Pharmacogenomics: The Public Health Perspective
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DR. WINN-DEEN: 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.)