Ethical, Legal, and Social Implications of Pharmacogenomics
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DR. WINN-DEEN: 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.