Update from the Pharmacogenomics Task Force
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DR. WINN-DEEN: So what I wanted to do for you today is to just give you an update on what the Pharmacogenomics Task Force has been up to. Just as a reminder and a thank you to all the people who serve on the task force -- from our own committee, that's Jim Evans, Kevin Fitzgerald, Debra Leonard, Julio, and Hunt -- and then a number of representatives from the ex officio side as well, trying to keep a balance and make sure we get input from all the folks who have a stake in this.

Historically we had our first session on this subject back in June with the goal to identify what the key issues were through a series of presentations and to identify areas for further fact-finding through the committee meetings.

We had a second information session in October where we heard presentations on some of the financial issues and the implications of pharmacogenomics for racial and ethnic groups. We outlined a report and started discussing a number of possible approaches.

In today's session, we're really going to try and focus on moving ahead with a meeting report from the committee, and we have the pleasure of being briefed by FDA on the just hot off the presses FDA guidance on Pharmacogenomic Tests and Genetic Tests for Heritable Disorders. So Steve Gutman is going to provide us with a short update.

Since the October meeting, the staff particularly has been extremely busy pulling together background information from a huge variety of sources. We have looked back at the SACGHS discussions, the presentations, a series of recent reports from areas outside of SACGHS, and in addition, the staff conducted and the agencies within the federal government were kind enough to respond with quite a bit of information in terms of what is going on already within the federal government, our goal being, again, to act as coordinators and to identify if there are overlaps which could be put to more efficient use, as well as if there are significant gaps where nothing is going on.

So in terms of the outside sources, staff went through a number of reports from outside groups that had looked at this particular subject. The U.K. has been particularly active in this through two different groups. The Nuffield Council on Bioethics, as well as the Royal Society, have both published quite extensive reports on pharmacogenomics. There's a book on ELSI issues edited by Mark Rothstein that was used that has some nice primary data on sort of the way people think about using these tests and how they feel about them.

So that information was pulled together and really digested down into a number of topic areas. You'll find that -- it's a series of white pages -- in your book under tab number 6. So we tried to, as a starting point, gather what thoughts had already been put into the public domain, so to speak, from other groups and see how that balanced with what we might be thinking.

Then we did a survey of federal efforts in pharmacogenomics that were organized by major issues and need areas that this committee had previously identified. The staff used both information gathered directly from the member organizations, as well as things from their websites and literature. That is a very long document also in the white pages of your tab 6. What is in your table folders is a very nice summary, which you might want to pull out for our discussion, where Fay has summarized under each of these different issues and needs what's going on in the different agencies. So it also references the more detailed information.

But also the task force asked staff if they would pull together sort of a third column here, which is this possible areas for future focus. So we probably will have some discussion about some of those areas as well.

So in terms of Federal efforts, we divided the efforts into a number of areas, the first of which was research and development. As we had heard the presentations over the last year, it became obvious that there is still a lot of research to be done in this area. So the specific needs were that there is perhaps a need to identify a different approach, a novel research team approach, given the fact that a lot of this information is involved with drug trials, which are typically run by the private sector versus NIH or other public kind of sponsorship of trials.

We raised the issue of how to get studies on already-marketed and generic drugs run, and we'd like to have some discussion of what it might take to get some of the things that are already on the market into studies that would result in the data that you need to decide if there should be a pharmacogenetic test.

What is the evidence of effectiveness?

What are the models for utilizing a test in an economic benefit sense? The last thing the health care needs is another cost of a test to be put in the way of getting health care. So how do we balance that out?

And then there obviously needs to be some coordination between the drug companies and the test developers. These are two separate groups who are not typically working together today. So we need to figure out ways to encourage that coordination.

Both the NIH and the VA support investigator-initiated research on both new and post-market therapeutics. So there are some investigators who have applied for grants under various programs. The NIH has the Pharmacogenomics Research Network, which was a very targeted set of RFPs and grants given out for this express purpose, to find associations and to validate them.

And the FDA has also been quite proactive in working with both the diagnostics companies, as well as the drug companies, to really start to understand their respective viewpoints and understand how, through working with FDA, those viewpoints and needs and desires can both be part of this and can be coordinated through an FDA review process.

Similarly, the CDC has the EGAPP program, which we're well aware of.

AHRQ has the DEcIDE Network and AHRQ also has a research initiative in clinical economics. I'm not sure if there are any of these economic incentives yet that are focused on pharmacoeconomics, pharmacogenomics, but it certainly is a place that such studies could be funded.

In addition to just gathering basic scientific evidence, we all know that there is another component that needs to happen before the practice of medicine is affected. So you could have great science, you can have all the other ducks in a row, but if you don't understand how to change clinical practice, then there won't be the end result, which is the desired result, which is to improve health care.

So there are certain barriers to integration that we need to be aware of as well. So you can't just say, well, this SNP is associated with better response to drug X. You have to provide the

information that the clinician needs to translate that. Does that mean that you give a different dose to different patients based on their genotype? Does it mean that you don't give that drug or you only give it to a certain subset? You have to provide that guidance to them and teach them how to use it.

Different medical specialties have different levels of receptivity to this kind of thing. I'd say traditionally the oncologists are the great experimenters. They're willing to try anything new because their tools are still so limited that they never have what they'd really like to have to help patients. Other specialties are much more set in their ways, and there's a lot higher level of show-me attitude that you have to overcome before you can affect clinical practice.

As we're well aware, you need to also make sure that tests can be reimbursed and properly paid for in order to have something be part of the routine practice of medicine.

Clinical practice is also highly affected by the sort of best practices guidelines that are put together by a variety of groups. AHRQ and HRSA are two of the government groups. There's, of course, also within most physician organizations varying medical practice guidances that are issued in terms of when and where a test should be utilized and how it should be utilized and interpreted. So all of those things need to be addressed.

In the realm of pharmacogenetics where you could presumably be genotyped at any point in your life and then that data utilized later to formulate decisions on whether or not you should receive a drug or at what dose you should receive a drug, there's a need to figure out how to make sure that that test information stays with you over your lifetime. So once you've had the test, for whatever reason it was ordered initially, how do you make sure that the next time a physician needs that information to deal with your health care it's available to them. From that point of view, the infrastructure that electronic medical records and data standards is working on I think is relevant to this particular area as well.

We've got a number of other infrastructure things going on within the federal government. I'll let you read all these different things, but part of this is aimed at trying to make sure that you have all of the information that you need to make a good decision about a patient at the time you need to make that decision.

Then there's the whole oversight issue, who decides how and when pharmacogenomics should be utilized. The FDA has worked extremely proactively with the pharmaceutical side to encourage them, as they do a lot of their biomarker research, to submit that research data just as that, as research data, so that we can start to understand among clinical trials if there is any pattern that's emerging that a specific biomarker is predictive.

I think the fact that there was a guidance document issued, a tremendous amount of consultation with the pharma industry that resulted in a finalized guidance document last fall, really is a model for how we can start to deal with the public/private issues and encourage groups, that normally would have perhaps a more adversarial relationship, to start to think about a more coordinated kind of relationship.

The hole right now that I see in the oversight. We have, as Steve is going to talk about, a new guidance document on what you need to do to get a pharmacogenetic test approved. We have the guidance document to pharma. What we don't have yet is a guidance document that really puts those two things together and says under what circumstances will a test be required, under what circumstances will there be a labeling change in a drug. If a test comes on the market, does that

go back and affect a drug that's already there? We have examples where those things have happened in the community, and I think through the process of those things happening as sort of pilot studies, it's possible that FDA -- I'll let Steve address this when he talks to the group after I'm done. Maybe starting to think about, now that they understand a little bit different scenarios, how they could formulate at least a draft guidance on when and where labeling changes actually get made on existing drugs or get incorporated as a requirement in a new drug upon release.

So we also have, within the Federal agencies, different mandates. FDA's mandate is to assure safety and efficacy.

CDC's mandate is more of a public health mandate, and they've been focusing on assuring testing quality both through the CLIA program, as well as through a program to help develop quality control materials for genetic tests.

And then, in terms of trying to organize how research information can be "standardized," there's a whole interagency effort on microarray data, now to report it, how to quality control it, how to normalize it among studies, all of these kinds of efforts so that you can use data sets from different studies to pool together and draw conclusions.

Again, science is only part of it. If we really want to have science implemented, there needs to be an education component. We need to educate patients so that this is not some strange word that they hear and they get a test, but they don't know really what that means or how good data is going to be used. Are they going to have to give informed consent for pharmacogenetics testing or is this outside of the realm of the informed consent world? And we need to educate the physicians to help them understand when it's appropriate to use this in their own clinical practice.

To that end, NIH has produced brochures to help inform the public about what pharmacogenomics is. NIH and HRSA both provide funding for NCHPEG's educational efforts, which are aimed at health care provider education for the most part, and AHRQ also has a center for education and research on therapeutics which is helping to educate providers.

When you think about how to make a public health impact, one of the things that needs to be in place is an effective surveillance system. Now, FDA has an adverse event reporting system, which has already been in place for a long time.

The other three areas are not as well surveilled in terms of, once you get through a clinical trial, does the effectiveness of the drug in the general population it's being used to treat the same as it was in the clinical trial population. Are there any unintended consequences of that? And are there any strange utilization patterns? We don't track that really at all. Probably the pharmaceutical companies have the best data on utilization patterns, but they typically use that as part of their marketing. It's their proprietary data. It's not something they normally would be sharing.

So, as I mentioned, there's a number of different mechanisms in place. Obviously, CDC's overall mission to protect the health and safety of all Americans. That's at a higher level, a lot more generic level, I guess I should say, than FDA's which is focused more on specific health and safety related to drug use. And then we've got work going on at AHRQ as well.

There was a desire from this committee, I think as part of our regular work with the agencies, to assure that there's coordination and attention and/or awareness of what's going on between all the agencies, and that was part of the reason that we did this survey of what's going on at the

agencies, both to allow all the agencies to know what's going on outside of their own world, as well as to inform this committee. So we hope that that will be a useful exercise in promoting communication. We'd like to see some mechanisms put in place to promote data sharing among studies funded by different agencies within the HHS and the health care system in general.

Now, the good news is that personalized medicine, whatever that means, is part of Secretary Leavitt's 500-Day Plan and is on the FDA Critical Path Initiative, which means that there is high-level interest in seeing the promise that pharmacogenetics offers implemented where it's appropriate.

NIH has stepped up to the plate and funded the PharmGKB database, and that has been out there, I think, for about four or five years now. We've seen some good evidence of sharing of information among the agencies, and the CDC has their Human Genome Epidemiology Network up and in place.

We have a number of ELSI things that we could consider making recommendations on or at least drawing the Secretary's attention to. These are pretty much the same kinds of things that we talked to him about on most subjects, but for sure, we want to make sure that we don't encourage any health disparities either on socioeconomic bases or on racial bases. We want to make sure that the whole informed consent and privacy protections that are needed are in place.

Debra will talk a little bit tomorrow about the impact that gene patents could have on this field in terms of availability of assays.

I think we need to keep in mind that genetic exceptionalism is also an issue in pharmacogenetics; that is, your response to a drug or the dose you should take is not only driven by what your underlying genetics is. What concomitant medications are you taking, what is your medical condition, what food are you eating? There are other things that can affect that, and so it's not a strictly deterministic thing, although it does provide some informative information to help guide therapy but it shouldn't necessarily drive therapy.

Of course, we've got ELSI programs going on all throughout the NIH. So most of these issues are being addressed already. We have diversity guidelines for clinical trials in place and specific groups focused on areas like treating children and making sure that minority populations are correctly included in any trials.

So the plan for today's session is to identify the broad areas for focus of our recommendations. What we've tried to do in the yellow pages at the front of your book is to draw together in each of these subtopics -- if you turn past the first three pages, there's a thing that says background for the session. What we've tried to do is pull together in that section the previous things that SACGHS has sort of identified, what's going on in the federal government, are there gaps, and are there some proposed recommendations. So I think what we'd like to focus on today is an assessment of whether we've got all the bases covered, are there things that we've missed as a task force --

DR. TUCKSON: Emily, hold on one second just to make sure everybody got that. There are two page 1s. You've got a couple pages of page 1. Go past that and then you'll see another page 1 and it will say "background information."

DR. WINN-DEEN: Right. The short version in the front I think was an attempt to do an executive summary, but it sort of leaves things out, and I think the one that has the background really has all the pieces. So it has what's going on in other groups, what's going on in the federal

agencies, what was SACGHS concerned about in the past. And then this is an area where we can sort of pull that information together and consider making some recommendations.

The task force and staff have inserted a few "proposed" approaches as starting points for our discussion. These are just that. They're starting points for a discussion. They're not, by any means, a set-in-stone recommendation or anything along those lines. We want to get the full committee's sense for what are the things that we really need to be talking to the Secretary about, what are the things that the Secretary of Health and Human Services can effect directly, what are the things where we need to encourage coordination between HHS and other groups, and then try and formulate recommendations.

I don't have a slide on this, but we're fortunate that the Office of the Assistant Secretary for Planning and Evaluation, ASPE, has found some funding in their bucket and has offered us this funding to support a report-writing by the Lewin Group. After the yellow pages, there's an outline of what the draft report would be. Actually it might even be after the federal pages. It's a two- or three-page outline.

The goal is to have a draft report to the task force by May 1 so that we can review it. So we definitely want all input that we can get today that might need to go into that report or affect the way that report is structured. Our goal would be to bring that draft report to the June Secretary's advisory meeting for both review of the report, as well as for review of first draft of recommendations to insert in various spots in that report, much as we did for coverage and reimbursement report.

So that is sort of the goal of what we're about today to try and ascertain whether there are some things that we need to do further work on, further information-gathering, and then try and rough out the priorities for what we want to say to Mr. Leavitt.

I think that's the end of mine.