

Pharmacogenomics Session
Q & A and Committee Discussion II
Facilitator: Emily S. Winn-Deen, Ph.D.

DR. WINN-DEEN: I want to thank both of our speakers for this session for very informative and insightful presentations. We have got about 20 minutes for Q&A from the committee.

Muin has his hand up already, so we'll let him go first.

DR. KHOURY: I'd like to thank both of you this morning. I have learned quite a few tricks today. But it is very interesting that we are embarking on what we call personalized medicine.

We still have to have a societal perspective on this. I think as a public health professional, I really subscribe to this endeavor.

I wanted to ask both of you sort of a question around this pipeline, the incentives or disincentives, and maybe use a couple of examples. When things are out and we discover that they are suboptimal or have side effects, they tend to be withdrawn from the market.

For example, the COX2 inhibitors which are very effective, unfortunately they double or triple your risk of heart disease. I don't know how much it translates into absolute risk with respect to patients.

In the area of vaccines, for example, and that's something you don't talk about, or we haven't heard about, a few years ago there was a rotavirus vaccine that was very effective. Unfortunately, a few percent, a few per million babies had intussusception, and as a result, the vaccine was pulled from the market.

We are talking about very rare side effects in some cases, which is the rotavirus vaccine. Although the benefits were really proven to save a lot of lives as far as diarrhea as a major global health threat, I guess around the world, much more than in the U.S.

In the case of the COX2 inhibitors, there were millions of people, and I'm one of them, sort of the back pain and other things depended on having a steady flow of that therapeutic.

So can you kind of revisit those two examples? I'd like both of you, because these were sort of distal to the pipeline. By then, I guess the drug is already on the market, the price has been set, but side effects emerged, and instead of studying why some patients are more susceptible to heart disease as a result of COX2 inhibitors, the drug was pulled from the market.

So there is a clear disincentive, economically at least, to study that. So help me out a little bit with that example.

DR. PHILLIPS: Well, that's very interesting. It speaks to the idea that some people think that pharmacogenomics is going to be a panacea. I'll return to the newspaper article this morning. Although I read it, my time is 4 a.m. in the morning, so I can't guarantee I read it correctly, but I thought it was very interesting that they mentioned Vioxx.

As far as I know, pharmacogenomics couldn't have helped that issue at all.

DR. KHOURY: But we need investment in developing biomarkers.

DR. PHILLIPS: Yes, yes.

DR. KHOURY: That's the question I'm asking is to find out why.

DR. PHILLIPS: But in this case, we don't know of anything that could have helped identify who was going to benefit and who was going to be harmed by Vioxx.

DR. KHOURY: Right. But it wasn't done before. Could it be done now retroactively I guess postmortem? Or is it too late to save those categories of drugs?

DR. PHILLIPS: Well, the other thing I thought was really interesting about the article, they never mentioned the word "pharmacogenomics." It was all grouped together in this idea about personalized medicine, and it was all portrayed as we can now cure cancer through personalized medicine.

So I get a little nervous when I see those types of messages going out to the public that are going to raise hopes that maybe it's going to take awhile to address.

MR. METCALFE: So just to maybe answer, I think the safety aspect of this, certainly Merck was highly incented to try to find a predictive marker. But I think it's probably, and I don't know enough about the specifics about it from the Merck perspective, but it is practically a very difficult thing to do, to reliably predict. So this is in terms of predicting, and not monitoring, to reliably predict who is likely to suffer an adverse event because of a drug when you're looking at something that happens in a very few percentage of cases, an extremely difficult thing to do.

It's not only difficult to find the predictive marker, but it's also difficult to validate it as well. You would require very big studies to validate that in order to demonstrate that effectively. So that's one thing.

The other thing is that in many of those cases, particularly in the Vioxx case, you still have a drug on the market which is an alternative, and obviously if you have one drug which has a higher frequency of safety issues than another, you are going to use the alternative which doesn't require the predictive marker. I think that's very clear.

There are some cases, as with, for instance, the use of the TPMT test, where that is a safety marker, you're looking at something which is relatively frequent. Unfortunately with that marker or that test, you can reliably predict who is most at risk from safety.

So there are some exceptions to this rule. I think that it's going to be very difficult to do this from a safety perspective. Certainly in the rotavirus case you mentioned, if one had been able to do that, then perhaps there would be a case to do that. I think the manufacturers are also reasonably well incented to do that at the moment, if there was something which was feasible.

DR. WINN-DEEN: Kevin?

DR. FITZGERALD: I'd like to thank Muin for his question, because I want to piggyback right on top of that.

Before I do, I just wanted to mention one other thing. I'm fascinated by the fact that an economics researcher would see incentives for the need for more economics research.

(Laughter.)

DR. FITZGERALD: But in any case, what I'd like to ask you, both of you, the flip side of what Muin was asking. He kind of focused on the safety. I'd like to ask what the incentives, the economic struggles, and challenges might be on the efficacy side.

What is the possibility here for rehabilitation of drug products that have failed in a sense in the past because groups weren't identified necessarily that could be identified now that might benefit?

So BiDil of course would be the perfect example recently. Now my understanding is that also received new patent protection, so that obviously would help. So you'd have to probably distinguish between when that might be possible, and when that wouldn't be possible.

Another drug I'm thinking of as a possibility of an example, I don't know if you're familiar with it, is Eflornithine, which of course originally was considered to be a cancer drug. It turned out to be one of the best treatments they found for Gambian sleeping sickness. Of course there's no market for that, but then it actually got onto the market as a facial hair remover.

(Laughter.)

DR. FITZGERALD: So it's these kinds of things, the beauty of it being of course now that it is back active, you can hopefully move some of that into Gambian sleeping sickness treatment. So I'm just wondering, what are the possibilities here to go back and look at different ways of rehabilitating old products?

MR. METCALFE: So I think you have a case where new insights would allow you to use an existing compound in a different indication. As long as there is sufficient patent protection, I think there is plenty of incentives to do that, and plenty of possibilities to do that.

I think from our point of view, the two biggest, or the area where the incentives are between what are out there at the moment and our view of what the societal perspective is are most misaligned, where you have a drug on the market already which is being successfully marketed where there is the potential for you say sharpening the target of that.

I think as I tried to lay out, there are few drug incentives for drug companies themselves to work on that. There are incentives for others to work on that, there are incentives of payer organizations to work on that, there are incentives to a certain degree for diagnostic companies to work on that, but there are few incentives for drug companies to work on that.

In general, I think the diagnostic industry doesn't have much incentive to invest heavily or speculatively in this area because it doesn't get value-based reimbursement. There are cases where there are companies now, diagnostic companies investing in let's say a test for improved prognosis of breast cancer, but that's because there are enormous general economic benefits from doing this.

I think that they are reasonably speculating that they will get a good economic return on this. But as soon as you go away from the biggest opportunities, the incentives for diagnostic companies decline quite rapidly.

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As for the cases that you mentioned, I think each case has to be looked at on its merits, but we don't see that as being a massive misalignment between potential societal benefit, particularly with orphan drug legislation.

DR. PHILLIPS: I will agree that's what I have heard. I will add the related issue of off-label uses where my industry colleagues tell me that the business models coming out all really heavily emphasize off-label use, in which they expect to make their money off of off-label use.

The insurance people I talked to are shaking in their boots because they have a really hard time dealing with the reimbursement of off-label uses because they don't have any evidence base to deny coverage. So they are caught in this in-between of they don't want to ration care, but they don't have enough evidence on which to turn back these requests for reimbursement for off-label use.

When you're talking about these very expensive drugs, they see it as a really critical issue.

DR. WINN-DEEN: James?

DR. EVANS: Yes, one of the things that has puzzled me is the lack of lawsuits that have been brought against, for example, physicians who don't use TPMT. For example, most of my colleagues don't, and certainly lawsuits are kind of an incentive or disincentive obsession with physicians.

I was wondering, from your perspective, I didn't hear either of you mention issues of liability. It seems to me those might be important in bringing pharmacogenomics forward or not.

My other question is unrelated, and that came up in the survey results we saw earlier today. That is in those gray areas, and it is almost always going to be a gray area about whether a pharmacogenomic test predicts that a certain person might respond better or might respond worse, do you think that insurers will tend to try to deny coverage for that drug for those individuals for which there is some evidence that they would not respond as well? So those two questions.

MR. METCALFE: So on the liability perspective, it is obviously I think a reality in the U.S. market. I think where you have a clear standard of care, and where that standard of care isn't adhered to, then there is obviously much more risk or chance, whatever way you look at it, of litigation.

I don't think we have a strong view of that, except that it makes sense to provide enough evidence to establish a clear standard of care where you have that evidence. So I think that covers the litigation issue from our perspective.

I'm sorry. The second question was?

DR. EVANS: Well, following up that first part, do you ever think there will be a disincentive among companies to even do such research because they really don't want to identify those in whom an adverse reaction might occur? Does that make any sense, or is that more of a conspiracy?

(Laughter.)

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MR. METCALFE: I mean, certainly it's one of the things that one takes into account when you look at litigation risk in general when you look at opportunities, but it's a reality which is out there, and I think that certainly we try very carefully.

Litigation I guess is the extreme end of the risk/benefit continuum, and we are very concerned about the risk/benefit continuum. We want to do as much benefit we can with as little risk as possible.

So you are going to shy away from the extreme ends of that and try and focus on where you are doing the most benefit with the least risk.

DR. EVANS: The second question.

MR. METCALFE: I remembered what your second question was.

DR. EVANS: Right. Do you think there is a chance that insurers would tend to deny coverage for drugs that were suggested that they would be less effective in an individual? Do you think that's a potential problem?

MR. METCALFE: I don't know whether it's a problem. I think it's a reality if you have clear evidence that a patient is highly unlikely to derive any benefit.

DR. EVANS: Right. I'm talking about what is going to be very common, which would be the less clear cut issue. So 60 percent chance of responding versus 30 percent chance of responding, which I think will be far more common with these tests than a really extremely clear cut.

MR. METCALFE: I think it's something that certainly we haven't debated this long and hard, so I don't think there's a clear cut answer.

One of the things that we look at carefully, though, let's take, and I think it is a good example that we've just seen which does inform us a little bit is the situation with Tarceva, where you have a patient, and there is no strong evidence base currently to deny patients, particularly Tarceva, based upon the EGFR expression rather than the EGFR mutation base.

If you are going to require patients to undergo a biopsy which is invasive which has potential mortality and morbidity in order to extract that test information, we think that's probably unreasonable to do that, lacking the strong evidence base, and even if the evidence base was there, that also might be questionable. So there are many questions which inform whether or not it makes sense to try and acquire the test information, and then the interpretation of it.

Obviously the clearer cut it is, the more likely I think it's going to be included in reimbursement decisions.

DR. PHILLIPS: I'll add very briefly that patients do play a huge role in determining what pharmacogenomics interventions went forward. In the case of Herceptin, originally Genentech was reluctant to move forward. There was a huge patient advocacy move, patients chained themselves to the gates of Genentech and demanded the drug.

In that case, it did have an impact, but of course they were talking about breast cancer, and that's quite different than a lot of diseases where there are no advocates.

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DR. WINN-DEEN: So I'd just like sort of a wrap up question for this morning's session to ask you both.

You did really a very nice job of helping us understand the financial decisionmaking and value proposition, thinking that a corporation goes through as it is making decisions about how to take things forward.

It is our charter to advise Health and Human Services. Do you have some specific things that you feel should be done at the HHS level that would benefit the industry in general? Advice, comments, anything? I'd just really like to give you a chance to make any pitches that you might have for government partnership in this.

DR. PHILLIPS: Well, of course I have to say economic research.

(Laughter.)

DR. WINN-DEEN: Okay, okay. Besides funding your grants.

DR. PHILLIPS: More economic research. I did try to cover that in my final slides, and I do think the government has an important role here, certainly in terms of the evidence base and helping facilitate the evidence base, and ensuring that value gets measured, that the perspective does get included. Otherwise, that might fall through the cracks.

MR. METCALFE: I think there are three or four things that we see. One is working on basically getting a clear regulatory framework and a clear set of standards. I think you've heard a little bit about some of that this morning. Companies can invest with confidence in some of the opportunities around this because there is a clear framework out there. That's one thing.

The second thing is in general, and I think that we're seeing a movement in this direction, more funding for translational research. Happily, we're glad to see there is a movement in this direction. But I think it's slower than it could be.

The third thing I think is clearly having the right incentives aligned for profit-oriented companies in this arena. The particular area we see there is value-based reimbursement. Kathryn quite rightly says that one has to understand who is getting which value, and to try and have a clear interpretation of what the value is.

But if there is a clear misalignment of the incentives of the value correlation, it is unlikely that profit-oriented organizations are going to invest in these areas.

DR. WINN-DEEN: I'd like to thank both of you very much for your participation. I know that you came a great distance to be with us today, and we really appreciate your time.

We're going to take a lunch break now, and we will resume the afternoon session promptly at 1:15.

(Whereupon, at 12:20 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m.)