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Pharmacometabolomics to Predict Statin Response: Ready for Prime Time?

Dr. Brown:

You are listening to ReachMD and this is Lipid Luminations sponsored by the National Lipid Association. I am your host, Dr. Alan Brown, and with me today is Dr. Rhonda Cooper-Dehoff, Associate Professor in the Department of Pharmacotherapy and Translational Research in the Division of Cardiovascular Medicine of the Colleges of Pharmacy and Medicine. She is also an Associate Director for the Center of Pharmacogenomics at the University of Florida.

Dr. Brown:

Thank you very much for taking time to come and talk to us.

Dr. Cooper-Dehoff:

Thank you for having me.

Dr. Brown:

I do not know if our audience knows that today we are actually broadcasting from the National Lipid Association Fall Clinical Lipid Update and you gave a presentation just before this session, I think, on pharmacometabolomics.

Dr. Cooper-Dehoff:

Right, it's a mouthful.

Dr. Brown:

It's a mouthful. Give us a synopsis of what you presented today to the members of the National Lipid Association.

Dr. Cooper-Dehoff:

So, metabolomics is really the study of all of the small molecules in our body, so the amino acids, the very small lipidomic molecules in our body, and we've come to a state where we understand that we can study effects of drugs on the metabolome or our small molecules by looking at, for example, people who respond well to a drug and people who don't respond well to a drug, and look at differential signatures of these small molecules. So, not only can we look at responses to the drug, but our baseline metabolite signature and try to understand who might respond or not respond in the beginning so we can develop a more personalized approach to selecting our drugs for really any disease whether it is hyperlipidemia or hypertension or what have you. So, that's kind of the field that we are in whether it is pharmacometabolomics or pharmacogenomics where we want to understand how does our DNA makeup predict what drug we might respond to or not.

Dr. Brown:

So now this gets into this hot topic of personalized medicine. However, we've had some schizophrenia in this field, right? So, in other words, we can find, for example, people's response to certain agents like aspirin resistance and clopidogrel and yet when we look at clinical outcomes, sometimes it does not correlate with clinical outcomes and other times it does. Maybe you could give us some examples where we have great data and maybe some examples of why you think occasionally the clinical scenario does not fit with the metabolic scenario.

Dr. Cooper-Dehoff:

You brought up the example of clopidogrel; it is an excellent example to look at. The first data emerged from clinical trials so those are the most homogenous sample sets where everything is very well-controlled. You look at genetic response to a drug and you can really identify who might not have the enzyme functioning that's required to metabolize a drug and make it work. In other cases where you look at epidemiologic data, the results might be very different. Or, if you look at contemporary patients who we now have these electronic health records that allow us to look at prospectively collected data but they're, much again, less homogenous than a clinical trial, then you have another opportunity to look at these results. So, for clopidogrel, we actually have a homerun there. So no matter which data set you look at, when you look at outcomes – and there's going to be emerging data in this that have not been fully presented yet—the data looked very, very good, that no matter what kind of populations you look at, that presence of a particular polymorphism effects how the patient's respond ultimately with regard to hard outcomes.

Dr. Brown:

Ok, I'll look forward to that. As an interventional cardiologist I will look forward to hearing the data. Since we are talking about lipids, let's hear a little bit about what we know about lipids, and I know there's been a lot of work about statins and, in fact, I'm starting to see some referring doctors ordering genomic testing and metabolic testing on people to try and determine which statins to use. Can you tell us a little bit what the science and the art is there?

Dr. Cooper-Dehoff:

Sure. So, with regard to pharmacometabolomics – that is the study of small molecules that might allow us to understand who's going to respond to a statin or not – there are now emerging data in the sphingolipids and the phospholipids, in the lipidomics platforms that clearly identify what a baseline signature looks like for someone who is going to respond versus someone who is not going to respond. The problem is we are probably not ready for primetime, as was indicated in my talk, because they're small

studies and they haven't been well-replicated. So, what we do know in this kind of field and before we can move into any kind of a precision approach or a personalized approach, we have to have well-replicated data. For the metabolites in statin use, we are not there yet. However, for the genomic area, where we look at who is going to develop myalgias, we actually do know and there are now what we call clinical pharmacogenomic guidelines for this that would suggest if you have genomic data available in a gene called SLCO1B1, which is a transporter, there are indications that people who have a particular polymorphism there will be more likely to have a myalgia when they are treated with simvastatin. So, clearly in that case, if you identify a patient with that polymorphism you would use an alternative statin. So, I think we're getting closer. We don't have any clinically available tests for that test yet, but if a patient comes to you with their 23andMe data that they have gotten and it is an indication that you might want to prescribe another statin other than simvastatin. I think we are getting there. Are we there in every case yet? No.

Dr. Brown:

As I said, I am starting to see those tests show up in my office when people are referred to the lipid clinic so that is very helpful. I think, going back many years, patients have said that their mother has a problem with a statin, back when simvastatin was ubiquitous, for example. I mean that was the most popular statin for many years. They say, my mom cannot take it, my sister cannot take it and I cannot take it, and folks thought it was just power of suggestion, but in reality we see that over and over again.

Dr. Cooper-Dehoff:

There clearly is a genetic component, especially for that particular gene in simvastatin users and that is because its particular pathway related to simvastatin.

Dr. Brown:

If you are just tuning in, you are listening to ReachMD. I am Dr. Alan Brown and with me today, I am happy to say, is Dr. Rhonda Cooper-Dehoff, Associate Director of the Center of Pharmacogenomics at the University of Florida. Tell us what else is fascinating in genomics and what you're doing. Are there any projects you are involved in that you're particularly excited about, maybe that haven't hit the clinical use yet but you think will be a real help in the future?

Dr. Cooper-Dehoff:

Our lab is doing a lot of work in hypertension, so we are also looking at how or why particular individuals might respond with regard to blood pressure lowering to one class of drugs versus another, for example, beta blockers versus thiazide diuretics. We are also looking at combinations of omics level data so we have genomics, transcriptomics, and metabolomics. In all three of those omics data in one clinical trial data set so we can really delve down into understanding why people respond and have adverse events to antihypertensive drugs. So, I think that is really something, again, not ready for primetime but we are getting there. I think with President Obama's precision medicine initiative, we are going to have data sets in the millions that really combine electronic health record as well as genomic data and biochemical data and metabolomics and transcript data. We really finally have the ability to put it all together and understand much more about an individual's potential to respond in a particular way.

Dr. Brown:

This is very exciting. I remember the days when we used to look at hot reactors versus cold reactors and trying to decide and look at

bioimpedance or impedance of people with hypertension and try to decide whether they would respond to a vasodilator versus a diuretic. So there has been this journey probably since the beginning of medicine to try and decide not just how you compare to a population of 1,000 people like you, but how you as an individual will respond to a specific therapy and help guide our therapy. It is sort of a dream come true.

Dr. Cooper-Dehoff:

Right, I think we have come full circle from those days and, while I say that, we still have another journey while we just got the precision medicine initiative, it was approved last year, and really just a couple of months ago we have identified that NIH has identified which sites are going to be responsible for enrolling all of those patients. We still have a million patients to enroll and so I would encourage all of the listeners out there that you can participate as an individual, your patients can also go online and participate as an individual and we really have a lot of work to accrue those million people to get to the point where we can put pharmacogenomics and pharmacometabolomics to its maximal and optimal use.

Dr. Brown:

Okay, for the sake of our listeners, a practical question as we are getting close to running out of time, these tests are out there. People are doing pharmacogenetic testing; they are showing up with a series of 50 different results that they got from a laboratory somewhere. I think sometimes mistakenly they are being ordered to diagnose genetic lipid disorders like FH, just somebody ordered them by mistake. For the clinician, when one of these tests comes in front of you, which things on that sheet are ready for primetime and what should we be looking at?

Dr. Cooper-Dehoff:

Right, so with regard to drug response specifically, really the things that a pair is looking at and the things that are most currently used would be CYP2C19 for clopidogrel, CYP2D6 for opioid response and adverse response. So we know people who cannot metabolize an opiate appropriately can have a build up and you can have respiratory distress and people have died because of that. Also, there are a lot of drugs that actually have guideline-approved use for genomic information. There is a disconnect between the number of guidelines that are approved and the number of tests that are commercially available and paid for. So there's really only two that I am aware of, the CYP2D6 and the CYP2C19. There was a lot of buzz about warfarin testing so that would be CYP2C9 and then VKORC1, but those studies have not really panned out at the large level the way we expected and so those tests are really not currently available. That's not to say if you have that data on your patient because they have brought it to you from an outside lab, then, absolutely, I would look at it. Especially if you are just starting someone on warfarin and you have their CYP2C9 and you have their VKORC1, the most important time frame for that information is right at the beginning, so to try to get them to an appropriate INR sooner rather than later. If they have been on warfarin for a year and now you have their test and they are at a stable INR, you don't need that information. Really, it depends on the drug gene pair and it depends on the individual – which tests you would really want to look at.

Dr. Brown:

Without you endorsing anybody, because I don't want you to, are there any situations where we should be wary of the results or are the commercially available testing laboratories good enough quality that when you get those results you can be pretty confident?

Dr. Cooper-Dehoff:

I would encourage people to reach out to their University affiliations to really see what testing they're doing, or reach out to get guidance from them because as an individual who is a primary care practice doctor, it's very, very hard to know which tests are appropriately done, which tests have clinical decision support that's provided in a way that makes sense, and is usable in a particular individual. So, I would reach out to your local, maybe larger, institutions that can guide you there. I know for the University of Florida we do have a personalized medicine program in our hospital where we are doing the testing in the hospital, returning the results into the electronic health record, and we provide the practitioner with clinical decision support that helps them understand how to use it. We are trying to do that within the hospital so we don't need them to reach out to these outside labs where we are not comfortable with what the results might be.

Dr. Brown:

Probably the best advice to give physicians is don't order a test if you do not know what to do with the results.

Dr. Cooper-Dehoff:

Absolutely

Dr. Brown:

Listening to a program like this and getting an idea of what's clinically relevant and then making a decision of who is the right patient to get the test makes a lot of sense. Do you agree?

Dr. Cooper-Dehoff:

Absolutely. Definitely.

Dr. Brown:

Well, I wish I had more time to talk to you, this is fascinating. Thank you very much. I know you were busy at the meeting and taking time out to come and interview with us on Lipid Luminations was a great pleasure, so thank you.

Dr. Cooper-Dehoff:

You bet.

Dr. Brown:

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