the priority areas, is there anything else that we have to address besides the pharmacogenomics for the next meeting?

DR. WILLARD: Large population studies is the other major one.

Well, with that, and seeing no other red lights, thank you to everyone, both on the committee and in the audience, and those who are still hanging in at home. With that, this meeting will be adjourned. Thank you all.

(Whereupon, at 4:21 p.m., the meeting was adjourned.)