Multijurisdictional Contractor Advisory Committee (CAC) Meeting Transcript
June 26, 2019

Dr. Berman speaking:
The chief medical officers and I want to welcome everybody to our multi-jurisdictional CAC meeting on pharmacogenomics in Psychiatry. I'm going to pause for a moment and let Juan our Provider and Outreach person tell us how to operate the webinar and what's to be expected in the technology. Juan will be operating as our moderator as far as technology in the webinar is concerned. Juan, take it away and tell us with your expertise how to operate the webinar?

Juan speaking:
Sure. Well, good afternoon everyone. Again, my name is Juan Lumpkin with Provider Outreach and Education. In the go to webinar control panel you should see a panel that says audio, what you want to do is just make sure you have entered your audio pin in order to allow your phone to be unmuted so that you can speak if you need to. To do that, all you have to do is click on that triangle right before the word audio, the Box will expand and it will show you what your audio pin is. Make sure you enter that into your phone keypad and hit the pound sign, this will allow me to unmute your phone. Of course those who are speaking panelists, as long as I know it is your turn to speak, I can unmute your line as long as you've entered your audio pin. If there any other questions and you're unable to enter your audio pin, then there is also a questions panel if you'd prefer to type in your question and we can accept questions that way as well. I believe that's it, Dr. Berman I will turn it back over to you.

Dr. Berman speaking:
Thank you so much Juan. So the agenda today will be moderated by Dr. Paul Gerrard from Palmetto who will be directing the questions to our panel of subject matter experts. Before we get started with that, I want to introduce the medical directors that are involved in the MolDX Program. Paul Gerard is the director of the MolDX Program through Palmetto, Dr. Gary Oaks is the medical director from Noridian involved with the MolDX Program, Dr. Ella Noel is the WPS medical director involved with the MolDX Program, Dr. Meredith Loveless and myself, Dr. Earl Berman, with CGS and we are involved in the MolDX Program as well. I wanted to tell you why we're having this CAC very briefly, and I'm going to turn it over to Dr. Paul Gerrard.

I'm having some feedback.

I'm not sure why but if you're not speaking, please mute your phone. May have to see if operator can silence. So the multi-jurisdictional CAC pharmacogenomics in Psychiatry is part of the new 21st century cures act for transparency and policy development Internet only manual is very clear that under development of a policy when a policy is being developed, That CAC should be formed and panel of subject matter experts assembled to assist the Max and developing evidence and answering questions to help in the development of evidence and understanding the evidence that's currently published. So the purpose of this CAC is multi-jurisdictional as I said with Palmetto. No, rhydian WPS and ourselves CTS is to ask subject matter.

From across the country specific questions to help define and help each one of the MACs understand the current state of affairs and current state of literature in regard to pharmacogenomics in Psychiatry. This information will be taken under extreme advisement as

we formulate an LCD in order to satisfy medical necessity, reasonable necessary aspects in regard to the topic which is pharmacogenomics in psychiatry. I want to give my personal appreciation to the subject matter experts. We also have CAC members who have sent their information, so they can comment at the end of today's session. Again, I really appreciate the subject matter experts taking time out of their busy schedule providing their expertise. Dr. Paul Gerard from Palmetto, I'll give it to you so you can start asking the questions to the panelist, and I look forward to hearing the information.

Dr. Gerrard speaking:
Thank you. My name is Paul Gerard. I'm a medical director with the MolDX Program and I want to Echo the thanks that Dr. Berman expressed all ready for our panelists as well as CAC members, who are taking an immense amount of time out of their day to answer these questions. So, today the panel will have four panelists. We have received some information that is written from some of these panelists as well. That will also be posted at some point but speaking today there will be four panelists: Mary Relling; John Greden; Annette Taylor; and Stuart Scott. I will let each of them provide more specific introductions on their backgrounds and what gives them expertise in this field. The way things will proceed is that there are a series of questions that have been emailed out to them as well as posted to some of the Medicare contractor's websites or emailed to their CAC members.

We will yield the floor to each panelist and the panelists will then have the opportunity to go through all of the questions all at once. We recognize that some panelists may have more or less expertise in respect to other questions.

Excuse me, if you're not speaking, please mute your phone.

We will let the panelists speak on those things about which they themselves believe that they have sufficient expertise to reply. Each panelist will have in the neighborhood of 15 to 20 minutes. There's a schedule/agenda viewable on the WebEx show right now. If we are ahead of schedule, we'll just move on to the next item and we will not attempt to fill the extra time. If we have gotten the information that we need following the panelists responding to questions. There will then be a number of follow-up questions and then we will yield the floor to our CAC members as well to provide their input. And so with that I would like to turn it over to Mary Relling to lead us off as the first panelist.

I will also set a timer so I can let you know if you're hitting the 15-minute mark. Dr. Berman asks Paul do you want to read the questions out loud, or does each panelist have it in front of them? Paul responds, well, I imagine each panelist has questions in front of them, but let me go ahead and read them out loud. Anyway, so the first question is just give a general background of how genetics related to the selection of medications or medication dosage. The second question is are there particular genes known to physiologically affect drug metabolism in humans. The third question is are there particular genes known to affect physiologically to affect physiologic drug efficacy in humans via pharmacodynamic pathways and generally speaking when does knowing the presence or absence of a genetic variant that affects pharmacokinetics and pharmacodynamics provide a physician with clinically actionable information is knowledge of lifestyle factors also necessary or is genetic information sufficient.

The fifth question is are there particular genes that are known to provide clinically actionable information in humans for the selection of dosing of psychiatric medications and can you get information about the evidence underlying this. The sixth question is for each of the genes that are known to provide clinically actionable information. What should be the minimum testing

standards in terms of variants identified? Seven is the evidence sufficient to conclude that large combinatorial pharmacogenomics genomics panels. For example, Gene site ID genetics CNS dose etcetera add something to medication selection above and beyond a single Gene testing. If so, in which populations and with what strength of evidence. Number 8 in which kind of circumstances would either single gene or combinatorial testing be used? And the final question is do you have any other thoughts or information that you believe should be part of the evidentiary record in the development of a coverage policy.

With that I will turn it over to our first panelist Mary Relling. Dr. Mary, please. Make sure you're not on mute, please. All right, well in that case, I will go to Dr. Greden as a first panelist instead.

Dr. Greden speaking:
Okay, can you hear me? Dr. Gerrard responded, yes, we can.

Dr. Greden, Okay good. So I'm John Greden. I'm the professor of psychiatry and clinical neuroscience at the University of Michigan. I spent several decades as chair and I'm the founder and the director of the national network of depression centers and the University of Michigan Depression Center. For most of my life I have been pursuing biomarkers for decades of NIH funding and others and along the way probably started looking at the whole question of pharmacogenomics well perhaps three and a half decades ago at one point in time began working with Dr. David Mazac when he was at the Mayo Clinic because I was running our depression centers treatment-resistant depression program.

And along the way I discovered that obviously then what I consider predominantly pharmacal kinetics was a variable and how people did and I would find you know, if statements like, doctor I can't tolerate these medicines at all. What have you given me? I'm tingling I'm upset or I don't feel a thing from these pills or they once work but they've stopped and so on. I became rather dedicated and proficient to finding books to look at metabolic patterns.

And I think that led me to making adjustments and some cases they were really important population. I was dealing with what treatment-resistant depression defined according to the Convention of having failed at least two trials well-established documented FDA approved medications and for adequate duration and dosage so we fought according to package instructions. And so that pattern getting used to that it actually led to the awareness that things were deeper than just looking at all. I was actually on an advisory panel with Dr. Mazac for a while to look at the amplitude and this disappointed, I mean it failed that was occasionally providing information, but not really. But I then started sending blood samples from that. I was collecting forwarding based on research funding that I had received as gifts generally and was using that information and over about five years six years seven years the information based school and I became invested in wanting to pursue these things even more in 2014. I agreed to see if I can mobilize a number of the other depression centers that I had helped start in the national network of impression senses to become part of a large-scale randomized blinded raiders long-term study that was going to be done using test. I was aware that the tests and that one was one that we had already started to play in. This was the genius test. Then the Assurex and that study has now been published is available. I think in your packet, but in essence it is 1167 people comparing treatment as usual versus guided treatment and that acronym that we all started to use among the investigator simply to help us not repeat the long title, but be the study itself. I think I could do it if you wish but I'd rather almost address the important questions that I think we are here to discuss.

Very summary fashion and that turn over to you Paul or one of the others. I believe based on the work that I've done and the reading that I've done that genomics and genetics genomic variation genetic variation via pharmacokinetics pharmacodynamics are very important variables and our value to clinicians, but we know much less than what the average practicing clinician would like, they want an answer tell me what I'm supposed to prescribe. We have a long way to go to get to that but the information is still extremely valuable. These issues are complex the drug metabolism pharmacodynamics and other things that we haven't even evaluated yet our complex interactive and this is never going to be a single Gene. It's never going to be just a predictive thing.

We will need to look at multi-gene variations and I think we're doing people an invaluable test that we basically look at 33, if I remember medications and eight genes and probably array anomalies. The question of are there particular genes known to affect physiological drug efficacy and humans Dynamic Pathways.

I think there are a group probably knows those people on the line are sophisticated such as the SLC 684 the dko rc1 these serotonin reuptake Inhibitors and some of the others they're well known even in other fields such as the Kor C1 is been used by medicine for Warfarin and the AAA genotypes are different than the AG genotypes in our field taking us back to Psychiatry the focus for this webinar clinicians are preoccupied because they don't have quite the sophistication that I would wish for.as they are preoccupied with this is a first line medication that's been approved.

Sometimes that's new one and if it doesn't work and we know from very large studies basically the John Rush the nuclear Trivedi groups and that essentially only about 38% of people respond to the first selection of antidepressant was with major depressive disorder and that's even on a first episode and then the clinician resorts to let's try this and it's generally another favorite and in essence sometimes they factor in lifestyle factors smoking Other Drug deals over the counters, but often don't and what I think is missing is the guidance that comes from the use of biomarkers. We are preoccupied not in this era of Precision Health to find those and they think we'll talk about the search for particular genes for Neuropsychiatric medications. I think that was like in question 5 and in essence what we're looking at we're just touching the surface now, but we do know things that are valuable we know that these are working through multiple metabolic pathways and we must be looking at a composite in my judgment and that takes us to the term combinatorial. I worked with Dr. Mazac and others when we were looking at single genes cytochrome p450 2d6 and we started doubling up and looking at multiple genes but in sequence and I recognize long ago that that was not going to be an approach that really didn't because all other frames structures don't work that way. So the search of particular genes is I think a misguided strategy and I think what we do need to do is we do need to be looking for combinatorial strategies large singles. They must factor in lifestyle and other medical considerations. We've got to look at epidemiological cost means to have these issues really prove their value and I think we need to provide guidance to the clinicians who will be using them. I don't believe that that should just be restricted to psychiatrists for very practical reason First World Health Organization data show pretty convincingly that major depressive clinical depression or major depression depressive disorder. All by itself is the second most costly illness in America and it is the world's most disabling illness of all the ones that we will study and so if we really want to add some impact we need to be doing something that just addresses how do we find these things early and not do what I've done for much of my life, which is to treat those who have already failed the treatment resistant depression one. And so we have started actually doing these in the earlier stages of treatment test results. I believe it helps. So I think in

a funny way for summarizing what I've just said, there are emerging data. It's exploding their books pharmacogenomic assays must include minimum testing standards.

I believe some Combinatorial assessment should be the standard ethnic and lifestyle considerations and concomitant medications and smoking and alcohol use and other over-the-counter variables must be considered when we're asking why or somebody struggling with not responding in the way that we would hope clinically validated assays and measurement based care outcome. Not something that still is routine for more psychiatric treatment measurement based care is not been in the one that has to be and we need long-term Studies major depressive disorder is an episodic recurrent lifetime disorder probably far more probable to diabetes that it is to something like an infectious disease and when we are assessing pharmacogenomic tests wind and Raiders are essential and for those who have had the opportunity the article we published had some shortcomings the guided.

You just poured out in April of this year. It's in journal and psychiatric research volume 111. And as a recommendation, I think it could be looked at and we have presented it now. It's epic and at several National meetings the largest and also some International meetings and all along the way we've been searching for people to say, these are shortcomings. This is what we should fix. I think right now the one issue speaking as somebody who also does clinical part that has to probably be addressed is the question of who has to diagnose has this is not a diagnostic test category. It's not a measure of severity. It is not something that actually This is the treatment you want to select very definitely not essentially inform when treatments can be stopped and it's not going to do the whole thing of identifying Which medicine or this one will be more effective than this one the wonderful situation that exists baited by pharmacogenomics an immunologic studies and cancer has a way to go yet and that's going to be the answered only by race, but we'll do a good job field testing in my judgment does help identify treatments that produce Adverse Events and alter adherence and in essence what we found is the ones that were most influence of these were fairly profound statistical differences with those that were identified as being on an income. Good choice medication and this is switched, so if your pharmacogenomic test results said this is a problem and then the doctor switched the lighted treatment blue.

Basically, the glutamatergic story ketamine we're seeing the full REX and alone story. They ignore steroids and postpartum depression. These issues are going to make pharmacogenomic testing routine parked here for the millions do 12 to 15% of these illnesses and I think they'll help address the massive a huge costs the disability and the suicide epidemic that we're certainly watching right now. So I think I heard I Believe by the way, just if I still have more time what we do we should be looking at safety. Everybody should be looking at actionable a patient outcome issues. I hope I've described some of those we should be using strategy of educating those how to use and interpret the test.

Just do some things the test that I do is just to be truth in advertising as a way to try to help educate Physicians using a fairly simplistic approach the green yellow red. It was understandable. I think it's got to be changed that's too simplistic and it gets misinterpreted. It has helped but I think we can do better and how we communicate clinicians and guide their choices. And that's something that I would be honored to help accomplish. So I will stop and I hope that I tried to address some of the questions. I believe this is part of our future and it's very needed and as it depression psychologist all of my life, I've helped establish the national network of depression service just so we could accomplish the things that are needed to address questions like this mainly our sinful standardized measurements following people for I'm sick of a tweak and 12-week trials. I think we need to do answer these. Slide your survivors

in year and with all of those things. We will be hated by Mark I think. I hope that got transmitted. What do I do now? Well, thank you.

Dr. Gerrard speaking:
Thank you. Dr. Greden. So we will certainly take into consideration everything that you have expressed. I have a couple of clarification questions, but I will hold them until after all the panelists speak and we will go on to Dr. Mary Relling who I think is available now.

Dr. Relling speaking:
Hi. Can you hear me now? Dr. Gerrard responds yes.

My name is Mary Relling. I'm the chair of the pharmaceutical department at St. Jude Children's Research Hospital, which is an academic research clinical institution and I've worked in the area of pharmacogenetics since the mid-1980s. I was a postdoc in Urs Myers lab when they cloned sip to D6 which is one of the genes will be talking about today and sip to C19 with clone shortly thereafter. So I come from the pre genomic era.

In pharmacogenomics and maybe it's worthwhile to just point out that we estimate that maybe about 10 percent of drugs will be so strongly affected by pharmacogenomics that it will be actionable in the clinic is could make up a larger percentage of prescriptions because some of these drugs are very commonly used so it might be maybe more like 20% of prescriptions in the United States and we estimate that this involves only something between thirty and a hundred genes that are likely to be actionable. So, of course, there's a lot of exciting discovery work and multigenic drug effects on drugs that what we're focusing on today are those genetic effects on drug disposition and variation that are so impactful that they're actionable in the clinic. So that's a little bit of background of course genetics.

With question one relates to the selection of medications or medication dosage for though that small percentage of drugs that have such strong effects that doing genetic tests is feasible and can give useful information about how one might choose to alter prescribing based on genetics for. The second question are the genes known to physiologic effect drug metabolism. Of course, the answer to that is yes, and and it makes sense evolutionarily, right? I mean genetic variation could impact enzymes whose role is largely to metabolize drugs, which have only existed for the last hundred years. So humans haven't had a chance to evolve out the very penetrant impactful genetic variations that can affect drug metabolizing enzymes as might be true for enzymes that are involved in metabolism of endogenous biological substrates.

And that's probably the reason that we have some examples for pharmacogenetics has such a huge impact on drug effect. So number three are there particular genes known to affect physiologic drug efficacy in humans via pharmacodynamic Pathways. And of course that is true. It may be that some of those are a little bit less likely to maintain these very strong penetrant effects for the reasons that I just mentioned that there would be some evolutionary selection against that but there are a few examples that have come through such as variation in HLA genes impacting on adverse effects of some drugs and variation in some receptors like vcore C1, which is involved in the response to drugs that are involved in preventing blood clots.

It is probably less clear what the pharmacodynamic genes might be that are actionable in the area of psychiatry. Number four when does knowing the presence or absence of a genetic variant that affects pk/pd provide a physician with clinically actual information and his knowledge of Lifestyle factors also necessary. Well, of course the the presence or absence of genetic variant will be important when its effect is so strong that it's observable despite all of the

environmental influences the non-genetic influences on enter individual variation and Drug response. So those quote lifestyle factors in which I suppose we can throw all non-genetic factors like age underlying disease renal function liver function is the patient adherent with their medication or not drug interactions. Of course, there are many many many other things that affect inter-individual variability in response to drugs besides genetics, but what we're talking about in terms of actionability are those very few.

Examples where the genetic effect is so strong that one can observe it despite all of those other messy background impacts on on drugs and we certainly don't want to say that genetic should take the place of other considerations that should guide prescribers and choosing the right medications and the right doses number five of their particular genes known to provide clinically actionable information in humans for the selection and dosing of psychiatric medications. And can we give information about evidence and I happen to be very involved in a group called see CPIC the clinical pharmacogenetics implementation Consortium, which was founded in 2009, and it was founded in order to provide guidance for clinicians about how to alter prescribing if genetic variants were present the whole notion.

CPIC is not forcing clinicians to do genetic testing. But with the assumption that genetic testing is becoming more common patients are doing this on their own to some extent sometimes patients are getting incidental genetic findings at a hospital like mine. That's a cancer hospital. We try to do the whole genome sequence for every single patient that walks in our door. We're going to find a lot of genetic variation. So in our clinical practice setting the challenge for our clinicians is not deciding whether to order the genetic test. The challenge is deciding what genetic variants are so strongly associated with drug effects that to not use that information would not be practicing good clinical medicine. And so what see pick does is really carefully evaluate all the evidence that links genetic variation with variation in drug response in one gene drug pair at a time.

And where the evidence is very strong and very importantly where the evidence that supports and alternative drug or an alternative dosage is also strong. We provide very specific guidance to clinicians on how to use genetic information to guide prescribing and all of the evidence used in CPR guidelines is from published evidence. There are examples for example that the FDA will utilize information that's not in the peer-reviewed published literature. So that doesn't go into CPIC guidelines. All of the evidence has to be reviewed by a group of experts that follow a procedure that's in line with the Institute of medicines best practices for clinical guidelines. So tries to minimize conflicts of interests and maximize the level of expertise and one of the services that see pick provides is too.

Provide a tentative level of action ability to Gene drug Pairs and in my written response. I provided a hyperlink to the webpage on see pick. This is an extremely highly visited page many tens of thousands of visits per year because it assigns a level of action ability for Gene drug pairs A B C or D depending on either a thorough review of the evidence in the few cases were guidelines have already been put together for the gene drug pair or a tentative review of the evidence in the case where the guidelines don't yet exist and only Gene drug pairs that have a level of a or b or considered actionable in the clinic and Gene drug pairs with C or D are not considered to be actionable and we do this as a service to the clinical community so that they can help differentiate between genetic tests.

Who might not quite be ready for prime time and those genetic tests that the evidence really supports using that information to help guide prescribing then on a guideline by guideline basis.

There's a lot of detail the didn't intend the devil is in the details about how every single one of those Gene variants May translate into variability in phenotypes and how those phenotypes translate into clinical recommendations for prescribing in every single guideline.

So yes, there are some particular genes that are relevant for some psychiatric medications and those are listed on our see pick website to of the guidelines that we've already completed and even updated at least once include a guideline that relates the gene sip to D6 and sip to see 19 to the try cyclic antidepressants and the same two genes to ssris and Just recently a guideline on sip to D6 and atomoxetine came out and there are some additional Gene drug pairs involving psychiatric drugs that have a tentative level of action ability of level B.

And therefore we anticipate that there will be some additional psychiatric drugs that see people come out with guidelines for question 6 for each of the genes that are known to provide clinically actionable information. What should be the minimum testing standards for variants identified? This is a really tricky area in my written response. I gave a few resources that can help provide guidance on this see pick does contain some information on minimum standards. That should probably be present in genetic test a MPD Association for molecular pathology is publishing Gene specific guidance, and they've already tackled sip to C19 and I think 2c9 maybe I'm wrong on that maybe that was 2D6. Anyway, that's a certainly trustworthy organization that recognizes that this is really a challenge.

The CDC has a project that's been focused on sending out pharmacogenetic testing standards to clinical laboratories and the College of American Pathologists offers proficiency, testing and genetics so there are resources out there that can help provide guidance on whether a genetic test is quote good enough to use for some prescribing always with the caveat that if one discovers a known inactivating variant in a gene especially if one discovers to known in activating variants in the gene that are known to be on different alleles than a positive results even from a week genetic tests can be useful for clinicians interpreting negative test is of course trickier, the you have question seven is about combinatorial panels and I think it's really important to make a distinction between what we mean when we say combinatorial versus panel because there's a lot of genetic Testing Laboratories that are offering services that include many different genes the gene testing being done as part of a panel and then an interpretation that's based on combinatorial analytical statistical tools to determine what is possible prescribing recommendations based on these combinations many times these use proprietary algorithms that are not transparent to the user. And so these can be very difficult to make any recommendation on whether these tests are worthwhile because how they get to these combinatorial recommendations clinical dosing recommendations is not clear but the idea of using panels, but whereby you test multiple genes at one time. Of course, that's just what makes sense in science. Now the over almost the same amount of money that we can test just a handful of genes. We can test hundreds or thousands of genes. We can easily have a panel that test almost every actionable pharmaco Gene since there's less than a hundred of those.

So of course the idea of using panels as an analytical tool, Laboratory makes perfect sense the idea of using a combinatorial statistical approach to translate the results of those genetic tests and to prescribing sometimes isn't very easy to evaluate from a scientific point of view and that sort of addresses question 8 in our opinion. It's always acceptable to use a panel test rather than a single Gene test analytically as long as the genes are being adequately interrogated, but the combinatorial approach is sometimes difficult to evaluate in terms of the prescribing recommendations. And then number nine anything else to add just this sort of General concept that there's a lot of attention on what level of evidence do we need to designate a gene drug

pair as actionable and to some extent that depends on how well understood the mechanism of the genetic variation.

For example many so far more than half of the actionable pharmaco genes that see pick is written guidelines for exert their mechanism on drug effect versus via straightforward effects on the pharmacokinetics of the drug. So although there's variability. I mean, obviously unless the drug is present at an adequate concentration to exert its effect.

It's not going to have the right effect and almost every drug when the drug concentrations get too high will be subject to having toxic effects or adverse effects and we recognize this and the FDA recognizes this because almost every package insert for a drug whose method of elimination is either renal or hepatic will have a warning in the prescribing information that states that doses should be altered in patients with renal dysfunction eg a high creatinine or doses should be altered in patients with liver dysfunction as evidence by high bilirubin or high ALT. And of course when we know that the pharmaco gene metabolizes the drug and we know how it metabolizes the drug either to active or inactive forms. We know that there's no way that that Gene can have variation that doesn't impact on drug effect. I mean, it's just not possible. So these very strong genetic variations that exert their effects via pharmacokinetic influence have to be clinically actionable and if we're going to say that they're not worthy of testing then we should never test for kidney function or liver function in a patient because it's exactly analogous to the everyday clinical decisions that clinicians are forced to make to guide their prescribing based on imperfect information and guesses about how each individual metabolizes each individual drug for those actionable genes that don't work for pharmacokinetics. Yes, then a higher level of evidence is required to prove.

The association between the gene variation and the drug effect and to help guide clinicians on what the alternative should be in those cases, but in the case for genes like sip to D6 and sip to see 19 that metabolize and affect the drug that as a levels of active drug in a patient again, there's essentially no way that those genes could not be useful in guiding prescribing of the affected anti psychiatric drugs.

I'll shut up now.

Well, thank you very much doctor railing that I think you made your thoughts very clear. And once again, I want to express our appreciation for taking the time and effort to give us your input on this and tell us about see pick as well. And so with that I will turn to Annette Taylor next.

Hello everyone. I'm delighted and honored to be involved in this groundbreaking meeting. I'm a board-certified clinical molecular geneticist and a genetic counselor with a PhD in microbiology and Immunology and a master's in genetic counseling. I'm currently associate vice president of LabCorp directing the lab in Denver that has provided cytochrome p450 testing and I co-lead the pharmacogenomics program at LabCorp and provide pharmacogenetics consults, and I've been a member of see pick since 2017 and I'm on the subgroup. They've created called the dissemination group to help folks know about the sepik guidelines historically I've been involved in pharmacogenetics since the mid-2000s been passionate about it for a long time back then.

Launched Warfarin. Do you know typing test at my company Campbell genetics? I have served on the pharmacogenomic subgroup at the HHS and the VA genomic medicine program advisory committee and put together a plenary session in 2008 at acmg about pharmacogenomics when I was thinking that group of Genesis weren't talking about it enough yet. I've been on the acmg quality assurance committee recently co-authoring the factor 5 and factor to guidelines.

So that's the background and I think on the questions, I'll just really briefly go go through the first ones because we've covered those quite. Well number one obviously genetic variation is one of a number of influences on medication response.

The effect can be major depending on the gene and if theft of the variant but many other influences as we've heard can be on drug response and the basis of selection of medications including patient age clinical measures such as liver renal function comorbidities drug-drug interactions and therapeutic monitoring of blood drug concentrations helps with dosing to An individual's genetic makeup influences pharmacokinetics and pharmacodynamics as we've been talking about sewing for question 2. Yes for sure. There are particular genes known to physiologically affect drug metabolism in humans and a particularly important family particularly important group of genes are the family of cytochrome p450 enzymes produced in the liver and the genes encoding these enzymes have genetic variations that affect the activity of the enzymes and the metabolic phenotype and as we've heard that can be quite dramatic when they're not Helios question 3 super briefly. Yes drug efficacy can be affected by pharmacodynamic Pathways such as receptors or protein targets.

However, the genetic variation of these Can be associated with advocacy effect, but that tends to be less strong that effect. Then the effect of the firm of Co kinetic beans and there's a little less curved actionability question for when is it useful to know about these genetic variants and it's when the genetic variant has a large effect on the drug response and and can become clinically actionable and an example outside of the site. The Psychiatry field is sip to D6 and folks taking codeine or Tramadol. Both of these medications are prodrugs that need bio activation to the active metabolites that provide pain relief. So presence of two non-functional variants dramatically reduces the enzyme activity and Metabolism. So leading to impaired pain relief and there.

Pick guidelines for to D6 and coding number five. That's a really meaty question. And yes several genes have been demonstrated to have clinically actionable information for tailing certain tailoring certain like heights psychiatric meds and evidence for clinical actionability is available from several key sources compiled on the pharmacogenomics knowledge base at pharmgkb dot org and all weird right about the see pick guidelines about the importance of them. She pick just generally is an NIH funded organization with a membership of more than 300 clinician scientist laboratory and send others knowledgeable about pharmaco genetics with a purpose of facilitating the use of pharmacogenetic tests results for patient care. There's a great slide show, which is an overview presentation.

About see pick that can be found on cpg except for resources see pick uses a rigorous and systematic system to grade levels of evidence and only the gene drug groupings with strong evidence for actionable prescribing are selected for guideline development. And there's a paper about that the guidelines help clinicians understand how to use available genetic test results guide prescribing and they're currently 23 such guidelines.

There was a quote from cap the College of American Pathologists saying cap applauds and supports the objectives processes and work completed by the clinical but by sepik These guidelines are a trusted resource for clinical decision making with pharmacogenetic information and patient care and they have been implemented the use of them has been implemented by many Health Systems academic centers and you can find a list of many of those on the sea pick website as well. So we'll see pick guided pharmacogenetic testing can improve therapy for patients clinicians agree that reimbursement is a challenge obviously. So let's hope that payers

embrace the see pick guidelines when considering future policy regarding pharmacogenetic testing in a similar fashion to how nccn guidelines are used. And then for the Psychiatry the drugs in Psychiatry, there are several guidelines and Mary went through those as well sip to D6 and to see 19 for the ssris and tricyclics.

Like any depressants atomoxetine and to D6 and for ADHD, that's the only Gene drug pair that has been shown to have that level an evidence enough to make a guideline and I wanted to mention that Under the Umbrella of Psychiatry. They're also anticonvulsant medications and their see pick guidelines for a carbamazepine and oxcarbazepine and the HLA B, 15:02 and hlaa 3101 that are combined in that guideline and there's also a guideline on phenytoin and to see nine and HLA B 15:02.

Putting this all together there has been a recent publication in 2018 by boozman at all that highlights the genes and alleles and Associated drugs that have the strongest actionable evidence in Psychiatry and what those authors did is they extracted information from all the gene drug interaction evidence based sources that are available on that pharmgkb dot-org for drugs related to Psychiatry. They created a network of network Maps accounting for the strength of evidence for each interaction and created a pulled Gene drug interaction Network including only interactions with the highest level of evidence.

And they Define that as availability of a see Picard are Dutch guideline a drug label indicating recommended or required pharmaco testing and level 1A or 1B and pharmgkb and they saw Through 448 448 Gene drug interactions and of those only 31 7% met criteria for the highest level of evidence and they concluded in that paper that the quote the current pharmacogenetics evidence base and pharmacogenetics based guidelines support the use of five genes sip to see 1926 to c 9h I a-- and hla-b and 16 alleles for the selection of associated psychotropic medications.

The publication addresses the lack of standard standardization of pharmaco genes Targets in Psychiatry and it seems helpful to clarify for clinicians, which genes the author Stone currently to be the most useful to test.

I could mention to that often. As you know people who are on pain meds are often on meds in the Psychiatry space at the same time as well. And so in the pain space there was a pragmatic clinical trial just published recently by Smith's that demonstrated that sub to D6 guided opioid therapy improves pain control and intermediate and poor metabolizers.

For question 6 we've heard about the allele standardization by amp, which is a fantastic effort by them as they keep rat and they have published on to see 19. It is to see nine is the other one and I think working on more for question 7 the one about evidence about the large combinatorial pharmacogenomics panels. I agree. It's important to point out that the word panel can have two different meanings. Number one the combination of more than one pharmaco gene in the test done analytically without use of informatics proprietary algorithm and be the large combinatorial panels that are referred to in the question.

So I think that's important so tests including combinations of genes the first definition of panel that Mention are important for some drugs and accordingly. There are some see pick guidelines that include recommendations for more than one gene for certain specific drugs and examples include to D6 and to see 19 for the tricyclics antidepressant amitriptyline.

Also HLA B, 15:02 and hla-a 3101 for carbamazepine and the other anticonvulsant medication that I mentioned. And another one is TPMT and nutty 15 foresight appearing. So those are sea pig examples of where they put a couple of genes together. Oh, and another one is warfarin.

The guideline for that has to C9 vkorc1 644 F2 and rs.12 777823 so I got to thinking in order to directly answer the question about whether these large combinatorial pharmacogenomics panels add more to medication selection than single Gene test. It seems it would be helpful to have an arm of the studies that compared the genotype guided dosing using those big panels with just a couple of genes that are the main actionable ones within them the like to D6 and to see 19, and then you could tell the difference of adding all those other jeans on there. Perhaps the large combinatorial panels do include the cytochrome teams that do are are known to have a large effect. So it's possible that the contribution of the numerous additional genes may not be as great as assumed.

And individually these additional mainly pharmacodynamic genes tend to have a smaller effect on drug response and these genes don't have C pick level as evidence for clinical therapy actionability and as mentioned a drawback of the large panels is lack of transparency regarding the algorithm behind the combinatorial result interpretation. Several Studies have shown therapy Improvement using this type of panel, but there's a recent publication. I found by Boost men and Dunlop 2018 the compared for commercial pharmacogenetic based decision support Tools in patients with major depressive disorder and it revealed substantial differences from panel to panel for genotype phenotype and medication recommendations. The study reported that 19 percent of recommendations flagged as actionable by two or more.

These decision support tools provided conflicting evidence to the Physicians about the same medication and then question 8 which circumstances so kind of looking to the Future Studies have shown that basically we're all walking around with variants for at least one actionable. I mean one actionable variant with the high likelihood to be for a drug that's prescribed some time in our lifetime as Precision medicine gains momentum and pharmacogenetic testing costs continue to degrade decrease pre-emptive. Testing was sets of actionable genes does make sense. The results are for a lifetime. So these interactive tools that are being developed to re-query medications and groupings of medications into the future on the same genotype result are happening and apps are becoming available.

Patients to carry their pharmacogenetic information around with them which seems empowering obviously not to change their own meds though standardization and focusing of the combinatorial pharmacogenomics panel testing to the jeans with significant impact on therapy would be helpful. And then just a point to make is pharmacogenetics informatics risk tools are available to determine which patients would benefit from pharmacogenetic testing given the medications that they're taking.

So not everyone needs to have a pharmacogenetic tests currently single gene or combinations of small numbers of high evidence genes are useful in many circumstances in cases of polypharmacy therapy failure or Adverse Events from pharmaco genetics actionable drugs or perhaps pre-surgery testing for the combination of To D6 and Tuesday 19 is useful for a wide range of drugs was he put guidelines?

And then nine the extra question. I wanted to mention that there are many reasons why randomized clinical trials shouldn't be considered necessary as cording evidence for pharmacogenetics implementation into the clinic a paper by Hud art at all in February 2009 teen on this topic States quote many prescribing decisions including drug selection and dose

adjustments are made without supporting evidence from clinical studies rather. These decisions must be tailored to the individual patient and take into account many factors including age comorbidities, which may not have been investigated in the setting of a randomized clinical trial pharmacogenetics can help to further refine these decisions. The authors do a parallel between altered dose changes in patients with renal or hepatic impairments not require.

Randomized clinical trial evidence to be added to a drug label and dosage changes needed due to Patient tip to T6 or to see 19 metabolizer status. The blood levels of drugs are associated with a majority of drug effects and measuring blood concentration is actionable without randomized clinical trials in many instances of regular Medical Practice.

And then the paper goes on to discuss more reasons why randomized clinical trials are not practical or ethical or financially kind of doable for all drug-gene pairs. And lastly. I just wanted to note that there's a gap between drug-gene Pairs identified as important by see pick and pharmgkb and the pharmacogenomic information on FDA drug labels. That's just kind of as a note level clinically valid pharmaco genes are not mentioned on the respective drug labels or their gaps in information such as for Clopidogrel where there isn't guidance on intermediate metabolizers or for Warfarin where there isn't guidance for variance Star 5 6 8 and 11 that are important in the African-American population.

So that's it for me.

Look like you very much. Dr. Taylor. We appreciate you taking the time to go through all of that and and and very thoughtfully review some of the evidence for us as well with that. I will turn it over to last but not least a Doctor Stuart Scott. Okay, so good afternoon, everybody again, like my colleagues. I want to thank everybody for the opportunity to be here today. It's a real pleasure. So my name is Stuart Scott associate professor in the department of genetics and genomic Sciences here at the icon of medicine in New York City. And I'm also a laboratory director in our Clinical Laboratory that we recently spoke to a commercial lab called semaphore and at some before I'm the division head of pharmacogenomics, and so I'm board certified in molecular genetics as well as clinical cytogenetics as well, too.

So I'm also a member of sipc that you've heard a lot about already as well as the AMT Farm cat Farm bar other pharmacogenomics Consortium research and clinical programs published in the area of pharmacogenomics for the last 15 years and recently co-edited textbook on pharmacogenomics as well. So it's a pleasure to speak today. So a lot of my colleagues have really done a thorough job kind of going through a lot of the questions. So it's a little bit tricky being last to add to all of that. But what I would say is that we've been doing pharmacogenetics here now from last 15 years when I was a trainee here one of my first projects was develop targeted genotyping tests for soup to D6 and to see 19, which is I think probably the two most important genes that were kind of talking about today for psychiatry.

And over the last 10 years of having that test available. We've really learned a lot about what clinicians appreciated what the field has moved towards and a lot of that has already been echoed earlier in terms of the resources for evidence supporting the utility and validity of these genes and these medications but more importantly are the resources for recommendations that are evidence-based dosing and therapeutic recommendations that we can now provide in our testing reports years ago. The our challenge was is that we were just giving genetic results for these pharmacogenetic genes that we would there wasn't really much available in terms of being able to provide the support to collisions in terms of what action they could take but over the last couple of years has been nicely already described.

There's been more clinical trials, especially in Psychiatry, but as well as all the additional clinical Practice guidelines that have been published by see pick and the Dutch working group. I've really enabled really facilitated the implementation of pharmacogenetics.

So a little bit more on the the testing side that's more of my expertise. So as mentioned previously, there are a lot of important genes involved in drug metabolism, both pharmacokinetic and pharmacodynamic Pathways. And so over time we started off as offering single Gene tests as I mentioned gradually. It just did not make any sense to offer them not only test for them as single genes but offered them a single genes. It just becomes more legitimately favorable to test them as a panel. It's more cost-effective. I believe it has much more utility because it can provide much more information.

Is the we have graduated from testing like the variance too much more broad channels and I could speak a little bit that as well too. And so we now have a well we had a multidisciplinary team over the last three years you there was available in the content. We would include in a pharmacogenetic panel and we ended up landing on cleanup themes that would be considered as a comprehensive set of genes that had enough evidence to support their include clinical panel from those 29 genes are we can report and we had a again a multidisciplinary team review the rotation literature to support providing dosing recommendations on over a hundred and sixty medications. And that's based on see pick recommendations European recommendations FDA label statements.

As well as Canadian pharmacogenetic recommendations as well too. And I think one of the important the other speakers and colleagues have mentioned is determining the level of actionability. So I don't want to imply that all a hundred sixty these medications are life-threatening emergent High actionability medication, but we have two categories. We have an actionable category and informative category for these medications and that's based on the level of evidence that supports their clinical utility So within that proper heads of panel, we also want to highlight based on the focus for today is that we have we have a subset that is based for Psychiatry is a medications used in Psychiatry that's broken down to eleven genes that informs on about 40 medications based on our review of the available evidence. And those are antidepressants antipsychotics anticonvulsant and see it.

Opioids that's what has the parents a few slides other medications that again those are broken up into actionable recommendations and informative recommendations and that's been supported by the very rigorous and thorough review of the available literature that's been really summarize nicely previously by the speakers and publicly available at see big. So in terms of the variance to detect I think I'll jump to number 6 because that's I think where we're at in the discussion. I'm a member of the a MP as previously has been highlighted and I think it's a very important question to ask in terms of what are the important variance to in there are considered actionable and so along with Vicki Pratt.

We have published two manuscripts in the journal molecular Diagnostics providing guidance on what are the minimum set of gene variants to be looted Marco genetic tests? And this is based on the frequency of these alleles in the general population the known function of these alleles and their their Association the drug response phenotype as well as the available reference materials and the support for inclusion into a clinical test. Genetic tests are I'm a little bit into being more progressive. So I guess I think in the future we have to be very careful of this as dr. Rolling already established rare variants in general population that are without question going to be highly functional and probably specific to certain populations.

So for us here in New York City when our patient population is highly burst we are on the side of being a little bit more expansive in our genotyping panel where we included many more variants that we know are more frequent in And ethnic groups like Hispanics African-Americans and different Asian subpopulation as well as the Ashkenazi Jewish population. So our panels we ensure that we have adequate coverage for the variants that are specific to these different populations. And we inform those justify them based on the evidence and that their recommendations are based on secret recommendations and other sources.

And in addition to the MP recommendations, I'm also involved in the A C and G the American College of medical genetics. We're working towards also working with see picketing and P and clicked Jen to provide a little bit more guidance on this important topic of significance of took what variants are clinically significant, which is kind of consistent with what we would speaking before should ability.

So in terms of combinatorial testing and panel testing, I also wanted to just kind of comment on that too because it was a little confusing to me. I wasn't sure if either the question was asking more towards is a panel test more useful or the combinatorial inclusion of different genes the the treatment recommendation so but I'll speak to both so similar to what previous speakers have mentioned, I would strongly argue for panel testing as being a recommended choice for pharmacogenetic tests. Just because logistically it is much more effective. It's easier to do it provides more information and it just makes more sense has a lot of these genes that might be important for us to kind of tree or also going to be important for cardiovascular medicine many other clinical specialties.

They're also more cost effective to produce and the results can be provided very quickly in terms of the panel report.

In terms of combinatorial Gene based recommendations that is a little bit. I think a little bit more sensitive until some some testing laboratories do provide kind of combinatorial testing recommendations. Where is Dr. Railly mentioned they do not have a transparent algorithm as to how they define that so to me that's a little bit of a challenge to that know how that evidence was derived. But there are many examples where more than one gene can be included in terms of a dosing recommendation as previously mentioned for CPR guidelines that have more than one gene for specific medications. And we also adopt that in our panels as well too. So again, I would strongly advocate for the use of panel based pharmacogenetic testing in Psychiatry as well as other clinical Specialties, but I would have a little bit more pause when it comes to combinatorial testing just fall.

The available evidence for that when it's available and not the make sure it's much more transparent.

So I think I would also maybe pause there but there's not too much more I can add Beyond others, but I would also like to Echo what a net said to and that one of the challenges that we recently have come up with is in terms of the FDA making comments about pharmacogenetics and clinical testing and having some concern over about genes included in tests that are not mentioned in FDA labels. So I don't think that's a fair assessment of the the current environment because what that suggests is that the FD labels are the current gold standard on the available literature and pharmacogenetics and I think everybody would agree that these labels are not updated regularly enough to really support that and that just really goes towards the strength of

the work done by see pick another groups to really do all the hard work of identifying that's to support these Gene.

One pair associations and I would encourage the the panel and other members of this call to really look up the sepik supplementary tables to see all the literature that is put in to the dosing recommendations. If they really want to have a current gold standard of the evidence supporting these Gene associations. And it also Echo what and x + 2 about the challenges with randomized controlled trials in pharmacogenetics. So that's one of the also concerns we have with our clinicians is to identify that utility however, in many instances it's very difficult to to run a pharmacogenetic randomized controlled clinical trial and they're also a lot of ethical issues with that as well, too.

So thank you for your time. I'll pause there and let Dr. Gerard take it from here.

Thank you. Dr. Scott. So we are running a little bit ahead of time and I just have a couple of clarification questions and I will start with one for well, so just to for the sake of maintaining order what I will do with each of these clarification questions is I will pose them to the panelists for whom I had them in mind. But then after that panelists answer is what I will do is I will sequentially call on each additional panelists in case they have any other input they would like to add to give the opportunity to each panelist to to give a comment. Once again, please don't feel compelled to give a comment. If you if you feel that that is unrelated to something that that you spoke to or or you just simply feel that that you're unprepared to comment on it. And so so dr.

Railing towards the end of your Russian you mentioned that there is a different sort of there should be different evidentiary requirements based on the the nature of the role of a gene in a drug. And and for correct me once again, if I'm if I'm not paraphrasing correctly, but you what you seem to indicate was that there are genes that are involved in metabolic pathways and that really it's you think that those genes that are involved in metabolic pathways almost seemed to be clinically actionable on virtue of the fact that they have a role in a metabolic pathway in much the same way as a serum creatinine does for really those drugs. And so what I wanted to ask is is first, is there any additional evidence that you think is required or is there they're Simply Having a known role in?

The ballot pathway sufficient and then I guess the flip side of that is for for drugs that specifically the genes that are involved in pharmacodynamic Pathways. Do you think that there are any analogies there or are all of the the drugs involved in pharmacodynamic Pathways such that you would really need that bed higher evidence bar to independently show clinical utility.

Okay it can you hear me? Yes. Yeah. Okay. So so one thing is my distinction is really between pharmacokinetic Ali based mechanisms and not so PK doesn't only have to be through drug metabolism. It can be to for example Transporters anything that affects the pharmacokinetics of the drug and it's a good point. I don't think that you know de facto involvement of a gene in the metabolism of a drug is enough evidence to lean one towards academic ability the the importance of the pathway of the gene for the disposition of that drug has to be high. So examples are if the gene product is involved in generating an active metabolite because many many drugs are to some extent prodrugs and they only work by virtue of their metabolites. 6mp is a great example cyclophosphamide Cody.

And there are many examples of drugs that the parent drug is an active that actually does have to be metabolized in order to create the active drug. So obviously obviously there's a defect in

the gene that activates the drug that could have a huge impact on drug availability to the patient, but it's more than just knowledge of the the gene product being involved in the metabolism or disposition it there does have to be enough data to indicate that it's very quantitatively important in the dosage range that's clinically important. And so what I know for example and see pick we do a lot of detailed examination of the if we're going to somewhat rely on pharmacokinetic evidence, there's a lot of detail evaluation of whether that pharmacokinetic evidence is strong enough then for the pharmacodynamic jeans.

Yes it definitely they do require a higher level of evidence that you could probably sort of subdivide that into whether the mechanism is known or not. So there's been a few examples of a firm ago Gene variant. That's so strongly associated with a terrible reaction to a drug like HLA and a back of ear life-threatening allergic reactions.

I mean at the beginning nobody really knew what the mechanism by what which that specific HLA variant causes patients to die who got a back of error, but because it was replicated in a couple of large randomized trials that level of evidence was so high that no one required any further Evidence nobody required any further proof of mechanism and people were willing and in fact compelled to not give a back of your without testing for HLA variance in that particular example, and there could be other pharmacodynamic examples where the Mechanism is more clear like the course T1 and Warfarin. So V Corps C1 codes for the Vitamin K. Oxido reductase. Jean Vitamin K is critical Acclaim in the clotting pathway. It's very intuitive that the amount of the vitamin K oxido reductase could have an impact on the efficacy or toxicity of anti-thrombotic drug or so so that you know, again your level of evidence might be that you require in order to say action ability for that might be somewhat less.

So I think that there are nuances in what the level of evidence is for each gene drug payer, but as has already been mentioned, it's very very rare for the evidence required to involve a randomized clinical trial that subjects half the patients to know acting on genetics and half the patients acting on genetics and as Stewart said that can really lead to ethical dilemmas.

Thank you, and I will Dr. Greeted any comments that you have.

Yes, I first of all I want continuing medical education credits for this wonderful discussion. It's informative and teasing but not this is available topic. I think picking up on something that Mary said there are two things. I just want to re-emphasize one is I think we need to be summarizing what we mean by actionable items and there are an array of things that can be in clinicians. It's not just that they clinician decides to make a change. So if maybe if you do the differences in chest just picking him up from top of my head the serum level might be too high lower doses might be required. That's what we used to do when you measure tricyclics levels that was in essence trying to look at something. That was a curable.

It might be too low, you know the serum level you may need to look at gu got about your medications and they all are metabolized by the same genetic structure to the sixth. Is he maintain whatever and and you've got conflicting variables and Metabolism because you've got multiple agents and that is the norm when you have elderly patients with depression. They're averaging generally what 4 plus medications that they're taking then it may be that the genotype Mayhew packed the drug mechanism of action. That's what we're talking about. Now. We need more research.

I think all of the panelists have a great honor and I think the evidence needs to be high but it's not going to be easy to just delineate all of those things for a very simple reason as I stated in

as I think Marion Scott and others also, Reiterated drug metabolism and pharmacodynamics are interactive. They're they're complex variation within a single Gene May influence metabolism of many drugs that the person is taking and the smoking and all of us and then the multi-gene variations may affect how a single drug is processed and I think as we look at all of these that's one of the reasons why I'm not into any of the company alliances. I'm into hoping that field of Psychiatry can get biomarkers and I think it's what those reasons that complexity is why I started to feel whatever we do that's going to Aid conditions in using pharmacogenomic testing for treating depression in a more Precision way is going to require a combinatorial approaches. And so I think we've got to start with number one.

That's the complexity is the reason and Mary made a comment which I sort of loved and I think it's difficult. It's costly it's going to require support from NIH and others but the comment was we need to essentially link the evidence to clinical outcomes clinical outcomes. And that's really what we're looking for is an actionable entity. We want to have people respond. We want to have people achieve remission possible and they're they're finding the data. If you go searching it's not very often that you do that. That's why we spent four years in this study trying to address some of the shortcomings of those things. We need 10 more studies like 20, I don't know but whatever it is, we need to be pursuing clinical outcomes as the final actionable item because those other variables that we've been tossing out all our great research paper.

But the real proof in the pudding is are we making people better? And then as I kind of get my opinion earlier, are we doing something with a test that will enable enable us to be guided in keeping them better and those are really games for why we're doing these tests. That's why we're developing and I think the other point is to make we all don't have an agreement may be another panel needs to be put together there needs to be an acceptable definition of what do we mean when we talk about combinatorial? I don't have a solution. I dislike it. I think all of the panelists would say the same thing.

I dislike the competitive proprietary approaches to the multiple tests be pharmacogenomic test cannot be assumed to be identical to another whether it is panel, whether it's combinatorial they are not Nickel because they aren't shared and literary aspects getting weighed but that's the same case for various medications that are developed. We don't get the secrets for everything and it's the same if we look at having looked at other biomarkers if we look at brain Imaging scanners one scanner is not identical to another scanner. So we're stuck with that. I really can get away around it. I think the way comes from evidence of having one strong thing. We're not there yet. But I think the Bozeman was mentioned shed Bozeman's meta-analysis support actionable benefits from combinatorial products. That's a funding. We haven't had very many of those things. That's a meta-analysis. It looked at for studies.

The other studying that was commented on a lot is also a great benefit now for us Chad's report to recommending what needs to be done. We are going to be migrating to looking at multiple agents and it's a question in this era of artificial intelligence and machine learning how we do it. Well and and I that's why I said this is a very valuable entity but knowing what we mean by actionable items those actual item should be linked to clinical outcome in my judgment. And that's the punchline that means that we are going to need clinical studies to really assess this and no study should be funded unless it picks up and all of the life of variables the ethnicity the smoking the drug drug interactions for multiple agents. This is not easy stuff. But boy, is it important. I'll stop there.

Thank you. Dr. Keller.

ER Dr. Keller, do you have any comments? Sorry my meat was on I said what a what a great discussion I am in agreement more studies needed kind of look under the hood.

It is complicated. There's a lot going on. Yeah. No, I think both of you said good things. All right. Well, thank you and finally, Dr. Scott. Do you have any thoughts? Well, could you repeat the question again? Oh, yes. So the the initial question was a clarification of a comment. Dr. Railing made regarding the the evidence bar that we need to determine that something is clinically actionable. And once again at the risk of paraphrasing something incorrectly, she discussed the the critical decision Point initially being at pharmacokinetic versus non pharmacokinetic genes and the evidence bars being different additionally for non-pharmacokinetic jeans when there is a very clearly known mechanism of action, the the evidence Barn need not be as high. We really should.

Be as high to say that that identification of a variant is clinically actionable. And so so really what I was getting at is just any thoughts or additional clarifications on on on that perspective.

Yeah, not too much. I think everyone did a great job too. But I would just kind of go with Mary had said to that there's a lot of examples where a really strong risk factor was identified prior to the biology being Lou sedated that supported that you know, I like Clopidogrel, for example, you know, it was approved to Market before the metabolism was even known or the effect or how that drug even worked was actually available. And so just as another kind of analogy as things being put in practice without you know, understanding the clinical validity behind it. So yes, I think it's kind of it's difficult to generalize across all PGX jeans, you know, what is the standard of actionability but I think that that validity is to be the term for that is kind of case by case whether you know, some of them you'll have a lot of biology hoarding it already in the science.

Whereas others will be identified through a really well perform genome-wide Association study that will identify a striking risk factor of a genetic biomarker with extreme effects on efficacy or toxicity and it might not have all of the other biology behind it already in place. I think it's kind of a case by case review in terms of balancing out those kind of contacts.

I'll stop there. I have another bad. It's an it on that. Yeah, so I agree that sometimes you don't have to have the clinical outcome as your end point. There can be a surrogate thing in the way. I'm thinking about Warfarin and high NR high INR is just known to be associated with higher bleeds. And so the genotyping to get the INR in range makes sense that that is that is a legitimate goal. And of course there was a recent gift trial that did show clinical outcomes were better. I know Warfarin has been controversial because the design of some of the trials etc., but it might be another example where you don't have to do an absolutely enormous trial and show bleeds going down if you're showing your control of INR is going down.

It's getting better.

Thank you for that. This is John Graden. Could I make one more just addition to this this nice discussion certainly and that and then it right after you do that. I have a question directed towards you. Dr. Frieden. I think what we're doing is so nice about this panel is that it's got people with differing areas of expertise and as whenever I'm aware of that I always see it as an opportunity to sort of say how do we build the bridges? So I think the various studies that we've been describing especially for the pharmacodynamic interactions is talking about what level of evidence do we need to be comfortable and move forward and it's therefore the pharmacokinetics and it takes us back 50 years. What's local talking about in these genomic

studies that provide that foundation and what see pick is done nicely in their literature is it's helping us discover what we need to test.

Step 1 the government helps we've got to have a come studies and I think that's the real actionable item. So I'm just reiterating what I was saying earlier and then there's one more Challenge and that's why I think we're going at the same time that the that it's getting away from us. Then we need to regain control of this whole process. So one discovering what we need to test is valuable if we test it and we learned if it helps and that's clinically and three is wholly implemented this how do we deliver it to those in need? And I think that's the piece if we put genomic studies together with outcome studies and implementation is implementation science is taking off then we've got the picture of how we're going to make improvements on the world's most disabling illness, which is depression.

Thank you. Dr. Gordon. And so the so you've spoken to a number of times now about the importance of outcomes and I guess you know a not so easy question is are there particular outcomes that you you think are specifically worth looking at? You know the as Dr. Taylor mentioned they're there in some cases, you know surrogate I outcomes may be may be valuable. So I guess the question is do you have a framework in mind or or even specific outcomes that you think are are worth looking at and Are there specific time frames that you think need to be looked at to say that that we've looked at an outcome and and the way we've looked at it is a meaningful way.

Yes, and and this is not just my opinion. I think this is actually something that's done in order to talk about introducing new products new treatments, whether those become pharmaceutical agents or transcranial magnetic stimulation or the other types of brain still functions. Now that are being tested in this field. It's also true with infectious diseases and Cancers what we really I think looking at first is this question of what's our goal and our first goal would be want to do something that makes people feel better. But safe, I mean helps them deal with the problem and it's got to have safety and it's not got to produce longer other types of problems so Improvement and that gets looked at when when people are looking at FDA and welcome to starting point.

It's gold. But how much is it worth it to do something even got some risks if it's animal so use we do statistical tests. And secondly, what we're talking about is the how much improvement there are clear definitions of there that people should accept in my judgment. The first one is in you.

Do you respond how that's done conventionally is to say we do a measure standardized its measurement based assessment at the beginning and whatever we're doing we should improve by at least 50% At some stage to you know, drop the a score. So if I have a Hamilton score of 30 and I get a treatment I should at least say if you've had a response you're down to 15 on knock down from 30 to 24. I'm still very depressed it that that rating scale. So it's a measure of response response has seen by most investigators as of that that's minimal standard almost and and then Real Recovery is really what it's a cliché a good one better but not well is not good enough we can achieve and I think what we're really talking about is if we can get people back to business. It's considered a normal score for example in a rating mayor chemical scores below 7 then we've achieved Wellness.

That's the goal when really what are we doing? And what are we trying to succeed in doing an outcome studies? I think we should be standardizing those things. We should be defining what we mean by combinatorial how we're going to study these things in the future integrating the wisdom that's coming out of see pick and others with the actual outcome studies and doing those in a way that actually instructs the people using them we found is we don't have answers

yet to advise people what to do, but in decided study what we found is that if you gave clinicians, by the way, this was comparing treatment as usual with guided randomized. So doctors could doctors get people better and they chose agents according to the combinatorial test that we used that were quite acceptable for 79 percent of the time 79% doctors aren't bad. They're pretty good.

And what happens is if you start doing that then what what occurs when you now say okay, but that means that there are 21 percent of the people who probably by some test this test that we use the be recommended to do something different if you give the doctors in those circumstances and they selected do it. Absolutely you ended up having improvements that were fairly astounding the symptom Improvement became highly significant .002 response became .04 better if they switch to agents that weren't incongruent and then the remission improved .007 the differences. These are big improvements and we're saving lives Ferb for 21% of the people potentially or at least putting families back together letting them go back to work.

So we when we look at symptom improvements and response and remission in outcome studies, we've got a pass a judgment as well as what do we mean by mean by actually think actionable item should be significant actionable items that include clinical measures.

Did I answer your question you did I thank you very much. Next I'll go to Dr. Scott. We went to you last last time so I'll go the other way this time. I don't know if you have any thoughts on on either specific outcomes or a framework for deciding if an outcome is sufficient to say that they test has something actionable.

Chirp it’s a little bit of a complex question. I think but I do defer to John on the on the Psychiatry anti-depression side that has not been our focus in terms of doing those kind of Trials and research programs, but I think that it all depends on the medication in terms of deciding. What is the level of utility or the marker that you're hoping to achieve in terms of the clinical validity and utility of that test?

So I think John did a great job of describing that well, what would be useful in the Hamilton scale but I think the other issue though with it is kind of what a net had brought up is that sometimes given the fact that it's so difficult to do these randomized trials for hard clinical endpoints, you know for some of these examples in cardiovascular medicine you need thousands and thousands thousands of And to identify some of these rare Adverse Events and it's very challenging to have a powered appropriately powered site to do that.

If you have the pharmacodynamic biomarker that you can run the study towards is the clinical endpoint and when you already know that that pharmacodynamic marker strongly indicative of an adverse clinical outcome either safety or efficacy, then I feel that my personal opinion is that that is an adequate clinical outcome to associate a genetic marker towards But I'll stop there.

Thank you very much. Dr. Scott. Dr. Taylor.

Yes, it is complex. I keep thinking about.

There's two things being said, I guess that it's okay to have an intermediary goal. That's not the whole clinical outcome. I mean, there are certainly some studies that go all the way to the clinical outcome. So I think it is kind of case by case. Basis what I keep coming back to in a slightly different in my mind is the part about all the genes that are going into the test. What is their contribution in that algorithm? Like is there any way we could open it up and kind of look at

that and see why they're different lab to lab and all work together to try and include the genes that are all useful.

How does one weigh the contribution of the different genes in a big panel to one particular Med?

But I'm guessing you don't have a good answer to that yet. So I'm wondering I'm yeah, I don't I'm not doing one of those big panels, but maybe you John would know about kind of what's behind the weighing part of the algorithm. Well, believe it or not. I wish I did because I think that's the part that's complex first. I don't know that I'd like to pretend that I not pretend I like to believe that I haven't sometimes maybe one does pretend have expertise that crosses boundaries, but I'm not a real expert in the framework of doing the actual genomic assessments and quantifying and watching her interactions with stuff. I do know that single genes didn't help the did that for 30 years well for at least some of that 30 years and I knew that just coupling measurements of the few relative things.

So if you look at to D6 and to see 19 and stuff like that. You start doubling them up. It still didn't help much because the complexity was greater than one genetic marker greater than probably to doubling up in maybe three and in some sense the reasons were they were interactive and all those other influences and the ethnic differences in the smoking and the other drugs all of us started to get complicated and that's what we're not really having the expertise or knowing how it's done. That's what actually led to my belief that a combinatorial approach was going to be at least the way to Improvement and one we you just toss it out. We have done that yet. The genes that were studied in the test that we did in the guided the one that's just been published in April.

The cytochrome p450 182 15 mils the to c96 alleles the to see 19:9 alleles the 3844 alleles the 2364 alleles the 2D sixth the one we all talk about 80 no meals the HT now, you know pharmacodynamic the HT R 2A basically one and the certain and reuptake inhibitor pattern that long and short forms the SLC 6842 long and short and you put those together and now it's suddenly enters into that distressing but totally understandable arena for me of being proprietary. So how they interact I think is done by a huge algorithm and I don't think we can benefit ourselves by sitting there saying you should share that would be wonderful.

Could play with it with multiple universities, but that's not the way our our economic world's work and it's not the with new products come out and I think in this sense, we're going to have to compare tests with each other. So this test will be different than one that comes from one of the other five or six testing companies and we'll have to do the work of saying okay when we match up with each other the stomach and Bozeman was actually recommending well, maybe get better and better but I think it's going to still be done without having the proprietary underpinnings right at our disposal and that's just because I can't see any of the companies saying here's ours. This is what we do and I you know, you share yours stuff so I could be wrong, but I'd love to hear what other panelists thing.

Yeah, this is this is Mary if I can just quickly address because we just had the a meeting here in Memphis with several hundred pharmacogenetics people there and I think there was a resounding support from the audience that combinatorial approaches that weren't transparent that didn't allow clinicians to understand what genes and variants were being used to make decisions would not be accepted. And of course in the cancer world where we have Myriad somatic acquired genomic variants are clinicians would always insist on knowing exactly what the genetic variants are and how they're contributing to clinical recommendations.

So I think that it's not a universally accepted view that clinicians would accept a proprietary Black Box combinatorial approach I would agree with that Justice. I'm interrupting. I hope not but but I was that's why I was listing I felt very strongly when we were working with the Jade site says that there should be awareness as to what it was. We were evaluating and I just listed those in those are published. They're actually on the supplement section. I think we're maybe the article of the excited test in April journalist. I Gadget research, but I that that's not with me saying I can tell you how those interactions occur in an algorithm. I agreed firmly that I think everybody should be publishing. What did they look at? And what are they evaluated think that's a pretty fundamental starting point. So want to be recommended by my this panel, I think.

All right. Well, it sounds like I I think we've gotten responses to my query vacations. I do want to open it up to the other Medicare CMDs from the the participating contractors who are here to see if they have any additional questions for any of the panelists in these last few minutes that we have.

All right. Well, I will take that as a no. So in that case, this is pi. This is why we do have a couple questions I came in and I need to I meet a couple lines here.

Okay.

First we have a question from Justin Simon and Hello, Justin, your life should be a meal just just to clarify our we're now open to CAC members. Is that correct? Hello. I'm sorry. I'm sorry doctor. I'm sorry.

This is Paul Gerard. I just wanted to that the portion of the meeting we are now in we are we have now opened before ipecac members. Is that correct?

T' also this isn't it to the attendees. I'm sorry.

Three this is the CMD this part of mode X was supposed to go first and then CAC members who sent in their Roi and permission slips. And those are the only commenters.

Whoever just was given permission to speak and you identify who you are. As far as a CAC number. I know you're not participating CMD, but if you identify if you're attacked member and if that would attack hi, this is this is Jonathan Simon. I am I was on the webinar and asked if I could ask a question. So the unmuted my line.

Is it okay if I proceed your attack number, please? I have not know if you could identify who you are and your involvement and if you have sending in our Roi, I mean a CI conflict of interest for more permission form prior fast. I have not submitted any of those things. So I'll go back back out of the conversation and allow you guys to proceed. I was just typing something into the questions on the webinar.

All right. Thank you. Well, I do any of the CMDs have any questions and if not then then then we'll open it up to the cast members. Yeah Paul, this is Gary Oaks.

I just got a kind of a general question from the practice Viewpoint having been out there and and knowing that a lot of times when you have and I'm probably over simplify it but you say you got everyday major depressive disorder that most folks will respond to with ssris it seems Not to be cost-effective in the front end.

To do a bunch of genomic testing perhaps until they have failed at least one trial of that and I'd like to get the expert panels opinion on that because you waiting on the test. You're delaying therapy.

And you know, it may take upwards of a week in some cases to get that back. Whereas you might already be having a response to one of the ssris in that timeframe.

So if they would be so kind as to address that All right, just for the sake of order. I'll call people's names in order. Let's Dr. Railing. Do you have any thoughts on that?

At just to emphasize that if you're taking a panel approach, so you're capturing the actionable pharmaco genes greater than 99 percent of European or African ancestry. People will have a high risk variant for at least one actionable gene. So the that pre-emptive approach one could argue is is cost-effective and worthwhile doing since it can affect so many different drugs including antidepressants and ssris and that waiting until a patient either fails to respond or has an adverse effect, of course has the undesired impact of bad clinical outcome for the patient and in cases where the drugs are even more dangerous like cancer drugs, you could accidentally kill a patient while you waited to see if they had an adverse effect.

So that's why we are in favor of Empty pharmacogenetic testing you can maybe make a very narrow argument. If you're only talking about patients who only have psychiatric disorders that you could do a complex cost-benefit analysis, but the bottom line is it's as cheap to type for all pharmaco jeans as it is to type for one or two.

And everybody's got an actionable pharmaco Gene. Okay. Well, thank you all let me go to Dr. Scott next sure. So I think to the question of the kind of logistics of implementation and the challenge there. It's a great point because for some examples the timing is critical, you know for Warfarin and for Plavix that you don't like kind of cardio examples where clinicians really want to have the answer in 24 hours because it's that's when the results could be the most useful to your question on ssris and antidepressants on all different John on the specifics of it too but to my knowledge they don't really kick in in terms of their efficacy and told her been used for for up to a month.

But again, I will defer to the expert there, but I think it's a really important point and It's also I am aligned with Mary and that that just argue is again for a more pre-emptive approach in terms of not wasting time waiting afterwards to do testing which is considered a reactive test to be but to support more pre-emptive testing that actually I think in Psychiatry. It's actually one of the good clinical areas where it actually is feasible to implement that kind of panel based testing preemptively because there is a window of opportunity there to my knowledge and also, all right. Thank you. Well, Dr. Greene and I think Dr. Scott set things up for you to go next. Okay. I'll see if I can be brief. So number one. I also agree with Mary. I think I'm mandated to say that that was a migration for me.

I mentioned in my earlier comment that I with TRD treatment-resistant depression predominantly and so I wasn't an advocate for doing testing as a step 1 I now am the reasons are that the evidence is just overwhelming and he C&P meetings and scientific literature that it's not good to have people sit with depression. You get hippocampal shrinkage you get a whole variety of brain changes other health disappears illnesses that are co-occurring our cardiac cancers Etc. are all have worse outcomes when people are simultaneously depressed early treatment is good. Number two ssris the first line from most psychiatrists failed to work for at

least 1/3 first only 282. Thank you, and then you can work hard over the next series of months and year and essentially get to the point and third of people still.

Have not responded and we don't know how much of that lack of response is due to maybe they have sleep apnea and it's not picked up or how much of it is due to what we're discussing namely the genetic influences and selecting agents that are incongruous of ongoing for their abnormalities, but I now believe that we should not only be probably starting at the front end, but we should be teaching people how to interpret, you know, and explaining what we don't know and I think three so I'm I'm for doing it now and I'm for pre-emptive type of thing and I'm forgetting guidance in the front end 3 in this really crucial. There are very few of these that are out there, but I'm aware of three studies that are actually usually found in literature that have looked at the economic implications.

And these are cost savings tests. You know, that stunned me for a while because everybody complains about the cost but expensive is the second. Sorry depression is the second most expensive illness in America after only heart disease sex. So I think strange way if this test guided us earlier, we got people better help for the next year and maybe never get them better. I think we would be saving society and we hopefully be doing something to prevent the 60,000 deaths by Suicide many of them the majority linked with depressions. So number one, let's measure cost. Number two. Let's be pre-emptive number three you let's actually teach people how to use tests and maybe make reimbursement requirements for having gone through some course or something like that.

But in a number four, let's look the whole picture and do the outcome studies to really show that it works.

Thank you. And Dr. Taylor. Yes to your point John. There are as you said quite a few cost Effectiveness studies. I started making a little library of them and you know, there are more than 24 in different areas of pharmacogenetics and there's one gross. Well, I'm sure you're aware of it don't know how to pronounce his name, but gross a little 2018 cost effectiveness of pharmacogenetic tests to guide treatment of major depressive disorder. So I think it is great when studies layer in that economic peace and show the benefit to health care as well and I'll throw my hat in the ring with the pre-emptive testing making making sense for sure. If you've got a patient in front of you I'm thinking John and you want to do the test and they just haven't had it yet.

I you wouldn't have to wait to medicate them. You could start on something and the results and then change it. I don't know if that's possible. But there are many models. Now that are published of pre-emptive testing that looked promising. I think the emerge group is a group of different centers and there's one ignite that are and I think Mayo did a pre-emptive one their various places that are doing this. I don't think they're reimbursed currently but moving the needle on reimbursement would really help with that model of pre-emptive testing.

II would I don't know that it's permissible but I'll just jump in by saying I would agree. I think we all should probably gather together and put out something about the cost because the cost issues have been a variable many insurance companies including number of the ones in Michigan no are reimbursing, but it's hard work. The biggest variable is I think misinformation or just lack of information. They would have discussions about the things we're talking about today secondly and it's been said the delay time to get a test result back is not long these with cheek swabs. For example with the one that we used in the most tests. Use results can be back within

about 36 hours and you can make a decision for people who have been depressed for a long time.

They actually sit and do fine with waiting before you start make a prescription and you Jay looks will call you. I'll see you then. We'll get started, you know, etcetera and I think that the interventions get things and if they are beneficial and that's the piece that still we have evidence that we published and others have and that's what Chad bausman reviewed in his meta-analysis and the evidence points to the fact that these actually are beneficial. So if that continues to be we should not let cost stand in the way.

Because it's going to be done. It's going to benefit it's not going to be a barrier.

All this gear I have one follow-up question to that. Certainly. Yeah. I'm just looking and you made a good point that I think there is a lack of good longitudinal studies to show that it really impacts in outcomes. And that's what we really need is by doing this test rather than at least initially generically prescribing. I'm I'm all for it. If you you know in two weeks, you're not seeing some improvement with an SSRI. There's probably not going to be a great one and you either increase the dose or you consider using another drug or you add on to it. I would love to see studies that showed by getting the test up front.

And moving on that that we do decrease the morbidity and actually the suicidal rate that goes with major depression. And if you know of those that would be very useful to this group as we make our considerations again, I've talked with several psychiatrist in different venues off the Record and they have not provided the evidence either. So I'm going to make that clear up front but most of them said that they would trust start with an SSRI increase the dose and only after they've increased the dose. Would they move forward with doing any testing or consider changing drugs and part of that was predicated on the current cost of the test that many folks are not able to bear. So I think that's another area that if we maybe if we had more people being tested it could drive the cost down.

I would hope but we don't look at Cost we look at how is it affect the Medicare population and how does it benefit the Medicare population and I have I've really enjoyed this conversation and the input from the subject matter experts. I'm still not totally convinced that we have long-term outcomes to demonstrate that a pre-emptive testing Force depression, not for Coumadin and not form any of the other drugs, which I do know there is a defined benefit for depression that there's a significant change in the outcome and that would be very helpful if that's out there.

If I if I could just respond to those very two important points first, you're very accurately stating. I think it is an area that has not been adequately studied in large samples for long-term with standardized measures rigorous approach has documentation rated one ratings and blind readers Etc. I think this is hard for me to say I come from Minnesota. You don't grow up this way. The only study out there that's really done at with any kind of long-term approach and the latter part of that was an open design is the one we've published. He had basically a blinded design until 12 weeks. And then essentially the people who grade were followed, but it was an open design, but we just stayed with those those that had the pharmacogenomic testing.

Continued to improve at a more rapid than continuous rate over time up to 24 weeks, which is when the measures stop. So even longer term there appeared to be benefits that should ideally be done in a blinded way that gets be expensive. That's a study that's going to have to involve National Institutes of Health. Number two. The reality is right. Now that this approach that was talked about by psychiatrists and I was chair of a department for 20 years and still had a major

program in it. I think the reality is that ssris don't work for everybody and we don't get people better by the butcher. Well, I'm only going to wait and see if they fail that is two thirds of the people failing almost on the front end right away.

We're off and running and sort of making things difficult for those lines and so I think that's when I did the shift instead of waiting for people to come for with treatment-resistant depression. I found myself saying it's life-saving. It's family saving its cost saving to essentially catch people. So that's the what Mary mentioned earlier but the pre-emptive and I think others joined in as well on that. And so I think I think we have the handwriting on the wall, but it's not well known to psychiatrists yet. That's the dissemination and they further ahead and this than the primary care doctor. So we have a lot of Education to do but I think you it can even be boosted by having Medicare and other programs go in and say this is the way we recommend we would like those in our population to be treated.

And Paul if I may ask one follow-up on real quick from Larry Clark and then perfect. That's what I wanted to ask. So then I'll be done Clark is asked me to he got disconnected not to think he may be reconnecting but he want me to ask what is the status of this testing as it regards the American Psychiatric association. Have they endorsed it? Are they still looking at it? Where is that at police? Thank you very much.

All is it set me just John let's let's start with you. Dr. Glenn Glenn, and then we'll move to the the other panelists if they have any thoughts on it as well.

The APA has not endorsed. They don't generally come out they put out guidelines and they update those periodically and this has not been addressed in detail. Some of the APA committees have leadership from some people who have not been involved in the testing but they have been relative critics. And I think they've been critics of the appropriate part that says we need more testing and I think we would agree the test that at least help put things forward was the one that we've talked about the guided test. That's the largest longest blinded Etc. and that there aren't a lot of other large tests out. Its population. All of the hints were moving in that direction from smaller samples and there have been a lot of small studies.

But I think at this point the APA has not yet taken position. Some EPA leaders have been vocal opponents. I think it's probably I've stated it enough times. I think it's probably a position. That's not based on data.

Thank you Doctor rolling any thoughts.

No, I have nothing to add. Dr. Taylor.

Um, I'm thinking about see pick dissemination project that were involved in and we're trying to reach out to some of these different medical societies to educate them about see pick guidelines. I think it's not well known in the General Medical Community how useful they are so there's some hope that you know attaching, you know, having some kind of Bridge to some of these ideas would be hopeful.

I'm hopeful but this is it. I don't know that this is appropriate but I'm going to be bold enough to say I have enough involvement with the EPA and with other societies. I think it would be wonderful if we brought together a group from the group that deals with the clinicians and those that deal with the wonderful advances in knowledge and understanding like cpec and a few of

the others and sort of said, let's talk about how steps could be taken to disseminate and implement.

Well, thank you. And Dr. Scott. Do you have any thoughts just I think I'll just make one additional point to that? So again, I wouldn't speak Towards the Sky Tree associations, but it just in general anecdotally in terms of our implementation with local clinicians here at Mount Sinai. There is kind of in a way there's almost kind of two camps regardless of whether they have Society recommendations or not. Those that are open to this and those that are resistant to it. And I think that really has to do with their level of Education. I think it's fairly not surprising probably to this group either and so they just underscoring the need for outreach and education and dissemination like that. I think is important across all pharmacogenetic examples because it's much easier.

For them to listen to to to be resistant towards it than it is to to kind of become educated on it and learn about it and accept it is my my opinion there.

Well, thank you just in the interest of time. I wanted to make sure that we leave adequate time to any CAC members who have thought so my thought is we should open the floor up to any CAC members who wish to speak and then if if we still have more time then then maybe come back to any additional questions.

Hello.

Hello. Hello if you could identify yourself to check e and which CAC are you with?

I'm representing the osteopathic contingency within the I guess it's the GBA group.

Okay, and we I will let you go ahead. I you know, I think that this is certainly the the future and there's a growing evidence-based clinical evidence and outcomes. And I think it's it's the right thing to do for our patient. I think it's going to help us provide better care. I've seen it in my own practice. I think the idea of pre-emptive panel testing.

And in the long run it would be great. If everybody did that just for safety and for better outcomes faster treatment, so I do support that and I sent in a message on the chat, but I think initially I was thinking failing one or two drugs, but when we're talking about like yesterday, you know, even the cancer drug the potential of life is I mean, it's just not worth it. So I think a pre-emptive approach due to safety is probably where we should go or at least if you have two or more chronic diseases or aged over 65, or if you're dealing with drugs that have significant safety concerns.

I think Yeah, some point maybe everybody would have something in their record or medical record where we would all have it so that it would just streamline the future as far as the choice of in medication and I I've had experience with the psychometric component and and just to go with what you guys were talking about. The community is actually embracing this as well the the psychiatrist in town on my last referral actually asked on my intake with I was referring a patient and one of the first questions was whether or not I had done genetic testing yet. So it's the word is out there and I'll just like hi. It's just that I've been in touch with are certainly interested in it and decision-making process.

But looking at the panel's I think the panel's would be important. It really isn't that much more as far as costs when you start expanding the panel, you know, the genes are the jeans. So it's just

a matter of expanding the panel a little bit at a small cost which would then allow the family doctor such as myself to look at blood thinning antibiotic coverage proper pain treatment. And of course if I guess component the patient an example, I had I had a patient with difficult depression and it took months to find the right drug and as we found the right drug, it just so happened that we did a gene test at her own cost and we found out all those previous medicines.

We tried were actually on the no-go list and it would have saved months of you know, and Thanks with the patient and you know, she eventually the hurt herself and ruined her marriage. So, you know, there's significant implications. And again, I just go back. I think this is the future and I think it's the right thing to do for our patients. That's all I got.

Dr. C check if this is Paul Gerard, if I might ask you one additional follow-up question, since you mentioned that you you are a primary care provider. Do you think that Primary Care Providers should be ordering these tests?

I do I do because we're the the gatekeepers. We're the ones that kind of manage all these referrals. And again if we have access to a panel like this, I think it would be very helpful to look at all of the different aspects and not just one component.

It's thank you.

So I understand there are a number of other questions. And so I think we got off the the moderator is able to ask some of those questions and and the they can be answered. Well, let me just ask is are they questions from the CAC or they questions from the general public all this is I scan through the questions in the queue. These are by the general population and one of them you ask is a follow-up. I'll praise it. The question was should form these be allowed to order this test and manage the depressed patient as they have the pharmacology background. So my question to include that is besides the APA opining but the published medical literature on the panels and and all the outcomes data.

The miniature I've read all looks at, you know, the the I'll paraphrase it the difficult to treat patient as opposed to those patients. I'm a general internist those patients that general interns and Family Medicine typically see what your the more basic depressed patient.

So, I guess I want to ask the panel what specialty should really be ordering these tests should be something in the primary care General position purview or is it should be they should follow our steps are the Fruit by the APA and these genetic tests are more in the armamentarium of The Specialist or should just be open to all Specialties to try and as you all have said treat quickly and quickly and treated early the published literature is all more specialty oriented and I had to get your opinion as General has having this as part of their battery of tests. And Dr. Berman. I just wanted to mention I I'm happy to sit back and let you moderate your the the answer to your own question as well. If you'd like, that's okay. You have the most of the people so that those that was the only question that came out of the queue that was not related or already answered. So once you introduce them, we should be up to date. Okay, so then let me let me start this. Let me start Dr. Kaler on this one.

Okay, I recall a good paper in the last year or year and your to from Vanderbilt. I believe that was about a model of primary care physicians teeming with psychiatrist to handle pharmacogenomic testing. There's always the education piece the primary care physicians. I mean, there's just not a lot of pharmacogenomic Education yet in general, you know medical

schools and the pharmacists are incredibly helpful and I've heard enjoy this kind of new field. So, you know, they're Naturals to be kind of expert at this. So anyway, just so you know, there's a paper and I can certainly find it for you. I can almost remember the author's name with Jeffrey Ginsburg group about primary care and psychiatrist team.

Yup. I don't know the answer about I think pharmacists can't order tests. Is that correct? But they could be on a team with someone. Those are my thoughts. I mean, obviously the specialist as well and I don't know what happens. If does a primary care physician keep a patient who's depressed and not refer them. I just don't know what's General disease usually end up going to a psychiatrist you all can help with that part.

Well, if I could direct the the answer to dr. railing next since I know she is a little bit of a time limit here. So if you have any thoughts, dr.

Railing I think and that is correct. What pharmacist can what level pharmacists can practice that is differs by state. I know at our institution all of our pharmacogenetic tests are ordered by a pharmacist, but it differs by state and sometimes by practice setting but I personally don't think there should be any restrictions on who can order the tests, you know, probably the rate limiting step. Is that for any genetic tests ordered on a patient? Once the result is generated we have to do a better job of making sure that those test results are transparently available to all the clinicians who could benefit from knowledge of that test result and that's that's probably a challenge that's even bigger than this group can handle but you want it to be transparent to all the prescribers and all of the dispensers and monitors of drug therapy.

Alright, well, thank you. Dr. Scott.

Not yeah, I think I would agree with what was it previously said to the importance of farmed. He's in this is crucial. We have struggled a little bit with post-test counseling and how that I think many have and how to provide that a genetic test is counseled by a genetic counselor. But we quickly learned is that after pharmacogenetic testing the counseling session will immediately turn towards what should I do with the medication that I'm on right now? Whereas with our been Julian testing it's more like your family the residual risk to the screening test any siblings or family history. No, it's a much different genetic story and that just supports the need for having pharmd expertise involved in the dissemination an integration of the PGX results to the question of specialist versus primary.

Care, I don't think I have the excuse to answer but I think I just agreed that all should have the access and to those transparent results. The one thing I would say is that to my knowledge the evidence and John will I'm sure clarify this for us to that. The evidence is in major depression, and so that just kind of underscores the need to just be thoughtful. I'm so the patient population that gets tested. You know, it's great to say that, you know, every single person should be tested, you know, when I walk in the door and a hospital or something like that, but as we get towards that interstate, I think this initial next few years would be identifying the appropriate patients that would be needed for testing and I don't know if that would be seen in primary care or if that would be at the specialist level for depression. Thanks.

Thank you, and Doctor Greed and I think once again you've been teed up for for your response.

Since it's a great question and commendations for asking it. I think that may be my best way of entering the Viewpoint is to briefly describe what we've done at Michigan, which is that the original discussions about doing pharmacogenomic testing and planning at work done in

collaboration between our depression Center and Psychiatry faculty with me reading that and the College of Pharmacy that dealing rod and and we have several farmed. He's that are involved in our delivery team and help with the evaluations and for every test that is done are available to consult about the result report when it comes in a day and a half later.

I think on these are really I would like to say it differently, but I really Many cases better informed about some of the issues were discussing today than some of our practicing clinicians and that includes both primary care and Psychiatry and in other Specialties as well. So my answer would be they ought to play a key role. I think they can be involved in evaluating the test. They should give advice. I think that the question of where are we as to who provides the prescriptions in the ongoing care. I said it earlier but I'll repeat it. It's it's just not know 175 percent seventy to seventy-five percent of those with major depressive disorder cared for by Primary Care Obstetricians pediatricians were Pedic people athlete in college sports Etc. Not by the psychiatrist and I'd like to say it differently, but there aren't enough of us and that won't change.

So we got to be doing these as a Care delivery thing and that's why I was recommending that pre-emptive treatment and an emphasis on primary care and Psychiatry. I would be happiest if the primary care doctors who were prescribing had a collaborative care arrangement with psychiatrists who were expert in these areas because I think sometimes the steps that you take the dosages that you take the other treatments that are needed the emphasis on exercise. All of those other variables are really a key part of getting people better. And so I think the psychiatrist plays key roles even when they should be treated in Primary Care.

And by the way, if I can jump in and say one more important thing, I don't think any of us have mentioned it. I have a strong opposition to something that has been happening some I don't know what to call them. But some people who have been advocating pharmacogenomic testing have been doing it Donna on a direct to sending things out and sending things to people literally using the web and saying if you'd like this test do it and then you can do it and there are clinicians who have complained to me. My patient can't have had a patient come in and show me this test result and saying you should be treating me differently.

I don't think that's good the direct from the vendor to the patient population with the recommendation of get yourself tested. I don't think it's a good approach.

Ouch, okay. Thank you. So I think in we're drawing to a close here and I just wanted to check if there were any other CAC members who wish to make any comments who had not yet made any?

This is a real Pollock from Chattanooga, Tennessee.

Hello. Hello, which which CAC do you belong to Tennessee Palmetto? Okay. Okay. Thank you. Just a question that doesn't pertain to the parameters that were set off but just expanding what the doctor just said in his last comment. Is there anything that he would suggest in terms of the reporting format that puts it in the boxes which can be misinterpreted beyond just that it's been go directly to patients?

Yeah, speak for instance the red box of fusing with caution with more frequent monitoring. Do you have suggestions on the reporting format itself? Is that directed towards the panel?

Okay, and any particular panelists in particular the panel at Large?

Judge, either the pain would large or was personally spoken to by the last panelist. In fact, my question was what's really in follow-up of what he said about who the results should go to in. My question. Is this a formatting need to change in any way or is that okay the for me and so that was Dr. Greene and Dr. Greene and do you have any thoughts I do I think I gave it already. This is my opinion. Now. This is not coming from any official posture and I'll just say it. I haven't said it to next I have no reimbursement and no Financial Arrangements that are beneficial to me for the tests that we've used.

Don't think that that would be appropriate as since I'm the principal investigator of the study that I have kept referring to namely the guided study the form that we've used. I feel could be improved. This is he is the caller nicely referred to the green yellow and red foxes. And and I think those are guidance that are simplified to try to tell clinicians. Here's something for you and it lists the medications within these boxes. There are instructions that actually do give things. So for example for certain agents, it will list serum level may be too high or it's difficult to predict the dose adjustments due to conflicting variations in metabolism or use of this drug may increase risk of side effects and that's based again on complex things or in smokers. The level may be too low. I mean, those are listed in the actual tests right now.

I think that's part of of the instruction of how to get psychiatrist Primary Care clinicians pharmacists. I mean anybody else who might be involved in future to really understand what those means and use those instructions for the best care. I think the bottom line right now is that that format while it in some ways is beautiful because it's made it seem simple as to what you choose isn't well understood yet by many providers and they see it as I can't use these agents because they're not in the green box or something and those aren't that's not accurate and I think this is where the complexity enters in so it's where the education enters them. But I think if this collar would like to join in to some future efforts and suggest how the information could be best disseminated to the clinical providers like him it would be good.

We need to be getting better.

Alright, well, thank you. Are there any are there any other cast members who would like to speak or ask a question?

I will take silence as a no. So let me going once going twice and I think we are drawing to a close. Dr. Berman. Do you have anything else to add?

Ed I just like to thank everybody this has been an amazing discussion and I think we've had dr. Gerard pull together an amazing subject matter expert panel the dialogue and the information has been very eye-opening to me I think as well as everybody else on the call. So I think we'll go ahead and close this down. We appreciate everything this meeting has been recorded and will be a permanent link to any further LCD determination or decision to proceed to an LCD and it will be permanently linked their of per the IOM again. I appreciate it and wand you need to close it out or can we just say hang up?

Now you can just hang up. That's why thank you very much. Again. Thank you everybody and to dissociate matter experts. It was amazing, and I really appreciate your time. Thank you, and I look we learned as well. So thanks, everybody enjoyed it. Thank you. Thank you for the time. Thank you.