

Economic Challenges of Integrating Pharmacogenomics into Clinical Practice
Kathryn Phillips, Ph.D.

DR. WINN-DEEN: We're going to go right into our next talk, which I think follows nicely on this. We're going to hear a little bit more about economic challenges of integrating pharmacogenomics into clinical practice.

Kathryn Phillips joins us from UCSF, where she is a Professor of Health Economics and Health Services Research in the Department of Clinical Pharmacy. We have heard from her colleague, Dr. Veenstra, in the past. I hope this will be a continuation of our education on basically the health economics of working in this area.

DR. PHILLIPS: Good morning. I appreciate the opportunity to be here today, and I know that I'm the only speaker between you and lunch. So I will keep that in mind. I won't be cruel.

We all know that there has been a lot of hype concerning pharmacogenomics. Some people are saying it's going to revolutionize our lives, but where are we now with pharmacogenomics? Some people would say it's here, you'd better get on the bus or you're going to get run over. But others would say well, where are the benefits? Where's the beef? I don't see anything good coming from this. I realize it's cruel to put a hamburger on the slide at this point, but hopefully economics can help us figure it out.

So today I'm going to go over some of the economic challenges of integrating pharmacogenomics in clinical care, I'm going to go over some of the steps needed to maximize the value of pharmacogenomics and how economics can help us do that, and I'm going to go over three case studies. If you read the newspaper this morning, you know that there is even more news regarding these.

So why is economics even relevant? Well, it provides both a toolbox and tools. The toolbox is a conceptual framework, and the tools are the methods that we bring to bear. Economics can be boiled down to two things. One is incentives. In other words, here we are interested in why is pharmacogenomics adopted or not? What type of incentives will maximize the value of pharmacogenomics?

The other critical piece of economics is value. And by here, I don't mean money only. What is the value of pharmacogenomics? How is value defined? How does value change by whose perspective we're looking at? And how can value be measured?

I think it was important to first tell you just briefly where I'm coming from, and that I do wear three hats. I'm primarily an academician. I do research on the application of economics of pharmacogenomics, on drug safety and policy issues, but I also do some work with the government which has helped me understand their view.

I work with the FDA, Steve Gutman in particular, advising them on pharmacogenomics, and I'm a member of EGAPP, which I understand the committee is already familiar with. I also do some work for industry, which has helped me understand their side of things in terms of how they define what value is.

So today I'm going to cover three steps. First of all, that we need to understand the importance of economic and non-economic incentives. We need to consider value from multiple perspectives, and we need to use innovative approaches to address new paradigms.

I'm going to use three case studies which you're probably familiar with. Herceptin, Iressa, and CYP 450 drug-metabolizing enzymes. First point, understanding the importance of economic and non-economic incentives. Pharmacogenomics adoption will only occur if there are properly structured, aligned, and built in incentives. I often hear, and I heard this morning, that physicians need to be trained, when economists would immediately jump up and down and say no, that is never going to be enough, there need to be built-in incentives for physicians to use pharmacogenomics, or it will never occur.

The problem is that incentives push in different directions, and the incentives for adoption may vary based on the characteristics of the intervention. Here is a laundry list of some characteristics that provide incentives for adoption. This is my own list.

In life threatening versus a chronic condition, if there is a strong advocacy group or industry interest, obviously there are high reimbursement coverage and rates, and I understand the committee has already talked about reimbursement. As my colleague was just saying, if pharmacogenomics is used early in the pipeline as opposed to later, if it is used for immediate versus future treatment decisions, if it is used for focused, narrow treatment decisions.

A very important one that I've been hearing a lot about is that if pharmacogenomics can be used for off label indications, there is a lot more interest in using it. If it's used for ongoing monitoring versus one-time use, if it targets an acquired versus an inherited mutation, when it dictates what treatment will be used as opposed to suggest the treatment or dosage, and then finally one that you might not have thought of, which is pharmacogenomics is more likely to be implemented when it is not considered pharmacogenomics.

In other words, we frequently call it personalized medicine, targeted therapy, smart drugs. Now, why might that be the case? Well, first of all, the concept of personalized medicine is much bigger than pharmacogenomics. For example, it includes use of family history. So it builds on existing approaches, instead of appearing to emerge de novo.

It is easier for people to understand and support the concept of personalized medicine versus genetic testing. One reason being because it emphasizes the drug as opposed to the person.

Let's look at some case studies. Herceptin. This illustrates a very fast and successful adoption. It is one of the best known examples, although people don't consider it to be true pharmacogenomics because it targets a tumor. It has proved that targeting to small populations can be feasible and profitable for industry. Sales keep increasing, they're going to go up today probably based on the newspaper articles.

In 2004, sales were \$479 million, a 70 percent increase in one quarter alone. It's important to note that testing here is for gatekeeping, not for dosage decisions. In other words, if you test positive, you get the drug.

Iressa is an example of a fast but currently unsuccessful adoption. Here we have a case where the FDA accelerated approval of the drug, but the drug has been essentially withdrawn from the market because post approval clinical trials showed no significant survival benefit. However, the drug does appear to benefit specific populations, but until recently there has been no diagnostic.

There is one now developed. We marked it by Genzyme, but right at the moment there is limited availability. It is an expensive test, and right now it is unknown what the benefits will be.

CYP 450 testing illustrates slow adoption. There have been many implementation challenges, the multifactorial nature of drug response, the lack of data linking mutations and clinical outcomes, variability not only across drug classes, but within drug classes as well. In this case, testing is of the person, and that raises more ethical issues. Testing here at the moment is not a strict gatekeeper test. In other words, the incremental benefit of the test is harder to measure.

The second point. Consider value from multiple perspectives. All stakeholders want evidence of value, but they're going to differ in terms of their perspectives. Unfortunately from a societal perspective, there is very little documentation yet of the value of pharmacogenomics. We did a review of all the studies to date, and we only found 11 cost effectiveness analyses of pharmacogenomic interventions. A very limited range of conditions have been studied, and the results were quite mixed.

What are some of the challenges to determining the value of pharmacogenomics? Well, first of all, differences in perspective. In the value, determinations are often made before the product reaches a clinical setting.

I was talking to Fay about my talk before I came, and she said you're talking a lot about the pipeline before you get to the clinic. I said, but that's because the economic decisions are often made long, long before the product reaches the clinical setting. Therefore, we need to consider economic incentives throughout the pipeline, and evaluations need to be conducted before the intervention reaches the clinical setting if the societal benefit is to be maximized.

There are a number of technical issues in determining value. Lack of data I've already mentioned, linking pharmacogenetics to outcomes, comparative effects on therapeutics, and on the products themselves, because much of the data are proprietary, so that economists like me can't get our hands on it.

We have to evaluate complex, multifactorial conditions. By definition, diagnostic drug combinations are more complex to analyze than the separate interventions.

There are a number of policy and political issues. There are few incentives to assess the economic from a societal perspective. We don't see those incentives for advocates, industries, FDA, CMS, insurers. That's not usually their role. Pharmacogenomics often has the benefit of preventing what has not occurred. It is always harder to measure the value of prevention. For example, avoiding adverse effects. It's very hard to measure what the true value of that is.

Also, with diagnostics. They often are harder to measure the value of. I often hear people say, well, the up front testing cost is going to outweigh the downstream savings.

Herceptin illustrates a successful adoption, despite the lack of documentation of societal benefit, and I'm going to pause on this slide because this is a very important slide. Many people do not realize this. Herceptin is expensive. In the newspaper today it says it's actually \$4,000 a month. It increases median survival by a few months.

There have been a few economic analyses. One was done by a group at Harvard and was considered to be well done. They concluded that Herceptin cost \$125,000 per quality-adjusted life year gained. The important thing to understand about that is that anything that's over around \$50,000 is usually considered we're not so sure if the benefits are worth the cost, and outside of the United States, approval of the drug for national formularies was slow because of the concerns about the cost.

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Iressa. Now, Iressa illustrates how failed adoption has the potential to create large, societal losses. Sometimes we don't think about that, in that a withdrawal of the drug from the market incurs large losses not just to industry, but to society as well because of the patients who don't benefit, the regulators having to spend all that time regulating, and in general it increases public concern about drug safety.

CYP 450 testing is an example of where widespread testing could have a huge economic and societal impact, but it is going to require some creative and complex approaches to assessing the value.

We did a study back in 2001 that found that there was a linkage between adverse drug reactions in P450 mutations, that was a first step. We more recently did a study just looking at CYP 2D6, and we found that it could have a large impact because many drugs are metabolized by CYP 2D6, that testing could be relevant to 189 million prescriptions, and \$12.8 billion in expenditures annually in the United States, particularly in the area of mental health and hard to seize drugs.

But, and this is a very big but, there is currently insufficient data to assess the impact of CYP 2D6 testing. There is very limited data on the clinical outcomes of testing, and Strattera mentioned the availability of the test.

My third and final point, use innovative approaches to address new paradigms. We have already talked this morning about the role of diagnostics, co-developed diagnostics, and drugs that are going to play an increasingly important role. As we know, that requires integration of historically divided industries and regulatory mechanisms, and it requires early consideration of diagnostics, which we just heard from my colleague.

I am doing a study for the FDA looking at barriers in the diagnostic pipeline where I'm interviewing a lot of key leaders. I have heard three major barriers mentioned. One is money, both in terms of initial investment, biomarkers, and then reimbursement rates.

The second is availability of data in samples, and the third is the clinical utility of tests are often not evaluated, and thus it is difficult to demonstrate the value of diagnostics.

With Herceptin and Iressa, we have seen that it will be challenging to develop and determine the most appropriate diagnostic. With Herceptin, several tests were approved, but there is still debate over which test to use, and the development of diagnostics is often going to require multiple stakeholders who traditionally have not merged forces, academia industry and the FDA.

With CYP 450 testing, it illustrates it will be challenging to adopt pharmacogenomics when it's relevant to multiple diseases and drugs, because P450 testing is only done once in your lifetime, but the results are relevant to multiple diseases, drugs, and clinical specialties. So it's unclear who is going to advocate for testing.

Another critical issue is whether the test will be considered diagnostic or for screening. For example, Medicare covers diagnostic tests, but they do not cover screening tests. In this case, it's a bit unclear which one the test really is.

So it's unclear whether consumers are going to seek this out. Providers will provide, industry will have incentives to continue to develop such tests, and whether insurers will cover these tests if they are considered screening.

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So to summarize, some of the next steps to address economic challenges of integrating pharmacogenomics, understand the importance of economic and non-economic incentives, incentives do matter. They're often contradictory, but they can be shaped by health policies.

Consider value from multiple perspectives, the definitions of value will vary, but value must be determined one way or the other. If it is not done from a societal perspective, then it will be driven by other perspectives. Therefore, I would argue that we need incentives for more economic research.

Third, use innovative approaches to address new paradigms which require a truly multidisciplinary approach in innovative funding mechanisms. Unfortunately, social science often lags behind basic science in this area. Why is that? Well, it's a riskier area to do research in. It requires more in-depth understanding of basic and clinical science, and it's hard to get funding in this arena.

It also requires development of an evidence base. The Pharmacogenomics Research Network is a good example. They are developing a database, however they explicitly do not include issues regarding application of their technology.

Then EGAPP once again is a good example, but ultimately EGAPP will end, and those issues then will need to be institutionalized if those evaluations are going to continue.

So to conclude, pharmacogenomics is here now, and will keep coming. I believe that there will be an inevitable push towards pharmacogenomics because it's part of a larger trend towards personalized medicine.

For that, genetics information is only one piece, but it will be a critical piece. I believe the government, therefore, has a critical role in facilitating the appropriate use of pharmacogenomics in order to maximize its benefit by shaping incentives, by ensuring that value gets measured from a societal perspective, and by facilitating innovative approaches. Thank you.