

Alan Hu Foundation Mental Health Lecture Series

Precision Treatments for Depression: Are We Getting Closer?

Webinar by Leanne Williams, PhD

The Vincent V.C. Woo Professor of Psychiatry and Behavioral Sciences at Stanford University and
Director of Stanford Center for Precision Mental Health and Wellness

April 9, 2024

[00:00:1]

CHIH-CHING HU: Welcome, everyone, to Alan Hu Foundation Mental Health Lecture Series. I'm Chih-Ching Hu, cofounder of Alan Hu Foundation and host for your webinar. Today, Dr. Leanne Williams will present "Precision Treatments for Depression: Are We Getting Closer?".

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We'd like to thank Three Valleys Community Foundation for their generous grant to fund this webinar. We'd also like to thank the Mental Health Association for Chinese Communities for providing simultaneous Chinese interpretation. Thank you to Ida Shaw for Chinese interpretation.

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Alan Hu Foundation's mission is to promote mental health, raise awareness, and remove stigma surrounding psychiatric disorders, and to support fundamental research for cures. Please consider making a gift to Alan Hu Foundation by using the donation link in the chat box. Thank you for supporting our programs.

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Today, it is our great honor and privilege to introduce Dr. Leanne Williams. Dr. Williams is Vincent V.C. Woo Professor of Psychiatry and Behavioral Sciences at Stanford University, and Director of the Stanford Center for Precision Mental Health and Wellness. Dr. Williams wrote the first book on Precision Psychiatry, published by APA, and has also contributed more than 380 scientific papers to the field.

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In today's talk, Dr. Williams will share the knowledge about her research findings. Using neuroimaging and clinical measures, she has identified biotypes of depression and anxiety. She will discuss results from trials to understand which types of depression respond to different interventions and why, as well as opportunities to translate these results into clinical care.

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This webinar is being recorded. The recordings will be available on the Alan Hu Foundation website and Alan Hu Foundation YouTube channel in about ~1-2 weeks. Please subscribe to Alan Hu Foundation YouTube channel.

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Following the presentation will be a Q&A session. Please use the zoom Q&A function to submit your questions. The presentation is for educational purposes only and is not intended for medical diagnoses. If you have any persistent symptoms, please seek professional help.

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With that, I'm turning to Dr. Williams. Welcome, Dr. Williams. Thank you for being here. Please take over the screen sharing.

[00:02:42]

DR. LEANNE WILLIAMS: Thank you. Thank you for that incredibly kind introduction. Chih-Ching, who I really appreciate yours and Xiao Fang Chen's invitation to present, and it's an honor to be contributing to the Alan Hu Foundation webinar series and to be invited today.

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The mission of the Alan Hu Foundation is very inspiring to me. That mission is to: promote mental health, raise awareness, remove the stigma that is surrounding psychiatric conditions, and to support fundamental research for cures.

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I say that with sharing my personal experience as well—but today, I really hope that I can communicate a message of hope based on the insights that we're seeing from the data and the research. I will welcome your questions about that as we get to the discussion session.

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As I mentioned, this mission is very personal to me. I lost a loved one to suicide nine years ago, and it's made my motivation to find solutions even stronger. This is a photo of the memorial we held for my personal partner. He was an emergency care doctor, and he was experiencing depression. But because of the stigma, he felt too ashamed to seek treatment and really worried that having depression on his record would make it not possible for him to continue or devastate his career. I feel an incredible dedication, even more so than when I started in the field, to accelerate new solutions.

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We can think of—as many as you would know—the global impact of not only depression but all the associated conditions that we need to find solutions for, and that we've all been touched by either directly ourselves or through our loved ones.

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So, globally, as many of you would know, there are 970 million people impacted by mental health disorders. And now, they're the number one cause of disability, meaning: disruption in our learning psychosocial function, being able to work, and so on. And of course—all too often—this is affecting young people.

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And because of that challenge of having our function being disrupted through these disorders and not having a way of immediately getting treatment solutions, the number—globally—of people who are losing their lives to suicide is 700,000 per year. And that's the world health organization number.

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And the challenge, or one of the challenges, is that typically it takes 11 years between the onset of the illness and being able to start treatment—and most importantly—start a treatment that is tailored to the individual person's needs and the root cause of the illness.

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And we know that this impact has increased since the pandemic. It's increased particularly for young people for depression and anxiety, and that's what I'm focusing on today is depression and anxiety. However, the findings that I present are relevant to other conditions, because we are talking about brain function that is impacting or disrupted in multiple different disorders.

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The question that motivates me is "Imagine the difference that we could see if depression and other conditions

are treated just like other health conditions". So just like diabetes, like viruses, just like heart disease... all sorts of other health conditions that we have access to testing and a way of knowing what kind of treatment do we need. We can think of the recent example from Covid, where finding the root cause was important for the treatment.

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I believe there is hope from neuroscience discoveries. What I'll present today is some of these discoveries that I believe can help drive down those numbers that I was referring to the prevalence and the impact on people's lives. And here, the transformation is to think about disorders such as major depression, or anxiety disorders and other conditions as disorders of how our brain functions. In that case, it's not about not trying hard enough, it's not about blame, it's about a disruption in brain function that creates—uh, generates—the symptoms that we observe on the outside.

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One of the challenges that I've addressed in my research is to look at the root cause of the different kinds of symptoms that, uh, contribute to a diagnosis such as major depressive disorder; a key thing is that—as many of you would have observed—there's a lot of variation in the symptoms that generate a disorder like depression and disorders that overlap with depression. Anxiety disorders like panic, generalize anxiety, PTSD, bipolar disorder... there's a lot of individual variation, because each of us have an individual brain in how it functions, how it's being shaped by our life experience. So that variation is important to understand if we're to find personalized treatment solutions.

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We can zoom in and look at the diagnosis of depression or major depression itself, and it illustrates this variation. So, when we diagnose a disorder like depression, we are essentially asking someone to tell us how are they feeling and to try and explain in words, the kinds of experiences they're having; and that can be difficult. If you think of—say another illness—say you're having a chest pain. You may not know what is at the root cause of it. You can describe what you're feeling, but you may not know what is the underlying cause. And so that's one issue that I'll focus on.

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And the other one is that these are different experiences or symptoms that make up the diagnosis.

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So there are nine symptoms making up the diagnosis of major depression, and the first two are the cardinal ones—the ones that need to be there, one or both, like persistent sadness and a loss of pleasure—but with the the others, you need to have five of nine of these, and that means there are many different ways that an individual could experience depression.

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The way that I've looked at how to understand that variability and to identify what is at the root cause of one person's experience of depression, is to directly measure our brain function. I do that through measures of what I call "brain circuits", and I'll talk more about how I measure those and what they are by doing it. I can identify what are called "biotypes". So these are different types of disruption in these circuits in our brain. These are connected regions of the brain and those different kinds of disruptions that are forming these biotypes can give rise to different kinds of symptoms, and by understanding those biotypes, we can then identify what treatment may be the most, uh, effective, or the one we would select out of the multiple options for targeting that underlying disruption, that underlying biotype. In depression and anxiety, we have identified eight different biotypes, and we can target those with different types of treatments as I will illustrate.

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Let's compare this biotype, this new biotype approach to our current situation. Right now, we typically diagnose a broad umbrella category such as major depressive disorder, and we do that as I mentioned by the presence of the symptoms. When we then look at how to select a treatment, it tends to be a holistic approach of trying one treatment, waiting about 8 weeks—maybe 8 to 12 weeks—seeing how it goes, “does it improve the symptoms?”, and if not, trying another treatment, and if that doesn't go well, maybe adding another or doing some and moving to another treatment. That process, uh, can for some—all too often, actually—take a long time. It can take years, and sadly, it means there's a diminishing opportunity for achieving remission with multiple trials. So the goal of my work is to accelerate getting the right treatment to each person sooner in that process, and the way I think about it is to unpack that heterogeneity. So, to identify, early on, what is the underlying biotype for each individual using test, and then in doing so, identify for that individual what is the disruption. So, illustrated here, with this individual colored in red, we can then look at their particular brain biotype. The idea is to be able to more quickly rule out treatments that are not going to be effective or not likely to be treatments that may cause side effects without having effectiveness, and be able to more rapidly consider alternative or different treatments and to expedite that timeline and make the selection personalized.

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And to do this, currently we are using functional MRI scans which is a special kind of MRI. It picks up the oxygen changes in the blood flow in your brain, so that when you are engaged in processing information or experiencing emotions, we can see bright spots on the scan where the activity is, and we can see when the brain function is disrupted. I will talk more about how we're thinking to add other measures to to make this more scalable as well.

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Let's think, though, of an analogy here. So 73 years ago, a study was launched called the Framingham study—which you may be familiar with—and that was launched at the time that half of adults were dying by heart disease, and we didn't understand the heart. We didn't know how to treat heart disease. And there was a huge explosion of research gathering information about the heart, and as a result we now have a deep understanding of how the heart functions and its structure. So what that means is if someone presents with a fairly general symptom like chest pain, we can use imaging of the heart at rest, and when we stress the heart a bit to understand what is the root cause of that chest pain, we can understand is it a temporary shift in activity of the heart for which maybe a lifestyle or diet change would be effective? Is it something instead that needs medication, or maybe it another extreme there may be a need for a pacemaker or surgery?

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So in our case, this transformation occurring in our field is to think about the brain as the organ of interest. So we're talking about brain function disorders. And now, thanks to very rapid advances in being able to image the brain with functional MRI, we can consider moving from this experience of emotional pain—which is expressed in the symptoms of depression, anxiety, and other disorders—and using the imaging to understand what is at the root cause. And so in our studies and what we're implementing clinically, is we assess the brain when it's resting and then when it's engaged in different tasks.

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So let's look at how those circuits are or what circuits we are measuring. Clearly the brain is extraordinarily complex. We have an extraordinary—thousands and thousands, uh, hundreds and hundreds of thousands—of connections. What has been identified, though, thanks to these rapid advances in imaging the brain; for example, there's a large project I've been part of called “The Human Connectome Project”, which is mapping out the human brain. Thanks to those advances, we can focus on six circuits that are tractable for being able to measure now, and that we know are implicated in depression and the mechanisms of treatment. I'll go through these six.

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So three of them we see when the brain is just resting naturally. One of them is called “the Default Mode”. It’s a set of five regions in the brain that communicate with each other, and what they do when they communicating together, is they help us reflect on our internal self. They help us remember our past. They help us project into the future and have a sense of ourselves. If this circuit is underconnected, you can lose that sense of self and feel a bit disconnected from yourself. If it’s overconnected, it will create too much focus on your internal worries and negative thoughts. The next one we call “Salience”, and this is a region of the brain or combination of regions that will read out emotional and physical pain. So this circuit is engaged when we experience physical pain and also emotional pain, and it orients us to the source of that pain. The one called “Attention” is a different set of circuits and this circuit helps us focus and maintain our attention. During the pandemic, this circuit was stretched a lot, and so there was one form of anxiety we were seeing which was where this circuit started to be underconnected and people were struggling to focus. Then in task conditions, we have a circuit we call “Negative Affect”, which responds to negative emotion. If it stays too active, we have the feeling like we’re feeling stressed all the time, maybe feeling like we’re in alarm mode. This next one, “Positive Affect”, helps us experience positive emotions. It gives us our sense of purpose and motivation, so if it’s underactive, we have a loss of pleasure and we can feel numb, which is another form of depression. This last one, “Cognitive Control”, is the executive brain. It’s the one that helps us plan ahead, inhibit unwanted thoughts, inhibit unwanted behaviors—and this, we’re discovering, is important in one form of depression that is very much about this particular circuit.

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These circuits, when they’re disrupted, they map onto specific types of symptoms. As I mentioned, if this Default Mode is overconnected, we can have a sense of rumination where we’re focusing on our internal worries. We tend to feel like we’re caught in a bit of a loop of negative thinking. The Salience one, when it’s disrupted, makes us feel more anxious, so you get physical states of anxiety. The ones to do with negative emotion can make us feel hopeless, make us feel pessimistic, and not see a way through. The one to do with threat makes us feel fearful and afraid and not be able to see a positive future. The one to do with positive emotion, when it’s underactive, makes us feel numb and slow. It’s hard to respond to other people’s happiness and positive experiences. This cognitive one, when it’s disrupted, makes it difficult to make decisions and difficult to be able to function at work.

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So, let’s look at this crucial question. Knowing about these circuits and being able to measure them, how can we personalize treatments?

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What we are finding in our studies is that each person has a primary dysfunction in one of these circuits when they’re experiencing depression or anxiety, and by knowing about what that primary dysfunction is, we can help rule out some treatments and rule in others.

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So when we look at Default Mode, there are some people—about 20% of people who have a disruption in this circuit—and what we see is, for those who have less connectivity, they tend to not respond on standard antidepressants. So these are like SSRIs for example. Whereas those with intact connectivity, it’s an indicator that you are likely to respond. So this is one measure that would help identify whether it’s worth trying something different, and in this case, we’ve been able to—in our clinical studies—refer people to different treatments such as uh TMS for example.

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In the Negative Affect circuit, when that is evoked by negative emotion, there’s a region in the brain called the “amygdala”, which can stay switched on. Normally we switch it off after feeling a negative emotion, but in some

people—here, about 15% of people with depression—stays switched on. And when it stays switched on, we know that there's a poor response to some types of antidepressants. These are the ones that impact both serotonin and norepinephrine. However, if it's not switched on, typically you'll have a better response to SSRIs. This is quite an accurate prediction in the data from my studies and from other labs.

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What we see is if we consider life events—like having a traumatic experience early in life—this prediction is even stronger. The way our early life shapes our brain is seen in the way that this circuit can be vulnerable to being switched on, for example. Of course, a question is if someone is, shows a signature in these brain circuits that suggests the anti-depressants may not be as useful, what are the alternatives?

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So in a study with my collaborator, Jun Ma, who is now at University of Illinois in Chicago, we looked at behavior therapy, which was focused on problem solving. We found very importantly that—for those individuals who had this higher amygdala activity—they actually responded well to the problem solving behavior therapy and it reduced their activity and produced a two-fold increase in their clinical symptom response.

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The next set of findings are from a different group of individuals. So this, in our studies, we found is about one quarter of people with depression—particularly people who are struggling at school or in their work—and you see that there's a basis in this Cognitive Control circuit. What we have found in large studies is that, for this type, this circuit is underactive compared to other people. It's lower and then behavior is affected, so the ability to perform daily functions is reduced, and there's a lower response—almost 11% lower on standard anti-depressants—and as I mentioned this is about one quarter of people that we've studied. We've been looking at what are the alternatives if this is the presenting underlying cause of symptoms, and we're looking at a new treatment that is already approved by the FDA but isn't currently, um, isn't currently indicated for depression, it's indicated for other uses.

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And it targets this part of the brain in a specific way, and it's been found to boost the activity and connectivity of that circuit. It is called "guanosine", and it's an immediate release compound.

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So in this study, we focused in on people experiencing depression who had this particular profile. When we scanned them, we assessed their behavioral performance and their symptoms, and we did that prospectively. This here's a lot of graphs, but it was very promising. We're very excited by these findings in that when we use this approach which is very selective, we find that the brain activity improves. It goes up. We find behavior improves. We also find importantly quality of life improves, and we find that severity of symptom improves.

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And we achieve a doubling like a two-fold increase in the number of people achieving remission, and a doubling of the number of people showing a significant response (so two-thirds more than two-third of the group), and this is now leading us to do a larger randomized trial to look at this in detail. Another way that we've looked at this type of depression is through transcranial magnetic stimulation which is a way of non-invasively stimulating this part of the brain, and we have found that the individuals who have this reduced activity shown in red... they improve after 5 days of treatment—so they move into this healthy range. It tails off a little bit but we're continuing the study to see if we can keep that improvement, to make it an ongoing improvement.

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If you look at the 43 people in the study so far—these are the individual profile— and it's encouraging to see even

though there's variation there's also consistency in the improvement in the people who started off impaired compared to those who did not weren't impaired in this circuit. So that's also going to be ongoing work in the coming few years.

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Our goal is to continually expand the treatment studies and make them more and more available, so that we can ultimately have a large understanding of which circuit in which person— which individual person—would indicate our likely hold of responding to which treatment and expanding it to as many possible treatments as we can. Of course, it's really important to think about how we can translate this information into our everyday lives. How do we make this available for a holistic understanding of the experiences of depression, anxiety, and ultimately other conditions, and then how do we make it available in practice?

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So one way we've been thinking about it is, first of all, knowledge dissemination about "how do we change how we talk about our symptoms and change that to think about what is changing and what is happening in our underlying brain circuits?" And why this is a message of hope is because we do know that the brain is changeable. It is plastic. It can change with treatment, so getting the right treatment is important for promoting the most effective change. But we can think about this in our everyday life because we know the default mode is involved in our tendency to worry and to have negative self talk. We can think about what can we do if we're starting to have these experiences, and we see that there are tips based on the knowledge such as actively scheduling time to worry and activities that promote breaking out of that ruminative cycle, strategies of deep breathing—for some people it's walking quickly—, immersive activities and so on.

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For the the amygdala that I was talking about that can stay switched on in alarm mode, we think of this is generating a kind of threat response where you feel literally like a sense of alarm. It can make people feel a bit jumpy or panicky, and here there are strategies of getting warm because this effect can kind of lower your body temperature as well. Talking about the kinds of experiences you're having out loud which allows the brain to process it can help um shape the brain and process the experiences differently.

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And then for this one, I talked about, it's the Cognitive Control circuit. When it's in that reduced activity mode—it can make people feel like there's a cognitive fog—like it's very hard to think, it's hard to remember things, can make you feel slowed down. And so for tips on that, it's like literally breaking down tasks one step at a time. It can help to write things down to make it tangible, and knowing that it's okay to take rest time so that this circuit of the brain has a chance to catch up with the information that it's processing.

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So that's a kind of knowledge transformation. We're also looking at how can we take these findings into the clinic and into practice, and we are actively focusing on that right now. So in the Precision Psychiatry book that was mentioned in the introduction, we present ways that we're making this happen across multiple centers in the US and globally, and the goal is to continue this improvement in doubling and then going further in the number of people who get better. So what we have done at Stanford and we are accepting for now a kind of limited number of referrals is, with my colleague Laura Hack, we've set up a clinic to deliver these or to make available these tests and we, for example, will look at individuals who we scan with the MRI and take additional assessments. So this is a snapshot of one individual case. This is a pseudonym that I'm using, not a real name and not a real photo but to illustrate. So this was a young woman who was 20 who we saw who'd been uh depressed since teen years and her symptoms were worsening after starting college. She was isolating, avoiding her hobbies, and she had this experience of anhedonia, losing a sense of pleasure, also feeling suicidal and losing hope. In this case, there's another new treatment that we're trying. It's called pramipexole, which targets this emotion

brain—the positive affect circuit—and we tried this with Jane and we were very happy that she did show a very positive response to this selective treatment. We saw the improvement in her brain activity and we saw her symptoms—specifically these anhedonia loss of pleasure symptoms reduce—and she told us how she felt like she was allowed to feel happy now, and she’s doing well after more than one year later.

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What we are very excited to hear from individuals who we see is that they feel like seeing their brain helps get insight into what is generating the experiences that happen having and importantly reducing that sense of stigma and self-blame. A lot of people experience that sense of “This is my fault. I should be able to control it”, but by knowing about what is the underlying brain profile, it can help choose what changes to make in everyday life—as well as engage in treatment planning and find the right treatment to target.

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In ongoing studies, we will be looking at “how do we scale the fMRI measures”, and we’re looking at... for example, once we have this foundation in the brain—similar to what has occurred for Cardiology—we can map the brain signature to digital signatures and to other measures that we can offer remotely and on scale, and show how they map to from the digital signature back to the brain. So we’re very excited about that, and we’ll be working on this in the next few years as well.

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So let me thank my important collaborators. There are many who contributed to the work that I presented, and I want to thank Alice Woo, who has supported me with a very important inaugural endowment which really makes it possible to accelerate this work, and thank you all for your attendance. I invite you to join our research registry. The link is here and also this QR code, and we really would welcome you contacting us and joining our various social media sites. They’re listed here. So thank you again for the invitation to present, and I really look forward to the discussion.

[00:38:03]

CHIH-CHING HU: Thank you so much, Dr. Williams for the wonderful presentation and sharing the promising result of precision treatment for depression. So now we are open up to a Q&A, uh, let me read some questions from the registration pre-submitted questions while we’re waiting for more questions to be submitted from the audience.

[00:38:29]

DR. LEANNE WILLIAMS: Would you like me to stop sharing, Chih-Ching Hu?

[00:38:32]

CHIH-CHING HU: Oh yes—Yeah. Please. Please stop sharing. Okay.

[00:38:41]

Okay, the first question: “What are effective interventions for depression? What are some common misunderstandings, mistakes, regarding depression?”

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DR. LEANNE WILLIAMS: It’s a really important question. So there are many effective interventions for depression, in fact, all of the ones that you’re likely to hear about. So behavioral therapy, like cognitive behavioral therapy, and the example I shared the SSRIs, transcranial magnetic stimulation... these are all effective. The challenge as I mentioned—and I think it’s not so much a misunderstanding but just is where we need to go—is that we are currently showing that they are effective on average, so it’s not the case that every single person is going to represent the average.

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So typically the effective interventions we have will be effective for about one-third of people, so the challenge is about how to identify which treatment for each person. That leads to the—what I would consider the misunderstanding—which is that depression is not a real disease. I think it very much is a real disease. It doesn't mean we can't find a cure, but it means we do need to think carefully about how can we measure it so that we can do better in finding those effective interventions.

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CHIH-CHING HU: Okay, so next question is from a doctor: "Is the Stanford study utilizing the data burst TMS technology?"

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DR. LEANNE WILLIAMS: We are. So at the study that I talked about is one that we are doing in a clinical setting, and there are three other sites involved. In the data that I shared we're using what would be considered standard TMS—which is once daily—but we've moved to using the accelerated form which will be delivered over approximately five days, and that study will be ongoing for several years.

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CHIH-CHING HU: Okay, um, next question a little bit longer one. "Can you talk more about applying your research to life by the patients themselves, their loved ones who want to help, and the professional to use questions to close in the right biotypes?" This person used to have depression 20 years ago and would love to look into the previous types to understand the units.

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DR. LEANNE WILLIAMS: Right. Right, absolutely. So for anyone who is able to come to Stanford, I would join that research registry. We will have the biotype measures available at other sites as well, so my collaborator Jun Ma, she'll be doing this in Chicago, and then we expand to other sites. What the the goal is, exactly as a question was framed, is to be able to understand for each person "what is the biotype that puts them slightly at risk for different types of depression/anxiety". So we can think of it like it's a rough analogy but a little like blood pressure where each of us has healthy range for our blood pressure, and if it goes a bit higher, we can make lifestyle changes to manage it; but if it goes too high and other factors are at place, we can end up with an illness. So the brain circuits function a little like that, so it's understanding what is the range for each person of being able to function with them.

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CHIH-CHING HU: Okay, next question: "What preventative measures can be taken for children whose parents are diagnosed with depression/anxiety? Will they inherit the depressive genes?"

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DR. LEANNE WILLIAMS: I didn't mention this study, but there was one where I did study the sons and daughters of parents with depression and anxiety, and what we found was that some of the the kind of disruptions in these circuits were present—not in the same degree, just in a mild degree—without the symptoms. So that told me that the shift in the circuits will come before the symptoms which leads to the preventative strategies being, um, thinking about this from a brain point of view. So if it's a feelings of stress and trauma, the more that that can be talked about, the more the brain has a way to process and actually, literally, inhibit the overactivity of the amygdala. Or if there's a sense of kind of focusing in on internal negative thoughts like the Default Mode, the strategy I suggest is any activity that makes it hard to talk. Because if you're struggling to talk because you're exercising or dancing or you're breathing deeply, if you can get into that state, you know that your Default Mode is engaged. So it's having that opportunity for the positive affect. One that if you— if the experience is about losing interest,

like not feeling interested in friends or you know withdrawing, being isolated—then I think it’s about really looking at things that will make an automatic sense of pleasure. It might be music, having inperson interaction will help engage the positive circuit we rely on the feedback. I know that’s a long answer but hopefully useful.

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CHIH-CHING HU: Okay, thank you. So there are several questions regarding fMRI: “How to get MRI to identify the path of the treatment, and is this available in regular clinical practice now, or—

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DR. LEANNE WILLIAMS: Right.

[00:45:48]

CHIH-CHING HU: —if they request the psychiatrist to get a fMRI, where they get it, and in order to understand what kind of specific biotypes?” All these questions.

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DR. LEANNE WILLIAMS: No, great question. So we have the fMRI available through this new clinic at Stanford. It is called the “Translational Precision Mental Health Clinic”. So what I would suggest for anyone who is able to come to Sanford or is already local, to ask their doctor to refer to that clinic and I can share with you— if by email if that’s appropriate— or I can share the—

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CHIH-CHING HU: Yes.

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DR. LEANNE WILLIAMS: —the name of that clinic.

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CHIH-CHING HU: Right, and then we can add the information into our News and Notes, email distribution list.

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DR. LEANNE WILLIAMS: Right. For having access to fMRI through the research, I would sign up to that research registry, because in the coming—starting in July we’ll be doing— we’re already are doing these studies—but in July we’ll be expanding our studies so we’ll be able to also do the imaging of the biotypes and offer some treatments through the clinical research as well.

[00:47:07]

CHIH-CHING HU: Okay. Also a group of questions regarding whether the, this—this methodology can be extended to the circuit mapping to other disorders like bipolar, anxiety, ADHD, ASD?

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DR. LEANNE WILLIAMS: Great question. The answer is yes because we are measuring circuits that are also involved in those other conditions, because they are the circuits underlying our human experience. I do have a collaborator at Stanford who is looking at ADHD right now. He’s using EEG measures—not the fMRI—but he can measure that attention circuit which is involved in ADHD. So that is one opportunity. I have another collaborator looking at bipolar disorder right now in Sydney where I’m originally from, but the answer is yes and this—this research is expanding to other conditions. I have one other collaborator Carolyn Rodriguez who is looking at OCD as well.

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CHIH-CHING HU: Okay, great. Next question: “Is your treatment similar to neurofeedback treatment?”

[00:48:35]

DR. LEANNE WILLIAMS: It’s similar in that the idea is to promote positive brain change where it’s needed. I don’t currently use neurofeedback itself. What we use, they are medications—but they primarily, although—so we use behavioral therapy, which we know changes the brain through changing behavior. We use the TMS, and we use selective medications which we know modulate particular circuits.

[00:49:15]

CHIH-CHING HU: Okay, yeah, I think that’s a part of questions from the presubmitted questions that “could you please provide your opinion on the the ketamine assisted psychotherapy?”

[00:49:29]

DR. LEANNE WILLIAMS: Right, thank you for raising that. I do have studies ongoing that are looking at “how do the biotypes relate to the effect of ketamine and the effect of the MDMA that’s also being looked at for PTSD”. So what we’re finding in terms of the immediate effects of ketamine is it helps with that those circuits involved in emotional pain, and so physical anxiety states and the experience of too much amygdala activity.

[00:50:14]

CHIH-CHING HU: Okay. Another doctor asked: “Many of my patients with depression also meet criteria for autism spectrum disorders. Any tentative findings regarding both types differences, treatment differences, etc?”

[00:50:30]

DR. LEANNE WILLIAMS: Right. Um, its— I haven’t studied it directly, so I am basing this on findings from my colleagues who have looked at these same circuits in autism spectrum disorder, and we do see—for example, the region I talked about called the amygdala—in some forms of depression it can be overactive, sometimes in autism you’ll see it’s underactive, so you can use the same scan to assess it, but it will be underactive—which means there needs it suggests that it would be effective to boost it to in order to expand the amount of emotional information being processed.

[00:51:22]

CHIH-CHING HU: Okay, next question. “If join the research, how many times the participant needed— needs to be at Stanford in-person?”

[00:51:37]

DR. LEANNE WILLIAMS: Right. For the clinic, we— it— it’s essential to come in at least once so we can do the the scanning and evaluate the biotypes and then look at what treatment may be relevant. We do suggest to people to come back after trying the treatment so we can look at the change for the studies. We do something similar, so I guess in some, two times.

[00:52:09]

CHIH-CHING HU: Okay. Also many questions regarding: “Is this available in other states and how— yeah, how soon that will be become widely available to patients?”

[00:52:26]

DR. LEANNE WILLIAMS: It’s a great question and one I’m glad was asked. I wish that we could make it widely available tomorrow. That’s certainly my goal and mission. What I am doing is, I developed the imaging processing as a technology that can be disseminated widely— so actively, I’m looking at how can we make this available at multiple sites. In research, I have it running in four other locations in four other states and have— we have one in Italy, and the goal is to find partners who can base the logistics in a way to make it available wherever some-

one is and they can access a scanner—so we're actively working on that.

[00:53:18]

CHIH-CHING HU: Okay, great. Next question: "How can a regular person help with your research?" In my— in this person's case of depression goes in family.

[00:53:30]

DR. LEANNE WILLIAMS: Right, everyone can certainly help. So there are several ways. One is through feedback about the approach and how we would communicate it and the questions about "how would you develop preventative strategies". Just thoughts about "how could this information become part of our discussion and how we talk naturally in the same way that we talk about other health issues". The second way is if it's relevant to come into our research. That can be families come as well.

[00:54:15]

CHIH-CHING HU: Okay, let me go back to previous questions submitted. "Have there been research efforts using computational Neuroscience, using artificial neural networks to gain insights into psychiatric conditions?"

[00:54:35]

DR. LEANNE WILLIAMS: Great question. Yes, absolutely, they have. There are using big data sets and AI and machine learning is being used with multiple types of measures to understand that variability, and the symptoms that I was talking about— we're using it. We have a paper that will come out soon that we combined all the data sets that we have and used an AI based approach to keep refining these biotypes and really getting a detailed understanding of how do—does a biotype map to the symptoms and the treatments, because we're dealing with a lot of different dimensions of information, so yes.

[00:55:25]

CHIH-CHING HU: Okay, next question also several people asked about that. "Does the research focus on adult population? Can the research result be applied to adolescent populations?"

[00:55:39]

DR. LEANNE WILLIAMS: Good question. Right now, my own research is focusing on adults 18 years and over. Part of the reason for that is because we're using these new selective medications, we need to start with adults because of the approvals. However, my collaborators are looking at adolescents, so I think by reaching out to the registry and indicating if there's an interest with younger people, we will track all of that information through the center that I lead. We have collaborators looking at adolescents.

[00:56:23]

CHIH-CHING HU: Okay, so next question: "How to identify early signs of depression?"

[00:56:33]

DR. LEANNE WILLIAMS: It's a— it's a big question.

[00:56:36]

CHIH-CHING HU: Yes.

[00:56:36]

DR. LEANNE WILLIAMS: So some—some things... let me step back a second. We tend to... we being our field and the wider community— we think of depression as being about sadness right. That's kind of our understanding it's being sad, and that focus came about because of how the main medications were developed, and I lead with that because what we do know is that the early signs of depression tend to be about sleep problems. The other

features sleep problems and that slowing—this slowing, so if you see speech starting to be slowed or difficulty making decisions and isolating and sleep problems, they're the signs of the other symptoms which can be really important in indicating the early signs; whereas the effect on sadness may actually come later.

[00:57:39]

CHIH-CHING HU: Okay, so Dr. Williams, it's about time, so I think I will stop here. I think we covered a majority of the questions today, and thank you for—

[00:57:53]

DR. LEANNE WILLIAMS: I'd be happy to! I'd be happy to answer them in written form later if that's useful.

[00:58:01]

CHIH-CHING HU: Oh, oh great! Thank you so much, yeah, and thank you for sharing your knowledge, and it's a very promising treatment for the depression. Um, and thanks everyone for joining our webinar, and we hope to see you again in the next webinar in May. If you live locally, we hope to see you at our benefit concert this Sunday. This webinar is being recorded. As I mentioned earlier, the recording will be available on Alan Hu Foundation website and Alan Hu Foundation YouTube channel in about one to two weeks, and please subscribe to Alan Hu Foundation YouTube channel. Also, please take a moment to fill out a short survey. Your input is critical to us to improve the program, and I will leave the donation QR code for a few more minutes, and thank you for supporting our programs. And with that, I'm closing the webinar and thank you, Dr. Williams.

[00:59:03]

DR. LEANNE WILLIAMS: Thank you so much! Thank you for the invitation.

[00:59:07]

CHIH-CHING HU: Thank you so much and thanks everyone, and take care and stay well.

[00:59:11]

DR. LEANNE WILLIAMS: Well.

[00:59:17]

CHIH-CHING HU: Bye-bye.