HHS Efforts and Future Directions in Pharmacogenomics
Muin Khoury, M.D., Ph.D.

DR. WINN-DEEN: 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.