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Session: Pharmacogenetics Trial of Depression: A focus on suicidal thoughts

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Heidi: I want to introduce today’s presenter, Dr. David Oslin. He’s the Executive Director with the Cohen Military Family Clinic at Penn, Chief of Behavioral Health, Director of VISN 4 MIRECC, and Professor of Psychiatry at the Perelman School of Medicine at the University of Pennsylvania. And with that, Dr. Oslin can I turn things over to you?

Dr. David Oslin: Yeah that’d be great.

Heidi: Okay you should have access. And your slides are on the screen.

Dr. David Oslin: Yep, thank you. And my audio’s good?

Heidi: Your audio sounds great, yes. Thank you.

Dr. David Oslin: Great. So thank you and thanks for those that are joining today. I’m going to do sort of two things in the talk today. Talk a little bit about where we are with pharmacogenetics in the context of psychiatry. And then somewhat of a teaser at the end to think about how we might use this trial to think about suicide prevention. So the bulk of the talk is really going to be about pharmacogenetics.

A few disclosures, sorry. I do some work with Janssen. I take grants from basically anybody so if you’ve got some spare cash around just let me know.

All right so pharmacogenetics, jokes are hard over these kinds of platforms so hopefully you’re laughing. Pharmacogenetics, so this is an NIH definition there’s many. But basically pharmacogenetics is the use of any genetic information in order to help change the treatment plan or to help a particular person with their illness in a way that improves their outcomes. So this is NIH’s definition. So how can we use genetics clinically to benefit patients?

So I have a poll here. This is going to work, Heidi? Yeah. So the poll is, in particular reference to antidepressants, which of the following best represents how pharmacogenetic testing might be helpful based on our knowledge today? So I think you can go ahead and do the poll now, it’ll take a minute? I don’t know how this works actually.

Heidi: Yeah the poll is open, and the responses are coming in. So they’re coming in slowly so we’ll just give them just a few more seconds to, for the attendees to respond. And it’s actually starting to pick up pace at the moment. When it slows down I will close the poll and read out the results.

Dr. David Oslin: Oh, all right. So I will be\_

Heidi: Okay.

Dr. David Oslin: I will address these issues as we go through the talk today, but to sort of see where people are.

Heidi: Okay, I’m going to go ahead and close the poll. And we have 49% that selected A, 20% selected B, 22% selected C, and 6% selected D.

Dr. David Oslin: Okay.

Heidi: Thank you and back to you.

Dr. David Oslin: Oh, great. Great. So we have some work to do. the answer is not A, I will tell you that. And hopefully I can help you with why it’s not A as we go through the talk here.

So why are we even thinking about this and isn’t this science for the future? No, it’s actually not. Pharmacogenetic testing is actually widely, widely available commercially right now. There is at least a dozen companies that I know that will do pharmacogenetic testing. And I will have to say that the vast majority of them actually focus on psychotropics because it’s the largest market of prescription medicines out there, it’s one of the largest markets. So they all think that they can tell you how to best pick medicines for patients particularly psychotropics. But it’s not just outside in the commercial [inaudible 04:11]. The VA actually started about a year or so ago a project called PHASeR in which it is providing testing essentially for free. It’s a partnership, it’s a donation to the VA of about a quarter-million Veterans. The Million Vet Program which is also a VA program, sort of the world’s largest DNA bank, is beginning to experiment with return of genotype results for particularly rare events or when patients might need them. So testing’s commercially available some of you may have used testing in your practice. Others of you may have had patients come to you asking for testing. It’s here and we have to know how to use it. A really important issue for us to understand is that there is no regulatory oversight on pharmacogenetic testing. The FDA does not endorse commercial products or any of these products. They don’t get approved. These are lab tests and so a major difference between pharmacogenetic testing and your typical lab is that if I order a sodium or a hemoglobin test as a physician I sort of have a really good understanding of the test results I’m going to get. But when I’m ordering that I am basically trusting that the lab, which is CLIA-approved often as one of the accrediting bodies, is doing that test accurately. Well the same actually is true for pharmacogenetic testing. So when I order a pharmacogenetic test I am trusting that the lab is going to give me right, back the right information, the right genotype for that particular patient. So the lab is accredited to give you the accurate test results. But I would venture that 99% of us on the call, and I would include me in that would have no idea how to interpret that individual genotype. And that what we were really hoping to get from that information is the interpretation of that genotype. And it’s that interpretation for which there is not an industry-wide standard or approval process for right now. There is some attempts to standardize but they’re not official at this point. So just keep that in mind. There is some fluidity, there is some fluidity if you send the same sample, same patient to two different companies. You might get in some instances slightly different recommendations. You’ll get the same genotype back so that test is the same but the interpretation might be slightly different. And that’s a little bit of a problem for the field right now.

So an important aspect of pharmacogenetics is it’s not the disease genetics I at least learned when I went to medical school a few years ago. When I went to school we learned about things like Huntington’s Disease and Alzheimer’s disease and the risk that genes will have for developing those illnesses. Many of us understand cancer profiling BRAF genes and other types of cancer profiling that really tell us about the disease itself. Knowing more about the disease actually might help us pick treatments for that disease and that happens a lot in cancer. It’s not actually pharmacogenetics but disease genetics. In the pharmacogenetics domain we actually have really two sort of fundamental principles; one is that that genotype can tell us something about how that particular medicine works in a person. So that would be pharmacodynamics. The idea is that this was answer A, the idea that this medicine actually works differently in this individual and may be better for that person. The other aspect that you can find out about medications with genetics is pharmacokinetics. And that has nothing to do with the disease that you’re trying to treat. It has to do with how our body manages that medication. This is usually metabolism. It’s almost all of it, what we’re talking about in pharmacogenetics is metabolism. And much of that metabolism variation is actually an aesthetic form of P450 system in the liver. So when you’re thinking about pharmacogenetics there are some examples of pharmacodynamic in our actions but the vast majority of where we are in 2020 is around understanding metabolism of medications and how a particular individual might metabolize a medication differently. That will in theory lead to different responses, right. Because it will change the dosing that we have to do in that particular person. So I’ll show you an example in a minute but it might mean that we either need to dose more slowly or dose more quickly. The FDA does sometimes in labels, actually all the time in labels, will have some profiling on genetically actionable genotypes. But they again don’t endorse particular tests in the process. Let me see if we can go forward.

So here’s the concept. The concept is that there’s a lot of things that go into our decision to pick a different medication for our patient. In psychiatry we are blessed to have a couple dozen or so antidepressants to choose from. Same goes with antipsychotics, et cetera. So there are choices to be made. In some areas of medicine there may not be so many choices. And these are all the sort of some of the factors that typically go into picking a particular medicine for a particular individual. There’s a lot of art involved in this. The idea is can pharmacogenetics be another one of these data points for us as clinicians to help us select a medicine that may end up benefiting that patient more. And I’ll keep coming back to this issue of efficacy versus benefit.

So in the psychiatry field right now almost all of the pharmacogenetics that you will get back from any of the commercial companies will almost exclusively talk about metabolism differences. They will at times include genotypes that will do, look at other things like the short and long arm or serotonin or some other markers that are a little bit more towards pharmacodynamics. But the vast majority of what they’re going to tell you is really about pharmacokinetics. So this is the concept. So this is not about efficacy but yet about drug level. So in a particular patient they may be an ultrarapid metabolizer so a given dose of X with that patient will have remarkably lower drug levels than a typical normal patient. If this is the normal patient in the normal blood level. And a patient that has a genotype that causes them to be a poor metabolizer for that particular medicine would end up having lots more medicine circulating in their system than the normal nongenetically influenced patient. You might understand that based on this information that ultrarapid metabolizers you might go the higher doses for that particular medicine. And the poor metabolizer you might go to lower doses and/or you might see more side effects. Because we know side effects are dose dependent. There’s a big theory here in the sense that serum levels mean something. We have a long history in psychiatry that we’ve actually not shown good serum level to response level interaction. So there is a question mark about whether knowing whether metabolism actually helps us in the treatment, but I will show you some encouraging news. So getting back to that poll question, C was actually the right answer. So we can right now tell you with confidence for a given individual through pharmacogenetic testing if medications for that patient are metabolized differently. What I can’t tell you with confidence is whether that actually matters in the outcome. I will show you some very, very encouraging results and I’ll let you be the judge. So efficacy is not the answer, metabolism is the answer.

So why might this be important to us? This should be old hat for everybody on the call today. In our best hands, antidepressants in the first line only work half the time. A third of antidepressants are not refilled. And at least 10% of new treatments fail because of side effects. And each successful course of an antidepressant leads to more and more drop out of care. So if we could pick medicines better rather than what we have typically done in practice where we’ve tried one and then gone onto another, theoretically we would have a much better public health response to the idea of depression.

So here’s the state of the evidence. I’m going to leave this open for a second and I’m going to show you one of these studies. So there’s a plethora of non-randomized, open-label things that you can read at your pleasure and do whatever you want with them. The reality is that where we are at the moment is that there’s four relatively good-sized trials. One of which is actually a very good size, a Greden study. Two are on the smaller side, the Perez and the Perlis. And Bradley’s in between. So we have four different studies, they all use different just happenstance they all use different commercial products that’s labeled here. These are all industry-sponsored trials so take that with a grain of salt. And I’m going to show you the outcomes of one of those so that you can, it’ll drive home this metabolism issue a little bit more.

So the GUIDED trial, that large trial, was funded by AssureRx, it’s now Myriad Genetics. It used the GeneSight battery and they had essentially 1,200 patients participate. These were all sort of treatment-resistant patients. So they had to have failed at least one eight-week course of an antidepressant to get in. They were randomly assigned. And interestingly they were blinded to the outcome of their report. Actually that’s, it’s a single blind not a double blind. So the patients didn’t get back the report and the raters didn’t get back the report the prescribing clinician obviously did get back the report. But the patients didn’t get the report. I found that to be a little interesting and I’m not really sure why they did that. They basically hypothesized that patients that, which you had this test result available to you to help you prescribe those patients would get better.

For those who have not seen, this is not a commercial endorsement of any particular test, this is what the GeneSight company provides as a test result. It actually does two things. You will, it’s about a 15 or so page-long report. The latter pages are actually all the genotypes which is the lab output essentially. So that’s the hemoglobin level if you will, the sodium level. But the, kind of the meat for the provider is the interpretation of those. And you can see what they, this company does. And every one of these has a little bit different way of presenting the data. It actually bins the medications into so use as directed meaning that we have no evidence that there’s a genotype that’s influencing metabolism. And significant gene/drug interaction meaning that these particular medicines in this patient are probably either in the ultrarapid metabolizer or the slow metabolizer group for these particular medicines. There are millions, literally millions of different ways that this report can come out. Even though they’re only really looking at eight genes. And there’s no pattern. There’s no pattern recognition from patient to patient on these reports. It really doesn’t work that way. That’s the beauty of pharmacogenetics is you can’t pattern recognize.

So this the first level of outcomes in this trial. The first level of outcomes is actually, did the test results actually assist in managing the choice of antidepressant. And basically the bottom line here is that in about 76 or 77% of the patients there were, the test result was not available to the prescriber. By chance 75% of the time the patient was put on a medicine that was in that green bin. In other words did not have a genotype that predicted metabolism. In the arm in which the test results were available to the prescriber at the end of the eight weeks 90% of the patients were now on essentially a green bin medicine or a medicine that wasn’t genetically influenced in its metabolism. So what this piece of the outcome says is that the providers actually looked at the test results, talked to their patient about it, and decided to use a medicine in which they had more confidence in how to prescribe or dose. And they avoided those medicines in which dosing would be more complicated. Remember it wasn’t efficacy it’s about the dose. So rather than choose a medicine that’s an ultrarapid metabolizer and increase the dose they simply chose something that did not have a metabolism, a known metabolizing influence from a genetics perspective.

And then the question is, does that matter? And this is their outcomes and it was positive. Well so this is actually a secondary analysis, but basically it was positive across the board. If you look at patients that ended up on a congruent medicine meaning a green bin medicine. In the randomized arm, and I’m sorry I pulled the wrong slide here, in the randomized arm they actually got significance for response and remission but not symptom improvement in this study. So when you looked at the continuous HAM scores it was close but not quite there. Response and remission were significantly better. And if you look at just based on whether somebody ended up on a green bin medicine versus something else then improvement was in all three of those types of outcomes. So I put this in the very encouraging domain of outcomes. So again, what this again, I just want to hammer this home because it’s not about efficacy. What pharmacogenetics did is it told the clinician look this drug, let’s just say sertraline, is heavily influenced by genetics and we don’t then what dose to use so given equal choices I will pick something that I know how to dose and that seems to have an impact on people getting better. Whereas if it’s random and you happen to pick some of them that are genetically influenced and not knowing the dose those people don’t get as well.

So here’s where we are. So three of the four trials are positive in the sense that the testing leads to better outcomes. And the smallest trial was not positive, actually the two smallest trials. So again I think this puts us in the domain of very, very promising in the sense of pretty close to ready for primetime. These companies obviously are marketing heavily to all of us. And think that this should be used all the time. We don’t still have a sense of are there particular patients for which this is useful. This is it. This is the entirety of the literature right now. It’s only in depression. These companies actually give you pharmacogenetic results often for other psychotropics like mood stabilizers and antipsychotics. You’re really out on a limb in terms of what they’re providing there because there’s no trial data in those domains.

All right so now I want to tell you a little bit about the PRIME Care study which is a VA-sponsored study that we’re actually fairly close to the end of the trial. It’s a VA study called pharmacogenetics, I’ll show you the participating sites in a moment. The goal is to randomize 2,000 patients in a very similar way to the GUIDED trial but we’re not blinding the patients, the patients get back the test results. Enrollment has been at 22 sites and were not at 22 right now it’s at 15 at the moment. And the patients are assigned, patients and providers are assigned to the intervention group or the delayed results group where they get test results about six months later. This is a really pragmatic trial so it’s not like any of the industry-sponsored trials which basically were a given study team that did all the treatment at that site. Here we’re using frontline clinicians, patients in clinics we’re not taking patients away from their provider. The provider orders the test and they’re randomly assigned to one of the two groups. And it just determines when they will get back the test results.

The hypotheses are one, that the providers will avoid those medicines that have more contraindication if you will and that not, will end up having higher rates or remission and depression. And there’s a whole bunch of secondary outcomes including suicidal ideation, which I’ll show you some data for in a minute.

These are the participating sites. If you are at one of these sites and you want to get test results by all means you have to be at one of the non-starred sites. Maybe I should’ve starred the ones that are still recruiting. We’re sort of in a wind-down phase at this point. Recruitment just goes until January, through January.

It's a pragmatic trial. So the frontline providers are the ones that actually determine patient eligibility but we’re asking them to make sure that who they refer is somebody that they’re treating for depression. That they’re on monotherapy basically and that they’re starting, which could mean a switch or restart as well, an antidepressant. And they can’t have more severe illnesses like schizophrenia, bipolar, or active SUD. And they’re not currently hospitalized. So the provider actually determines all that. We don’t do a long lengthy SCID or other lengthy interview at the beginning. We actually are doing this trial now in the COVID time with studies being done completely virtually the patient does not have to come in to do consent or do their cheek swab or anything, everything’s done over the phone. Not the cheek swab, the patient does that in their home on their own. They do have to have a PHQ-9 of greater than nine and have to be 18 to 80.

So these are just some interesting findings that will lead to a couple notations about it. So similar to you guys and the poll questions you didn’t know a lot going into the trial. So I’ll show you in a minute that that led us to have to, for this trial is we had to develop a whole educational portfolio for helping providers understand pharmacogenetics. And this bar graph on the left just shows that the two red bars are mental health providers they have very little experience ordering tests or ordering pharmacogenetic tests. This is basically about a year and a half ago. And while primary care providers have more experience ordering sort of disease genetics they also don’t have much experience in ordering pharmacogenetic testing.

So some of the opportunities we’ve had to adjust in this study along the way is one to develop training for the patients and providers. It’s just there, sure there were commercial-level brochures and stuff but we wanted to make sure that people had a real good understanding of pharmacogenetics and what the state of the art was. Particularly around this issue of efficacy versus metabolism and side effects. We essentially had to develop subject matter experts at each site that became the local site PI. And to, as a different trial really develop a recruitment strategy for engaging primary frontline providers. That has been not an easy task. It’s been an even more difficult task as we’ve gone remotely but we’ve done pretty well. And we do all the outcomes through a centralized call center to be able, and as part of that call center we also had to develop a strategy for addressing high risk which translates into some of the response that we have for the suicide ideation.

So this is just a graph showing you where we are. The blue line is where we wanted to be at this point. The red, I think that’s red I can’t tell the color, line is our actual recruitment. And you can see we’re not far off. We just passed 1,700 I think or pretty doggone close, we’re within a couple of patients of 1,700. So we’re pretty hopeful that we’ll at least get the 1,900 by January but more likely hopefully we’ll get the 2,000. With maybe some help from some of you guys out there if you’re not an improper site so to speak.

This is just some of the demographics of people getting into the trial. So they look like Veterans, not surprisingly enough. Average age of 48, they’re probably actually I’m doing a talk tomorrow on geriatrics, that is actually substantially lower than the average age in the VA which I hadn’t realized. More minorities than Caucasians more than what the VA typically sees and that’s great because I can also tell you we know very little about these genes in minority groups. And almost all the data is based on Caucasians or European Americans. More women, this probably relates more, more women in the VA, this probably relates to affective illness being more common in women, I don’t know. And as suspected more of the patients are coming from mental health than primary care. The average PHQ-9 score is a 17, so these are not the worried well, these are patients with real depressive symptoms. Excuse me. And a lot of them do have PTSD, 58% of them endorse PTSD. That’s not an exclusion. Again the provider is saying that they’re using the antidepressants for depression but it could be also with PTSD at the same time. Fair number with anxiety. And some drink, some use marijuana. There weren’t supposed to be any that used other drugs but of course some got through. And about a quarter are tobacco users.

So the test utility. One of the things we are very interested in is, okay so is this something like a rare disorder like Huntington’s disease. Are you telling me that this test will be useful in one out of a hundred of my patients? Or how often is this going to be useful for me? So we took the participants, this is a paper that was just submitted this past week, and we looked at the, so some of them are coming into this study and they’re switching medicines, right. So they’re going from drug A to drug B. And those patients what we did is we took their current medicines and compared the genotype on the test to see whether that medicine which of those three bins essentially from that company, those were on prior to randomization. So what proportion of those patients were on a medicine that was highly genetically influenced and therefore the clinician could have benefited in the past from that test. The other thing that we’re doing in the study is at the time of referral we’re asking the provider to say okay so what medicine, if you’re in the delayed arm group, what medicine do you intend to prescribe in this patient before you get the test results back. So this is their guess at what they would use if the person’s in the control group. They do not have the test results back so this is based on where they know the patient and what they’re doing. And we also wanted to look at, so we wanted to look at the proportion of these two groups or medicines in terms of how many were genetically influenced and we also wanted to see if we could start to understand anything about patient characteristics that would tell us whether some patients would benefit more from a test than others. And that’s the treatment history we used for here.

So this is the outcomes of this paper that’s under review. The current treatment, so the medicine, so about half the patients come as a switch and of those patients about 20% of the time they are on, they are currently taking a medicine that is highly genetically influenced in its metabolism. So that’s one in five is I would say your cholesterol test is probably less well at screening than that. So that’s actually, from a public health perspective that’s a pretty high utility score. And then in the next intended group it’s actually a similar story about 19% of those are in that red group or highly genetically influenced. Here’s the other thing that these other papers haven’t looked at. So I told you there was a middle group that sort of was, maybe the evidence is there but it’s a little bit more soft. So 50% of the patients were in that group on the current treatment and about 45% of the next intended were in that yellow group. And many left so that leaves you 50, that leaves you about 30% or so in both of these groups that actually either by choice/by chance their current treatment was in a non-genetically influenced group or the next intended was. We also did look at whether past treatments, so this question was whether, should I test everybody or should I target people and we picked past treatment. We looked at some demographics as well. Past treatment does predict a higher potential for the next intended medicine to be red. So that does suggest that we should consider sort of targeting people that are treatment-resistant if we find another positive outcome from this trial.

All right. I did promise you something about suicidality. This will be the, so the last little hoorah here. So why do we care about suicidality in this project? It’s obviously highly correlated with major depression. We had an opportunity, we have some opportunities here. We have actually not looked a lot at a lot of this data. I had said earlier that we had to create a paradigm for which when we’re doing outcome assessments we were able to manage or deal with suicide ideation when we encountered it. Basically there’s research assistants that are calling people for their outcome assessments. And so what we did with that is actually, in the second bullet here, we actually have a clinician get on the phone with them at that time, it’s triggered with a positive CSSRS or a positive PHQ-9 on item nine of a two or a three. And a clinician will actually conduct a risk assessment over the phone. So we have done hundreds of these risk assessments that we then sort of feedback to the local site if they are, particularly if they are high and the patient’s not engaged in treatment. We use some discretion there. We have been doing the CSSRS and I’m actually going to show you some intriguing data about that both at baseline but then at all the outcome assessments, which are basically monthly during the six months of the trial. And again this is a dataset that will eventually become available for study.

But I do want to show you some intriguing issues. So there’s two ways to score the CSSRS. There’s the Columbia way in which you lump people into no risk, low risk, medium risk, or high risk. And there’s the VA way which you use it as a screener as true or false essentially. And this is the baseline risk level. And so about 10% of the folks that have screened positive in a sense of needing a risk assessment in the way that we’re doing the CSSRS in the VA. But there are many folks who have low risk or medium risk and about 8% have the high risk in the traditional way of scoring the CSSRS.

Here’s the outcome over time. And I’m going to show you, so this is what it looks like. You can see this taller bar is the low risk. So these are people who answered no to the first two questions. And it doesn’t change a lot over the course. I want to pull out the high risk which kind of goes down and the medium risk which goes up. And I just want to show you those as it’s somewhat intriguing.

So these are patients we followed repeatedly over time. And there is a course here in this sample, now this could be treatment working. These are all patients in treatment, right. High risk does tend to decline, doesn’t go to zero. And the medium risk group increases. It’s interesting that the high risk doesn’t go to no risk, right. So the no risk patients are fairly stable. This is not a within subject’s comparison, there’s no stats done on this. This is, I put this together simply for this talk. So don’t take this as a gospel in terms of thinking about how this works. I think we don’t have a lot of repeated measure data on the CSSRS in which to kind of think about but it is intriguing that there is, that for the, as a population at least in those 1,700 or this was actually in about 1,000 patients, the population risk will decrease with time but it actually doesn’t decrease to zero. It seems to switch or to lower in magnitude. But not a lot of these patients increasing to no risk. And I find that very interesting and something that we will need to explore.

And I think, yeah that is it. So I intentionally gave us some time for questions. I have no idea how we do questions on this, hopefully you guys have some. And hopefully you learned a little bit. So we will open it up for questions at this point.

Heidi: Fantastic. And I do have some pending questions here so we’ll just get started on those. And if anyone out in the audience does have a question please use that question screen to submit that into us. Okay first question here, to what extent is pharma funding this work to be able to get people to use certain antidepressants related to this? is this research influencing the types of drugs pharma is developing?

Dr. David Oslin: Two super questions. There is no, I can’t speak for every one of the dozen companies, but for the companies that I know better there’s no relationship between pharma and these, essentially think of these as lab companies that are no different than LabCorp or I don’t what your local lab company is but any testing lab. They are not, the choice of where they put the medications is not at all influenced by pharma. So there’s no quid pro quo here in terms of a relationship between pharma. And I can say that with pretty good surety. That would bring tremendous scrutiny from the FDA. And they would get in a lot of trouble. And they would basically lose their license to do their lab testing. So I feel pretty confident about that. I get a related question which I’ll answer in a second. As pharma, in search of things that aren’t genetically influenced you better believe it because this could totally help them in terms of market niche, right. So it’s not so much, now we continue to learn about new genes all the time. The cytochrome P450 system is not something that’s new. People have known about it for many years now. So I think they’re always looking for something that gives them a market advantage. You would notice in that example that I gave you, it’s actually a bad example but it allows me to make a point. There are more meds in the red bin than the green bin. I think there were only two or three meds in the green bin. There are some medications that actually aren’t metabolized through the hepatic system. And there are always going to be, for the most part where we are with the science since the science is mostly about cytochrome P450, they’re always going to be in that green non-genetically influenced category because that’s what we know. It actually because they’re renally excreted and not hepatically metabolized. It doesn’t mean that two years from now that we find a gene that actually does predict something about that drug, but right now we don’t have any information about hepatic metabolism for that medicine. So, no pharma influence. Those four trials, I mean so this is the flip side of that, those four trials that I showed you all done by those four companies. The VA trial no interaction with one of the commercial companies. We did choose to use a commercial product for the trial rather than creating it in the VA’s own infrastructure. And we went through a vetting process to choose the company that we went through. It had nothing to do with, they had no influence on the design, they have no access to the data. So I feel pretty confident that we’ve created a complete firewall between the VA and the research piece of the PRIME Care study and the company that we’re using for the trial. These are very important issues. Next.

Heidi: As I’m digging through, that is the only question that I have for you. I’m hoping that somebody else is typing in a question for us. We do still have about 15 minutes left of question time if anyone else out there does have a pending question, please send that in. We do have time to handle a few more questions here. We’ve got comments that this was a very helpful presentation.

[silence 43:10-43:25]

Heidi: Okay here we go, can you speak to the suicide data especially since the, you guys I’m not a subject expert I don’t know abbreviations, PGx panels were not built out to address suicide ideation. Does it speak more to that medication efficacy?

Dr. David Oslin: That’s a good question. We don’t know. We are actually in this trial taking a second sample to do whole genome in these participants. If you’re going to do a trial of this magnitude you want to try to collect as much as possible. So we will be able to look at disease genetics in the sense of are there genetic predictors to suicidal ideation. That is a plan of ours. Although 2,000 subjects is not a lot although 10 or 15% of the people with high risk is a fair amount. So there will be plans in looking at sort of the traditional disease genetics of, are there genetic predictors to suicidal ideation. The panel that’s on the pharmacogenetic sample I’d be shocked if that related in any way, shape, or form to a suicide. But I was more interested in with the CSSRS data that we have it is actually how the patients over time how does their suicide sort of evolve. The reduction in high risk I would hope that’s an influence of treatment. These are all patients that are actively or at least at the beginning were actively engaged in treatment at a VA getting psychotherapy, getting medications, getting a plethora of different things. So I’m glad to see that the high-risk number goes down. And hopefully that’s not just patients saying, I’m tired of answering the question. I am a little disappointed to be honest that the number of low risk patients doesn’t increase. And it’ll be interesting to have some people, and a couple of the sites in the study actually are people that are doing a lot more suicide research than I am but I think there’s some really robust data here for us to mine and think about in terms of suicidal ideation over time.

Heidi: Great. Thank you. The next question here, do you think that this type of pharmacogenetics testing will be sustained in the VA after the study ends?

Dr. David Oslin: So here’s my take, so I have a couple of opinions here. So PHASeR is available in the VA now. PHASeR’s not at every site. PHASeR is a clinical way, it’s not a research project, to get pharmacogenetic testing done on a given individual. PHASeR was not, the panel that’s being used by PHASeR is from Sanford Health, not Stanford no T, Sanford Health. That’s the company that’s doing the genotyping. Their panel is not as comprehensive around psychotropics. And they actually only comment on about I’d say 13 or 14 psychotropics in that panel. But I think, my guess is some providers will be frustrated with that. Commercial testing is available now the problem is getting your local lab to pay for it. So right now this is a send out lab, it costs about $1,000 per test. You only have to do the test once though. So I think of it more as an investment not a recurring cost. So $1,000 spread over 10 years is only $100 a year. I think if I did my math correction. So in the grand scheme of things if it really does help one in five patients that we treat that’s not a huge investment. I think the VA’s stance on this so far is, I have seen this is a very encouraging field of study. Everybody has eyes on this project. I think if the project shows similar results to the other four of the five that have been published I think you’ll probably see a dramatic shift in policy. You’ll see actually a fairly dramatic shift in pressure to change policy, not from me I don’t have an investment here. But from the commercial firms and from patients, patients who will want it more and the commercial firms will fuss more that we’re not doing more if the results are positive. If the results are negative you know I think it puts this thing back a few years. I came into this study having really, I was totally [unintelligible 48:43] I thought this was a little bit of snake oil in terms of where the field was. I, those that don’t know my background I was one of the co-chairs of the last depression CPG, clinical practice guideline. And in that document we strongly did not recommend pharmacogenetic testing and that was only about four years ago, five years ago. We’re about to start redoing that. My guess is that even before this trial has ended we would say that it’s a much more promising and should be done sort of at the discretion of the provider. That said I know that right now most of your sites if you put in a request to do testing it will be denied. That actually happens here in Philadelphia. Sometimes I’m able to tell the lab look this is a really good case for doing this and they will do it. Everybody is so cost-conscious in the VA right now, it’s ridiculous, both pharmacy and labs are held to high scrutiny around money. So I think, my guess is there’s a lot of eyes on the project. The one good thing about this project is we have a lot of senior leadership involved in the project from an advisory perspective. So people know what we’re doing in this trial. And I think they’ll be sort of, see change from what happens if we are able to demonstrate value. But so when is that going to happen I guess should be the next question. So the trial ends recruitment in January that means the last person, six months period of time is next fall. So I suspect you’ll start hearing results next winter. So another year from now before we start spilling the beans on what we found, whether it be positive or negative.

Heidi: Sounds good. Okay next question that I have here, what percentage of patients show non-normal metabolic response patterns? Does everyone have problems with some medication or are most people normal to everything?

Dr. David Oslin: That’s a great question. So it depends on what groups of medicines you’re referring to. So if you take the field of pharmacogenetics broadly, so I’ve mostly focused on psychotropics let’s divide that out. So if you take the field broadly we actually wrote a paper where we did a simulation exercise and we took Veterans’ current medications that they’re on, so we took existing patients’ medications and we applied known genetic marker, allele frequencies and asked that broad question. Who broadly could benefit whether it be from a cardiovascular med, a cholesterol-reducing med, from a psychotropic, et cetera? And that broad question if you apply is almost everybody. It was very surprising. I was actually very surprised at that. So that is the impetus sort of behind PHASeR. Although PHASeR’s panel is not that broad. So they are looking at the highest known markers if you will or the most, the ones that are most accepted. If you look in with just psychotropics that’s the one in five, is the idea. It’s about one in five of people would have benefited from a test. So the 20%, that’s our best guess at that right now and normal to everything. So the other, we often have those questions so that’s one way of thinking about this question. The other part of this question is, so I can answer this from the psychotropic perspective is for a given patient they end up with more than one of these markers. So I told you that one panel the AssureRx panel looks at eight genes right, so they look at eight markers on different genes actually. How many people are unlucky to have six or seven or eight of those markers influencing their metabolism. And what I can tell you is there is a proportion of people it’s around 10 or 15% that have multiple metabolic genes that are highly impacted. And essentially for that 10 or 15% of patients almost all the psychotropics end up in that red zone except for the ones that are renally metabolized. And so there are some very unfortunate people when it comes to what you’ve inherited from your parents. Hopefully that answers this question. So I answered it with two different answers that are very important I think to understand. I see that how expensive the test, it varies a little bit but most of them are in the, so the VA pricing which is different than your commercial pricing, the VA pricing is in the 1,000 to 1,500 range. Almost all of the companies have contracts with the VA. So there on a fed viz [phonetic] or whatever that thing is. But again it’s mostly that your local lab is going to not want to spend the $1,000 on a patient. They see it as a slippery slope and I totally understand that. If you’ve gone one you’ve got, you know we’ve got 20,000 Veterans here that may benefit in Philadelphia, that becomes real money.

Heidi: Exactly. And it looks like that is all, we’ve covered all of the questions that were sent in. just got another comment in, great talk, thank you so much. Dave, do you have any closing remarks you’d like to make before we close this session out?

Dr. David Oslin: No, just I mean feel free to contact me I’m in the VA system, so [Dave.Oslin@va.gov](mailto:Dave.Oslin@va.gov). You know we have, either through PHASeR or through PRIME Care there is now a good cadre of people that have really good understanding of pharmacogenetics and happy to answer questions for people or find an answer for you if I don’t know it or, and get it to you. But use us as a resource, use PHASeR as a resource. PHASeR is being done out of Duke but happy to point you in that direction as well.

Heidi: Great. Thank you. Just before I close out here I wanted to let the audience know we have a new series starting up the beginning of October from our new COnsortia of REsearch SPRINT Center. Their kickoff session will be on October 7th and it is titled Brief Interventions to Prevent Suicide: An Introduction. Our registration information was sent out to everyone a few hours ago as part of our monthly announcement. So if you take a look at that monthly announcement, the big long list, it is one of the first sessions right near the top. We hope you all join us for that introductory session. Dr. Oslin I want to thank you so much for taking the time to prepare and present today. We really do appreciate your time. For the audience, I’m going to close the session out in just a moment. When I do you will be prompted with a feedback form. Thank you very much for taking a few moments to fill that out. Thank you everyone for joining us today and we hope to see you at a future HSR&D Cyberseminar. Thank you, everyone.

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